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AN INVESTIGATION INTO MEMORY CONTROL: NEUROMODULATORY APPROACHES AND POTENTIAL CLINICAL TARGET POPULATIONS

Coordinatore: Ch.mo Prof. Francesca Peressotti

Supervisore: Ch.mo Prof. Giovanni Galfano

Dottorando: Davide Francesco Stramaccia

ABSTRACT

The present doctoral dissertation is composed of six studies investigating various aspects of cognitive control, with a focus on selective memory retrieval: The brain areas that support this ability, the possibility of modulating its behavioural manifestations with transcranial Direct Current Stimulation (tDCS), its relationship with motor stopping, and its integrity in two clinical populations. Results provided by these experiments highlight four major achievements of this line of research: Firstly, we provided causal evidence for the involvement of right PFC in supporting the cognitive processes underlying memory control, because interfering with the activity of this region was sufficient to disrupt the RIF effect. Secondly, we demonstrated the effectiveness and viability of tDCS as a tool to modulate this peculiar effect. Thirdly, we provided compelling evidence for the advantages of analysing RPP data with a statistical approach that is more consistent with the nature of the data, as well as informative in respect of the different dimensions of the data that contribute to the results. Last, but not least, we contributed to the characterization of the cognitive profile of patients affected by substance-related and addictive disorders and EDs, paving the way to future research that could further investigate the extents and specificity of the previously unexplored memory control deficits that we unveiled in these patients.

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LIST OF ABBREVIATIONS AND ACRONYMS

DLPFC: Dorsolateral Prefrontal Cortex

EEG: Electroencephalography

FAC: Facilitation

fMRI: functional Magnetic Resonance Imaging

IFG: Inferior Frontal Gyrus

MEPs: Motor Evoked Potentials

NRP+: Non-practiced items from non-practiced categories in the RPP; control for RP+

NRP-: Non-practiced items from non-practiced categories in the RPP; control for RP-

PFC: Prefrontal Cortex

rDLPFC: right Dorsolateral Prefrontal Cortex

rIFG: right Inferior Frontal Gyrus

RIF: Retrieval-Induced Forgetting

RPP: Retrieval Practice Paradigm

RP+: Practiced items from practiced categories in the RPP

RP-: Non-practiced items from practiced categories in the RPP

SART: Sustained Attention to Response Task

SST: Stop-signal task

tACS: transcranial Alternated Current Stimulation

tDCS: transcranial Direct Current Stimulation

tRNS: transcranial Random Noise Stimulation

tES: transcranial Electrical Stimulation

TMS: Transcranial Magnetic Stimulation

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PREFACE

The study of cognitive control has attracted increasing attention from both researchers and clinicians, in particular for its trans-diagnostic value as a set of abilities which appears to be consistently challenged across a broad spectrum of psychological disorders, thus potentially constituting a common factor at their roots. Because of that, the many facets of cognitive control are currently privileged objects of scientific investigation. Importantly, over the last thirty years, a set of cognitive models of memory has gained prominence, in which a role for cognitive control in both retrieval and forgetting is postulated. As a result, the concept of forgetting has also been profoundly revised, from a limitation or failure of our memory systems to an active process that benefits from cognitive control to allow for an adaptive and efficient functioning in the every-day life. In particular, it has been hypothesized that inhibitory mechanisms, putatively similar to those involved in response selection in perceptual and motor tasks and therefore sharing common neural substrates in the prefrontal cortex (PFC), may be responsible for a peculiar instance of forgetting that is detected when retrieving an information from our memory storage impairs later recall of related information, compared to unrelated ones. This finding, traditionally termed retrieval-induced forgetting (RIF), is thought to represent the mark that is left behind by inhibitory control mechanisms recruited to overcome interference during selective memory retrieval, i.e., when we actively engage in effortful retrieval from memory in the face of competing, irrelevant memory traces. The mnestic representation of these interfering memory traces would be weakened by inhibitory mechanisms that promote selection and emission of the correct, task-relevant response, so that on later attempts to retrieve the previously interfering memories their availability may be reduced. Given that this particular instance of forgetting has been associated to a range of abilities closely tied to our well-being and cognitive efficiency, ranging from working memory to creative problem solving and motor inhibition, it is not that surprising that it has been found to be impaired in a broad range of disorders traditionally characterized by impulsivity, anxiety, or rumination. For this reason, there is a great interest in investigating RIF in previously unexplored psychiatric and psychological disorders, identifying its neural underpinnings and strategies to modulate their activity, and clarifying its relationship with other expressions of cognitive control in different domains.

In my doctoral dissertation, I will focus on the alteration of the neural substrates of RIF in the PFC by the means of non-invasive brain stimulation, and on the assessment of the integrity of the ability to overcome interference in selective memory retrieval in patients suffering from substance-related and addictive disorders or eating disorders (EDs).

In the first chapter, I provide the core background for the present work, by presenting a comprehensive review of the theoretical debate, applied relevance, and the contribution of cognitive neurosciences, concerning retrieval-induced forgetting (RIF) as an instance of adaptive forgetting.

In the second chapter, I present a brief outline of the main features and applied potential of transcranial Direct Current Stimulation (tDCS), which is employed in several experiments presented throughout the present work.

In the third chapter, I present the first experiment to provide evidence for causal involvement of the right prefrontal cortex in control over interfering memories, as well as paving the way to subsequent investigation of neuromodulation of RIF by the means of tDCS.

In the fourth chapter, I take a brief detour from the main topic of inhibitory control in episodic memory, to the neighbour domain of inhibitory control of motor action. To this end, I present an experiment that tested the efficacy of various tDCS montages to modulate motor stopping ability in a delayed stop-signal task (SST).

Results from the experiment presented in the fourth chapter, together with the previous one, enabled the designing of the two experiments presented in the fifth chapter, which were aimed at evaluating the effects of tDCS over RIF on a different prefrontal area, i.e., the right Inferior Frontal Gyrus (rIFG), and subsequently attempted the concurrent modulation of memory control, as indexed by RIF, and motor stopping, as indexed by the SST, based on previous evidence of a relationship between the cognitive mechanisms underlying the two abilities.

In the sixth and seventh chapters, I present two experiments that aimed at assessing the status of memory control abilities in clinical populations typically characterized by impulsivity and poor cognitive control, compared to matched healthy control groups. In particular, the two chapters focused on patients suffering from substance-related and addictive disorders, in the sixth chapter, and anorexia and bulimia nervosa, in the seventh chapter.

Finally, in the last chapter, I present a general discussion of the main findings from the present work, their relevance to the study of memory control, and their implications for future research efforts.

1 RETRIEVAL-INDUCED FORGETTING (RIF)

Part of this chapter has been published in **Stramaccia, D. F.**, Braga, M., Fardo, F., Penolazzi, B., & Galfano, G. (2015). *Retrieval-induced forgetting:* gli effetti negativi della pratica sulla memoria episodica. *Giornale Italiano di Psicologia*, 195-217.

Over the course of our everyday lives, we accumulate memories that share similar features and common retrieval cues. Under some circumstances, this can quickly become a nuisance. For example, we could struggle to recall the PIN code associated to our new credit card, because the PIN code from the previous one intrudes while we are typing at the ATM machine, which could very well act as a retrieval cue for both. However, generally a few practice attempts on the new PIN are sufficient to override the competing old one. Everyday life is filled with similar instances of interfering information and unwanted memories, thereby suggesting that mechanisms deputed to overcome such interference would be highly adaptive.

Researchers of memory and learning have been struggling for long with the observation that retrieving information from episodic memory can have two effects. On the one hand, retrieved information may get strengthened so that future recall attempts will be easier. On the other hand, later recall attempts may also show poor recall of un-retrieved information associated to the retrieved information. This phenomenon has been termed Retrieval-Induced Forgetting (RIF) by Anderson, Björk and Björk (1994), and describes the detrimental effects of retrieval practice due to (at least partly) inhibitory mechanisms. Previously, the term “output interference” was mainly used to indicate such phenomenon. The new wording was meant to indicate that forgetting can occur at an intermediate retrieval stage (between initial encoding and subsequent memory testing), and to in introduce the concept on inhibition in the domain of forgetting, whereas output interference refers to a mere consequence of limitations in human memory. In fact, RIF was first investigate with the output interference paradigm (Roediger, 1973), where one would observe that memory for previously learned items declined with increasing serial position of the items at test.

In 1973, Roediger ascribed the negative effects of retrieval practice to output interference. In keeping with past work from Tulving and Arbuckle (1963), Roediger assumed that the very act of strengthening an item in episodic memory would have reduced accessibility of additional items, due to the strengthened item being given priority in the act of recall, compared to weaker items that would become temporarily inaccessible, as attempts to retrieve them would also result in additional reactivation of the strengthened ones (as if they were sampled with replacement).

However, in 1994, Anderson and Colleagues introduced the retrieval practice paradigm (RPP) as a new method to test the loss of information occurring due to repeated practice on related information, and proposed a role for inhibitory mechanisms in the act of forgetting. These inhibitory mechanisms would be recruited *unintentionally*, to serve the *intentional* purpose of efficient memory retrieval by facilitating the emission of task-relevant information in memory by weakening competing and irrelevant memory traces. In this theoretical framework, memory selection and inhibition should be considered as a special or a parallel case of action selection (e.g., Levy & Anderson, 2002) and subsequent inhibition, in a similar fashion to the typical Go/No-Go or Stop-Signal tasks commonly used to measure inhibitory efficiency in motor action.

In the following paragraphs, I first describe in detail the RPP and the typical findings associated with this experimental procedure, followed by a discussion of each of the main points around which the theoretical debate on RIF is articulated. Subsequently, I review the literature on the main applied venues for research on RIF, and I discuss the importance of RIF for efficient functioning of memory, within the context of a “positive forgetting” framework. A final section is dedicated to the contribution of studies that employed a broad range of neuroscientific methods to investigate RIF, along with the theoretical implications of their findings.

1.1 Retrieval practice paradigm (RPP): a method to study RIF

The typical RPP, devised by Anderson and colleagues (1994), is structured in three temporally distinct phases. Firstly, participants are shown categorized lists of word pairs, with each word pair (e.g., FRUIT-LEMON) composed of a semantic category (e.g., FRUIT) and an exemplar of that particular category (e.g., LEMON). The word pairs are presented once each for a few seconds, and the participants are instructed to memorize each exemplar in relationship with its category.

Secondly, immediately after the initial study phase, participants perform repeated retrieval practice on half the exemplars from half the semantic categories. Participants are shown retrieval cues that probe memory for a specific exemplar each (e.g., FRUIT-LE___), and they are asked to retrieve the exemplars seen in the previous phase (by saying them aloud or typing) that match the retrieval cue provided. According to the Authors’ theoretical stance, upon presentation of a retrieval cue, the target item in memory is activated, alongside a number of competitors, namely the other items that have been learned in the study phase and belong to the same semantic category as the target item. Because the activation of such competing items in memory could interfere with the retrieval process, inhibitory mechanisms would be recruited to overcome this interference, weakening the representational status of the competing items in memory in order to promote the emission of the correct response. Each retrieval cue is shown several times (usually three or four times), in order to provide more chances for the successful recruitment of the purported inhibitory mechanisms underlying RIF. The retrieval-practice phase gives rise to a subdivision of the experimental stimuli in RP+ items (practiced exemplars from practiced categories), RP- items (non-practiced exemplars from practiced categories), and NRP items (non-practiced exemplars from non-practiced categories).

Lastly, after a 5 to 20min break or unrelated filler task, a final test is administered where participants are asked to recall all the experimental stimuli that were presented in the initial study phase. Memory for the exemplars is typically assessed with a category-plus-stem cued recall test that is generally more difficult with respect to the testing modality employed in the previous phase (e.g., FRUIT-L___).

Figure 1.1 below provides a schematic representation of the RPP.

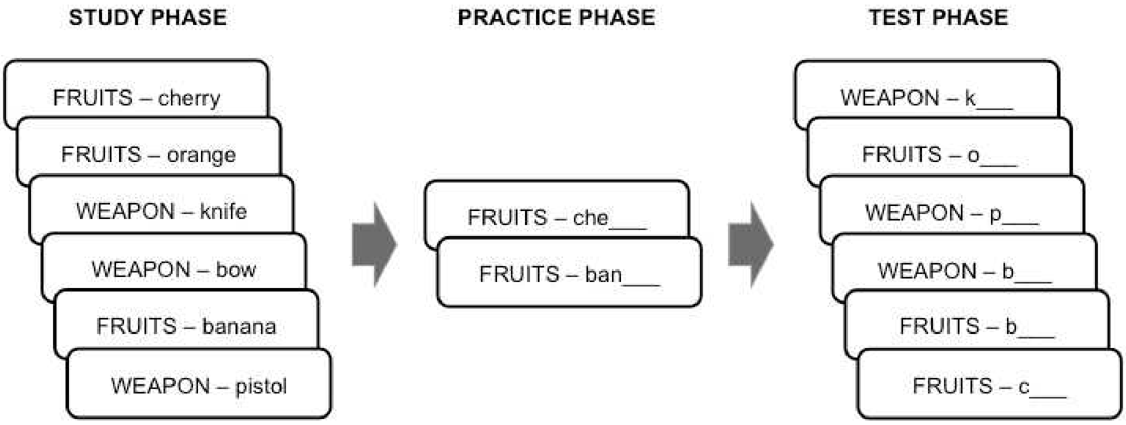

Figure 1.1 Schematic representation of the three phases of the RPP.

This procedure allows for measuring the two faces of selective memory retrieval. Typically, on the one hand, RP+ items are better recalled than RP- and NRP items, due to the well-known testing effect associated with retrieval practice (e.g., Chan, 2009), usually termed facilitation (FAC) in the RIF literature. More surprisingly, NRP items are also better recalled than RP-, even though none of them underwent retrieval-practice. Crucially, NRP items belong to categories that were not shown during retrieval practice. This apparently paradoxical finding constitutes the behavioural manifestation of RIF. Figure 1.2 shows the typical pattern of results observed with the RPP.

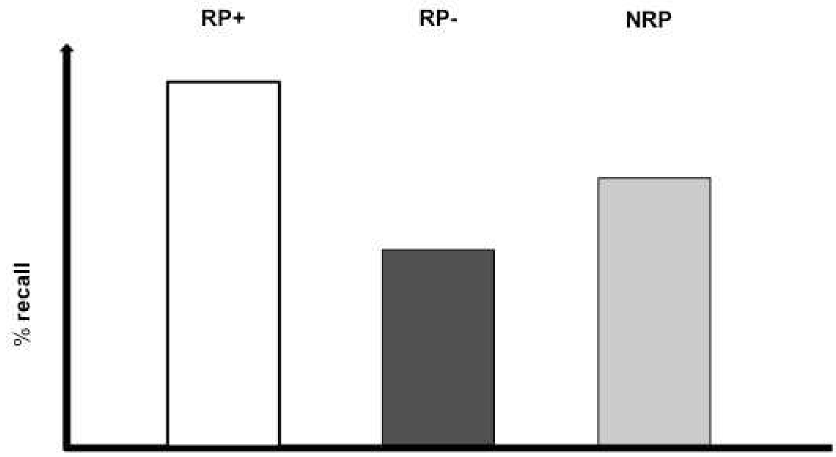

Figure 1.2 Typical results in a RPP paradigm. FAC = RP + vs NRP; RIF = NRP vs RP-.

1.2 Theoretical models of RIF

Even though various mechanisms have been put forth to explain RIF, it is possible to differentiate between two main families of theoretical accounts, based on either inhibition or competition. Anderson, who is the main developer of the RPP, is also the main proponent of inhibition as the principal mechanism underlying forgetting observed as a consequence of retrieval practice (e.g., Anderson et al., 1994). In his view, retrieving information from memory activates similar, competing information, which may interfere with the correct retrieval of the target information. In order to mitigate this interference, inhibitory mechanisms would be recruited to inhibit the mnestic representations of the competing information. This, in turn, may impair later attempts at recalling the previously interfering. According to other Authors, inhibition may instead act on the associative path between the specific cue used for retrieval and the target information (e.g., Storm & Levy, 2012). In any case, all proponents of inhibitory accounts of RIF agree on describing the phenomenon as the consequence of an adaptive process that promotes retrieval by reducing the accessibility of competing information.

Proponents of competition-based accounts of RIF, on the contrary, argue that the strengthening of information during retrieval practice blocks the accessibility of the non-strengthened associated information at test, when the shared retrieval cue is presented, thus ruling out inhibition as an explanatory mechanism of RIF (e.g., Perfect, Stark, Tree, Moulin, Ahmed, & Hutter, 2004; Raaijmakers & Jakab, 2013; Verde, 2012). It should be noted that these different views on RIF are not mutually exclusive (Anderson, 2003; Storm & Levy, 2012) and both mechanisms, i.e., inhibition and blocking, may contribute to different extent to RIF. There is, however, a strong debate about the need for inhibition at all in the production of RIF. In particular, as mentioned before, proponents of competition-based accounts often argue that inhibition does not play a role at all in RIF. This debate is centred on what Anderson (2003) described as the fundamental tenets of the inhibitory accounts of RIF: independence from output interference, cue independence, retrieval specificity, strength independence, and interference dependence. The inhibitory account of RIF is central to the present dissertation, and the experiments and related results presented here were carried out and interpreted within this particular explanatory framework of the phenomenon. Nonetheless, alternative explanations are always discussed and considered.

In the following sections, I will briefly review the current status of the evidence about each of these critical properties of RIF (for extensive reviews, see Anderson, 2003; Storm & Levy, 2012; Verde, 2012; Raaijmakers & Jakab, 2013; Murayama, Miyatsu, Buchli, & Storm, 2014). After that, I will provide a critical assessment of a recent, diverging theoretical stance of RIF, which assigns a key role to context as the main force behind this phenomenon. In the final section I will present and discuss the two-factor account of RIF, which could be better suited to explain the phenomenon compared to other account based on single mechanisms.

1.2.1 Output interference

Decades before the RPP was conceived, there was already awareness in the field of memory research about a “disparity between availability and accessibility” of information (Roediger, 1973), and that under some circumstances retrieving information from memory could impair later recall of similar information. Tulving and Arbuckle (1963) termed this phenomenon "output interference", i.e. the observation that recall performance decreases as the serial position of the to-be-remembered item increases. When the RPP was first proposed (Anderson et al., 1994), the Authors acknowledged that output interference may have very well played an essential role in the pattern of results, without the need to resort to inhibition as an additional explanatory mechanism. Specifically, because the first instance of RPP employed category labels alone (e.g., FRUIT) as retrieval cues at test, and because RP+ items would have been more accessible due to their strengthening during the retrieval practice phase, it could have been argued that participants confronted with category cues related to practiced categories would have systematically retrieved the RP+ items first, thus impairing recall of RP- items. Because of that, the Authors devised a strategy to control for output interference in subsequent iterations of the RPP, which consisted of presenting item-specific retrieval cues (e.g., FRUIT-L___) so that the output order could be controlled by systematically presenting RP- retrieval cues before RP+ retrieval cues. Numerous studies found reliable RIF with this strategy (e.g., Anderson et al., 1994; Anderson & McCulloch, 1999; Storm, Björk, & Björk, 2007, 2008), even with materials other than the standard category-exemplar word pairs (e.g. Anderson & Bell, 2001). It is worth mentioning that, in contrast with the above, Butler, Williams, Zacks, and Maki (2001) failed to observe RIF when output interference was controlled for with several types of item-specific retrieval cues, as opposed to when category cues were used instead. However, Goodmon and Anderson (2011) argued that uncontrolled semantic associations in the experimental material used by Butler and Colleagues (2001) might have shielded competitors from forgetting, due to semantic integration dynamics (Anderson & McCulloch, 1999). It is also important to note that controlling for output interference reduces the magnitude of RIF (e.g., Murayama et al., 2014), suggesting that both mechanisms (i.e., output interference and inhibition) may play a role in shaping the results.

1.2.2 Cue independence

According to the inhibitory account of RIF, the forgetting measured with performance at test phase originates during the retrieval practice phase, when interference arising from competing memories calls for inhibitory mechanisms that target them. More specifically, inhibition would take place at the representational level of the interfering memory, weakening its later accessibility irrespectively of the retrieval cue, and therefore retrieval route, that is used to probe such accessibility. On the contrary, the blocking account of RIF does not allow for cue independency, because blocking would occur by strengthening of the connection between the specific retrieval cue and the to-be-retrieved item in memory, but not of the item itself. A number of studies produced evidence in favour of the cue independency of RIF, even though a few ones failed to do so. Anderson and Spellman (1995) first manipulated the RPP by introducing a new, cue-independent test phase format, which they refer to as the "independent probe" test. In their study, participants engaged in a cross-category cuing variant of the RPP, where categories were characterized by semantic relationships that allowed inhibition to act on exemplars of non-practiced categories that were later used as recall cues at test. For example, participants may have studied LEMON and STRAWBERRY within the FRUIT category, and BANANA and CORN within the YELLOW category. Given that LEMON is also a member of the YELLOW category, and BANANA is also a member of the FRUIT category, performing retrieval-practice on FRUIT-STRAWBERRY should impair later recall of YELLOW-BANANA. YELLOW would also act as an extra-list cue, ensuring cue independence of RIF measured with this procedure. Anderson and Spellman (1995) were able to induce RIF with this RPP variant, although smaller in size in respect to the RIF effect observed with the typical RPP. An alternative independent probe method consists of assessing memory performance at test through extra-list retrieval cues, which were not shown during either the study or the retrieval practice phases of the RPP (e.g., SODA-___, in place of FRUIT-L___). Relevant to the inhibitory account, the magnitude of RIF appears to be similar between item-specific and non-specific cues when using cue independent designs, reflecting a reduced susceptibility of this procedure to blocking dynamics at test (Murayama et al., 2014). Regarding the smaller RIF effect generally observed with these designs, it could be argued that the RIF effect measured with more typical designs is determined by more than just inhibitory mechanisms, and that part of forgetting may take place at test (e.g., due to blocking dynamics), whereas cue independent designs are able to highlight the net contribution of inhibition to forgetting. An alternative or concurrent explanation concerns the possibility that inhibition during retrieval practice affects both the competing items' representational strength in memory and their association to the retrieval cue. Because the strength of such association is irrelevant in cue independent designs (unless the independent cues are largely semantically overlapping with the study cues), these designs may be able to detect only part of the inhibitory effects.

However, some Authors have argued against the cue independence of RIF (Jonker, Seli, & MacLeod, 2012; Perfect et al., 2004; Raaijmakers & Jakab, 2013). For example, covert cuing has been widely proposed as an alternative explanation to forgetting in cue independent designs. According to the covert cuing hypothesis, participants provided with independent cues (e.g., SODA-___ in place of FRUIT-L___) may be engaging in covert retrieval of the original category cue (i.e., FRUIT) to facilitate retrieval, thus jeopardizing cue independence (e.g., Camp, Pecher, & Schmidt, 2005, 2007). Ironically, the inhibitory account of RIF predicts that covert cuing should reduce or abolish RIF, because practiced items rather than to-be-suppressed items would benefit more from the availability of multiple cues (Anderson, 2003). Indeed, a recent study failed to show any RIF when participants were explicitly instructed to adopt a covert cuing strategy during the final, cue independent test phase Weller, Anderson, Gómez-Ariza, and Bajo (2013). This result could also suggest that the cause of smaller RIF in studies employing cue independent design is caused by covert cuing strategies spontaneously adopted by the participants. Finally, cue independence is also supported by studies that used implicit memory tests to probe recall in the final phase of the RPP, such as in the second experiment from Veling and van Knippenberg's study (2004, experiment 2), where the Authors observed RIF with a lexical decision task.

1.2.3 Retrieval specificity

A core assumption of the inhibitory account of RIF is that forgetting takes place during the retrieval practice phase, and only a competitive retrieval practice format, as opposed to simple additional study, should induce forgetting of non-practiced items, since they would not compete for retrieval if additional study was performed in place of retrieval practice. On the contrary, strength-based accounts of RIF predict blocking of non-practiced items due to competition that arises at the final test of the RPP. Therefore, non-competitive re-exposure to a subset of the study material should be sufficient to impair later recall of the non-practiced subset, as long as it is able to strengthen that subset of the material. Many studies addressed this fundamental tenet of the inhibitory account of RIF. Past work employed restudy or non-competitive retrieval practice format in place of the typical retrieval-practice phase. In the former case, participants were simply re-exposed to a subset of the study material (e.g., Ciranni & Shimamura, 1999). In the latter case, participants were asked to complete the category label, given the exemplar and a letter stem as a cue (e.g., FR___-LEMON; e.g., Anderson, Björk, & Björk, 2000a). None of these studies found RIF when non-competitive retrieval practice formats were used, in line with the inhibitory account of RIF.

However, some Authors (e.g., Raaijmakers and Jakab, 2013, Verde, 2012) recently argued that studies employing restudy or non-competitive retrieval practice formats may still be interpreted within the strength-based account of RIF, depending on the particular format implemented. In this view, it would not be surprising to fail at observing RIF in a plain restudy retrieval practice phase, because it may selectively strengthen the practiced items without affecting their association to the cue, which could in turn produce insufficient blocking at test. However, recent studies (Raaijmakers and Jakab, 2013, Verde, 2012) that challenged the retrieval specificity tenet employed non-competitive retrieval practice formats that were effective at strengthening the practiced item's association to the cue, and managed to induce RIF-like forgetting. In the former study (Ciranni & Shimamura, 1999), participants retrieved category labels upon presentation of associated exemplars (e.g., ___-LEMON), so that the retrieval practice phase was reasonably more difficult than in Anderson and Colleagues' study (2000a) discussed before. In the latter work instead (Anderson et al., 2000a), participants either judged the appropriateness of the category labels associated to the practiced items, or rated the pleasantness of the practiced items. In both cases, the category-exemplar word pairs were shown in full (e.g., FRUIT-LEMON), and both methods lead to RIF-like forgetting. Moreover, Saunders, Fernandes, and Kosnes (2009) used a mental imagery task in place of the typical retrieval practice phase, where participants were asked to mentally visualize physical features of the practiced category-exemplar word pairs (shown in full, e.g., FRUIT-LEMON), such as the shape, size, or colour. This manipulation was effective at inducing RIF-like forgetting. Moreover, in their recent meta-analysis of RIF, Murayama and colleagues (2014) found that even the category retrieval practice format (e.g., FR___-LEMON) used in Anderson and Colleagues' study (2000a) was found to elicit reliable RIF-like forgetting across a number of studies, in contrast with the retrieval specificity tenet of the inhibitory account of RIF. One potential explanation in line with the inhibitory account is that the category cued retrieval practice might elicit competition, especially when more demanding retrieval-practice formats are used (e.g., ___-LEMON), and therefore it might require inhibition similarly to what happens when typical category-plus-stem retrieval cues are employed. However, it is not clear why retrieving category labels from memory would elicit competition from exemplars belonging to the target categories but not used as cues. Additionally, it is possible that strengthening the category-exemplar association elicits interference independently of whether the category or the exemplar is retrieved during the retrieval practice phase, causing blocking at the time of test. However, as discussed in the next paragraph, this strengthening should also positively correlate with the amount of RIF, which however is not the case in studies controlling for output interference at test.

Nevertheless, this body of research is not sufficient to fully challenge the retrieval specificity tenet of RIF, and the inhibitory account of the phenomenon as well. In fact, studies employing a typical competitive retrieval practice format have found RIF with recognition tests (e.g., Hicks & Starns, 2004), whereas studies that used a non-competitive retrieval practice format and probed recognition at test failed to show RIF (Grundgeiger, 2014; Rupprecht & Baüml, 2016). Importantly, these studies employed non-competitive retrieval practice formats that were able to induce RIF in cued recall tests, thus suggesting that recognition tests may be the optimal test format to capture the pure effect of inhibition over competing memories. At the same time, cued recall test may be partly influenced by blocking dynamics, suggesting that a two-factor account of RIF, where both blocking and inhibition contribute to forgetting, might be better-suited to explain the wealth of results obtained so far with the typical RPP. Consequently, RPPs employing recognition tests may constitute a more reliable benchmark for the ability to inhibit competing memories.

1.2.4 Strength independence

Competition-based accounts of RIF explain this phenomenon on the basis of strength-based associative interference (e.g., McGeoch, 1942; Mensink & Raaijmakers, 1988). According to this theoretical stance, retrieval practice would strengthen retrieved information, while at the same time blocking subsequent retrieval of related information, even when the test format is controlled for output interference (see section 1.2.1). One problem with this account is the fact that RIF and FAC are usually found to be uncorrelated (e.g., Hulbert, Shivde, & Anderson, 2012), even though it would be logical to predict otherwise, if the magnitude of RIF is assumed to reflect the amount of strengthening of practiced material. The lack of association between the degree of strengthening of RP+ items and the degree of forgetting of RP- items is referred to as strength independence. Strength independence is also closely tied to retrieval specificity (see section 1.2.3), because the absence of RIF with RPPs employing additional study instead of retrieval practice further supports the notion that strengthening of RP+ items does not necessarily lead to forgetting of RP- items. Indeed, other studies suggested that strengthening of RP+ might not be necessary at all to observe RIF. For example, RIF has been observed in a RPP employing an "impossible" retrieval practice phase, where non-existing exemplars (e.g., FRUIT-WO___) were cued instead of study material (Storm, Björk, Björk, & Nestojko, 2006; Storm & Nestojko, 2010). In this condition, only inhibitory accounts of RIF would predict forgetting of RP- items, as competition would arise regardless of successful strengthening of RP+ items. Similarly, receiving feedback during retrieval practice benefits RP+ items without positively affecting RIF (Erdman & Chan, 2013), a finding which is also more easily reconciled with inhibitory accounts of RIF. In addition to that, when participants perform retrieval practice on items characterized by low-taxonomic strength (e.g., Anderson et al., 1994), and output interference is controlled for, RIF is not observed, thus suggesting that strengthening of RP+ items is not sufficient to induce forgetting. Therefore, the current status of the literature speaks in favor of the tenet of strength independence.

1.2.5 Interference dependence

As mentioned earlier, the inhibitory account of RIF predicts that, without competition, there would be no need for inhibitory mechanisms to facilitate retrieval, and forgetting of RP- items should not be observed in the test phase of the RPP. Therefore, it follows that non-practiced exemplars of practiced categories have to exert a sufficient amount of interference during the retrieval practice phase, by competing for recall upon presentation of the relevant category cues. Indeed, when competition within the retrieval practice phase of the RPP is manipulated (i.e., by manipulation of the taxonomic strength of the RP+ and RP-), it is often observed that exemplars with high taxonomic strength (i.e., e.g., LEMON for the FRUIT category), which are thought to exert more competition, are also forgotten the most. Because these exemplars are strongly associated to the corresponding category cue, and thus likely to be reactivated upon its presentation, performing retrieval practice on weakly associated exemplars of the same category may incidentally activate the former as well, which however are irrelevant to the task at hand (being RP- items). This, in turn, would trigger inhibitory mechanisms, aimed at reducing interference from the RP- items. On the opposite, exemplars with low taxonomic strength (e.g., NECTARINE for the FRUIT category), which are unlikely to become activated upon presentation of their corresponding category cue, do not suffer from forgetting (e.g., Anderson et al., 1994, 2000a). This evidence not only corroborates the notion that RIF depends on mechanisms that overcome interference, but is also at odds with non-inhibitory accounts of RIF, where forgetting should be observed regardless of the amount of competition during the retrieval practice phase (but see Jakab & Raaijmakers, 2009).

Interference dependence has also been tested with other approaches. For example, Storm et al., (2007) found that the instruction to remember a set of items (later used as RP- items in a RPP) makes that set more susceptible to RIF, compared to the instruction to forget it. Interpreting this result within a theoretical framework of RIF based on inhibition, the Authors argued that the former instruction made the items more likely to interfere during the retrieval practice phase. In another study, Shivde and Anderson (2001) had participants perform retrieval practice on either the dominant or the subordinate meaning of a homograph. Retrieval practice on the dominant meaning did not lead to forgetting of the subordinate meaning, whereas retrieval practice on the subordinate meaning was able to induce RIF for the dominant meaning, which was assumed to be more likely to interfere, and therefore to trigger inhibition. However, not all studies found evidence consistent with an inhibitory account of RIF. For example, Jakab and Raaijmakers (2009) manipulated study position of RP- items in order to probe the effect of primacy on RIF. In keeping with inhibitory theories of RIF, forgetting should have been stronger for items studied earlier on the list, due to primacy making the items more likely to interfere during retrieval practice. Instead, they found that study position did not affect RIF. Similarly, increasing the amount of study time in the initial study phase of the RPP does not generally enhance RIF, even though it could promote interference by making RP- items more accessible on later stages. However, study time is also thought to promote integration of studied material in a coherent framework (see 1.3.2), which is detrimental to RIF (e.g., Anderson, Green, & McCulloch, 2000b; Goodmon & Anderson, 2011). Inconsistent findings in studies of interference dependence of RIF have been at least partially addressed by Anderson and Levy (2010). The Authors argued that, while on the one hand demand for inhibition increases as a function of interference, on the other hand inhibitory effectiveness decreases as a function of interference. Indeed, a recent study found suggested that an inverted U-shaped function, rather than a purely monotonic one, might describe more adequately the relationship between RIF and interference (Keresztes & Racsmány, 2013), although this pattern was only supported by a statistical tendency.

Given its importance for theoretical models of RIF, the interference dependence assumption warrants further investigation and invites the development of experimental manipulations capable of providing a more accurate description of the relationship between RIF and interference. For example, to address the need for stronger evidence regarding the interference dependence tenet, a recent study by Chan, Erdman, and Davis (2015), manipulated the amount of competition exerted by RP- exemplars during the retrieval practice phase of a modified RPP, and found that only retrieval practice under high competition induced RIF in category-plus-stem cued recall. The Authors subsequently replicated this result with a RPP where a recognition test was used to probe memory in the final phase. However, employing a category-cued final test (thus contaminated by output interference) lead to RIF under both high- and low-competition at retrieval practice. Importantly, competition across these experiments was varied only by manipulating the input order of the study items, thereby ruling out a series of possible methodological objections arising from experimental manipulations of the retrieval practice format (as in previous studies that manipulated competition), of the associative strength of the experimental material, and of the taxonomic strength of practiced/non-practiced material. Therefore, results from Chan and colleagues (2015) are highly consistent with the interference dependence tenet of the inhibitory account of RIF.

1.2.6 A context-exclusive account of RIF: Summary of recent evidence

Recently, an alternative account of RIF has been proposed that relates to effects of encoding and retrieving information within a specific context on subsequent retrieval in a similar context. Past research highlighted the influence of context on memory performance, exploring a broad range of physical (e.g., time, location, presentation modality), internal (e.g., mood, altered states), and task-related (e.g., varying format and features) contexts manipulations. For example, Godden and Baddeley (1975) found that recall performance was maximized when encoding and test context matched (manipulated by the means of different locations), as opposed to a change of context. Based, on this body of literature, Jonker and Colleagues (2012) proposed a context-dependent account of RIF, which attempts to rule out both inhibitory and blocking mechanisms. This alternative account of RIF is also based on the observation that the transition from passive learning tasks (akin to the study phase in the RPP) to more active memory tasks (such as retrieval practice) can induce an internal change in context that affects performance (e.g., Sahakyan & Hendricks, 2012). The two main assumptions of the context account are that RIF is observed only when a context shift takes place between the study phase and the retrieval practice phase of the RPP, and that the context surrounding the final test phase has to be more similar to that of the retrieval practice phase, more than that of the study phase. According to Jonker and Colleagues (2012), upon presentation of a category during the test phase od the RPP, participants may search for the appropriate answer within the more recent context where that particular category was last presented. Because practiced categories (contributing to RP+ and RP- items) were encountered in both the study phase and the retrieval practice phase of the RPP, while non-practice categories (contributing to NRP items) where only processed in the study phase, during the test phase participants may end up searching for RP- items in the retrieval practice phase context. This, in turn, would make RP- items less accessible than NRP items, because the former were not encountered at all within the retrieval practice phase context, thus leading to a form of “RIF-like” forgetting (the definition “RIF-like” is used to highlight the fact that forgetting of RP- items would depend on presentation of RP categories, rather than retrieval of the RP+ items, and that retrieval-practice is merely one method to induce a context shift). Therefore, the reinstatement of the retrieval practice context for the practice categories, along with the reinstatement of the study context for the non-practice categories, are both critical for observing RIF according to the context account. Importantly, neither inhibition nor blocking would be playing any role at all in shaping the results.

In a series of experiments, Jonker and Colleagues (2012) provided evidence in support of their context-account of RIF. In one experiment, the Authors succeeded in inducing RIF-like forgetting with a RPP that employed a restudy format at retrieval practice (whereas past work generally failed at this, e.g., Anderson et al., 2000a), which is at odds with both the retrieval specificity (see 1.2.3) and the interference dependence (see section 1.2.5) tenets of the inhibitory accounts of RIF. To do so, they implemented a context shift-inducing task between the initial study phase and the restudy, since in their view the normal transition between the two phases is not sufficient to induce a context change, which would also explain the lack of RIF in past work employing restudy in place of the typical retrieval practice phase. In a subsequent experiment, Jonker and Colleagues (2012) abolished RIF by strongly reinstating the study phase context prior to the test phase, and therefore argued that due to this manipulation participants were now able to search for the appropriate context at test, thus circumventing the context shift that would otherwise lead to forgetting of NRP items. Moreover, in another experiment that employed a typical RPP, Jonker and Colleagues (2012) manipulated the context where participants would search for when presented with retrieval cues at test. To this end, during the study phase, they associated all exemplars within a category to a specific context, induced by the concurrent presentation of a video segment, and subsequently paired the practiced items with a new context (a different video segment). During the test phase, participants where shown either the original study phase video, or the one saw during the practice phase. Critically, the Authors observed RIF only in the latter condition. Therefore, proponents of the context account of RIF argue that forgetting at test depends exclusively on the context shift induced by the structure of the RPP, and thus it does not predict the retrieval specificity property of RIF, because the effect would only depend on the inappropriate context search that takes place during the test phase. Moreover, the context account is at odds with the cue independence tenet of RIF, because presentation of the original category cues at test is necessary to reinstate the retrieval practice context for the practiced categories.

Past work seems to be at odds with the predictions of the context account of RIF. For instance, RIF can be reduced or eliminated by manipulations that reliably induced stress or negative mood in healthy participants prior to the retrieval practice phase of the RPP (e.g., Bäuml & Kuhbandner, 2007; Koessler, Engler, Riether, & Kissler, 2009), even though these manipulations might have reasonably led to critical changes in context. Moreover, presenting an instruction to forget between the study and the retrieval practice phases of the RPP, which should be an effective method to induce an internal context shift (Sahakyan & Kelley, 2002), was in fact detrimental to RIF, as predicted by the inhibitory account of RIF, according to which the instruction to forget would reduce the amount of associative interference exerted by RP- items, as opposed to the instruction to remember (Storm et al., 2007). In addition to that, Román, Soriano, Gómez-Ariza, and Bajo (2009) have shown that RIF is abolished when the retrieval practice phase of the RPP is performed under divided attention, which does not fit well with the context account of RIF since the context shift from study to retrieval practice would be enhanced by such manipulation, but is instead more compatible with the inhibitory account of RIF, which predicts that under divided attention executive resources would be less available to suppress interfering items under. Importantly, even though this alternative account of RIF is a relatively recent proposal and needs further validation, a few studies already challenged its specific predictions. For example, Miguez, Mash, Polack, and Miller (2014) failed to observe a decreased RIF as a result of a context shift between retrieval practice and test, with the context at test matching the study context, whereas the context account would have predicted no RIF in the same circumstances, because RP categories were not selectively reinstated. However, the internal context related to retrieval practice (e.g., presentation style, task features) might have been still active, and the effectiveness of the context shift induced by the Authors was not assessed independently. Therefore, it could be argued that selective reinstatement of RP categories was not entirely prevented in this study design.

More recently Buchli, Storm, and Björk (2016) and Soares, Polack, and Miller (2016) failed to replicate Jonker and Colleagues' work (2012). Buchli and colleagues (2016) carried out a series of experiments with the intent to both replicate and extend their findings, by testing the prediction that stronger context shifts between the study and retrieval practice phases should increase forgetting. However, none of their three experiments provided evidence supporting the context account of RIF. Instead, the results of this study are in line with the retrieval specificity and the strength independence tenets of the inhibitory account of RIF. Indeed, RIF was found only when a typical, competitive retrieval practice phase was employed, as opposed to additional study, regardless of the magnitude of the context shift. The Authors suggested that the dissimilarity with the results of Jonker and Colleagues (2012) might reflect either a false positive in the original finding, or subtle discrepancies in the study design (e.g., study time allotted for each category-exemplar word pair, different filler task between retrieval practice and test phases) or major ones (e.g., different final test phase formats) that could have impacted on the results unpredictably. Related to this point, Jonker and Colleagues (2012) employed a test format that was blocked by category, with RP- items probed before RP+ items for each category, which could have interacted with the probability of reinstating the study context. Soares and Colleagues (2016) instead performed a series of ad-hoc experiments to demonstrate that context shifts alone are not sufficient to provide an "inhibition-free" explanation of RIF. To do so, the Authors manipulated the contextual features typically embedded in the RPP, such as demands and presentation format within each phase, as opposed to the manipulations employed by Jonker and Colleagues (2012), which resulted in fairly atypical RPP formats. It is worth noting that proponents of the context account argue that RIF in the standard RPP results from context shift caused by the constituting features of the paradigm. Indeed, none of the manipulations employed in the study impacted on the magnitude of RIF.

Moreover, in the study carried out by Rupprecht and Bäuml (2016), which was designed to investigate the effects of competitive and non-competitive retrieval practice on RIF, as measured by either cued-recall or item recognition in the final test phase, the Authors found that only non-competitive retrieval practice induced RIF when an item recognition test was used. This finding cannot be accounted for by the context account of RIF, which predicts that context effects should be observed in RPP employing item recognition regardless of competition during the retrieval practice phase (Jonker et al., 2012). Taken together, the results from Buchli and Colleagues (2016), Soares and Colleagues (2016), and Rupprecht and Baüml (2016), suggest that while context may play a role in shaping RIF, it cannot provide a general explanation of the phenomenon that fits with the entirety of the literature. Therefore, additional studies are needed to shed light on the exact influence of context on RIF.

1.2.7 A two factor account of RIF: Where inhibition and blocking meet

So far, the majority of studies addressing the theoretical debate on RIF have focused on either inhibition or blocking as exclusive general mechanisms underlying the phenomenon. However, some Authors suggested that both inhibition and blocking might contribute to the typical findings on RIF (e.g., Aslan & Baüml, 2010; Grundgeiger, 2014; Rupprecht & Bäuml, 2016; Storm & Levy, 2012). According to this view, competition during the retrieval practice phase would mobilize inhibition of the representations of RP- items in memory, while concurrently the strengthening of the cue-target associations within the RP+ items would lead to blocking of RP- items in the subsequent test phase. Importantly, a higher specificity of the retrieval cues would correspond to a lower involvement of blocking in the observed RIF. Therefore, the relative contribution of inhibition and blocking would primarily depend on the format of the retrieval cues employed.

Numerous findings in the literature of RIF are consistent with a two-factor account of RIF. For example, Murayama and colleagues (2014) showed that RIF and FAC are correlated only when category cues are employed in the test phase. Moreover, Schilling, Storm, and Anderson (2014) found a positive relationship between control over interfering memories, as measured with RIF, and motor stopping, as measured with the stop-signal task (SST; Logan &

Cowan, 1984), when item-specific recall cues were used at test, whereas a relationship in the opposite direction was observed when category cues were used instead. In addition to that, other studies addressing RIF in clinical populations (e.g., Soriano, Jiménez, Román, & Bajo, 2009; Storm & White, 2010) and young children (Aslan & Bäuml, 2010) observed RIF in these classes of participants only with category cues at test, whereas the same participants displayed no RIF with item-specific recall cues, thus suggesting that the latter type of test format is more adequate to capture individual differences in memory control.

Recently, Rupprecht and Bäuml (2016) investigated the possibility of a two-factor account of RIF in a series of experiments. Their main finding was that RIF was observed in both recall and recognition when a competitive retrieval practice was employed, whereas re-exposure induced RIF only when recall was tested, as opposed to recognition (see also Grundgeiger, 2014), thus demonstrating retrieval specificity for this particular test format. The Authors argued that blocking cannot cause RIF on its own, and inhibition is a necessary mechanism underlying RIF, at least (but not limited to) when recognition tests are used, which rules out the contribution of strength-based blocking dynamics on the effect. In this regard, it is also worth noting that the net contribution of inhibition to RIF could also be isolated by the means of independent-probe testing (e.g., Anderson, 2003; see 1.2.2), which consists of employing retrieval cues at test that were not shown before in the earlier phases of the RPP (e.g., SODA-L____ to probe LEMON, previously associated with FRUIT) and should be immune to strength-based interference at test, similarly to item recognition test formats.

1.3 Relevance of RIF

The pattern of results presented above has been directly and conceptually replicated with a broad range of variations and manipulations related to the different phases of the procedure and to the experimental material used. Importantly, several lines of research on RIF are characterized by a strong applied potential. In particular, a wealth of studies has been dedicated to the occurrence of RIF in relationship to individual differences, in eyewitness testimony, in educational settings, in social scenarios, and in relationship with reasoning and creative problem solving. In this section, I dedicate a paragraph to each of these different lines of research. Because the abundance and variety of the literature on RIF strongly suggests that its underlying mechanisms may be ubiquitous across all memory systems, two concluding paragraphs are dedicated to the pervasiveness of RIF in memory, and to the importance of efficient memory control mechanisms for well being, respectively. For a more extensive review on the subject of the various applied venues pertaining research on RIF, the reader may refer to Storm, Angello, Buchli, Koppel, Little, and Nestojko (2015).

1.3.1 RIF in the study of individual characteristics

A great deal of research has been devoted into characterizing which individual differences correlate with or predict the efficiency of the ability to overcome interference in memory. In particular, since the inhibitory account of RIF claims that optimal control over interfering memories depends on efficient executive systems (e.g., Anderson, 2003; Levy & Anderson, 2002), it has been hypothesized that indexes of executive control such as working memory capacity (e.g., Kane & Engle, 2002) should be correlated with the former ability, and that specific populations known to exhibit executive deficits (patients suffering from psychiatric disorders characterized by impulsivity) may also exhibit memory control impairments.

With respect to the association between the ability to suppress competing memories and working memory (WM), Aslan and Bäum (2011) found a positive correlation between RIF and performance at the *Operation Span* (Turner & Engle, 1989), a common measure of WM. Importantly, the correlation was specific for RIF, whereas no relationship was found with FAC. In their study, participants with higher WM capacity exhibited the least amount of RIF. A more recent study by Storm and Bui (2016) provided additional evidence in favour of a positive correlation between RIF and WM across three experiments, and further clarified some of the boundary conditions of this association (but see

Mall & Morey, 2013). Related to this point, Román and Colleagues (2009), provided converging evidence in favour of a relationship between RIF and executive control, by showing that RIF was impaired when participants performed the retrieval practice phase (where inhibition is supposed to come into play) under a dual task manipulation. These results are difficult to reconcile with a purely interference-based theoretical of RIF, as it would not be clear why individuals with higher executive abilities would also suffer more from interfering memories, compared with individuals equipped with fewer executive resources.

Concerning RIF in populations that may suffer from reduced executive control, as well as prefrontal lobe damage (which may affect RIF; see 1.4.4), the first studies addressing this line of research found evidence that does not speak in favor of a relationship between RIF and executive functioning, and thereby are also at odds with the inhibitory theory of RIF. For example, several studies found typical levels of RIF in young children (Ford, Keating, & Patel, 2004; Zellner & Bäuml, 2005), older adults (Aslan, Bäuml, & Pastötter, 2007), patients with Alzheimer’s disease (Moulin, Perfect, Conway, North, Jones, & James, 2002), and patients with schizophrenia (Nestor, Piech, Allen, Niznikiewicz, Shenton, & McCarley, 2005). However, Aslan e Bäuml (2012) highlighted the fact that the normal RIF observed in the experimental groups investigated by these studies failed may have been determined by the test phase formats employed in the RPP, which did not allow to rule out common confounds like output interference or associative blocking. Importantly, populations suffering from executive control deficits would probably be even more susceptible to these forms of interference, compared to healthy adults. Therefore, interference could have very well masked memory control impairments in these populations. As a matter of fact, later studies employing RPP variants that controlled for these sources of interference found abolished RIF in patients suffering from ADHD (Storm & White, 2010), clinical depression (Groome & Sterkaj, 2010), obsessive-compulsive disorder (Demeter, Keresztes, Harsányi, Csigó, & Racsmány, 2014), schizophrenia (Soriano et al., 2009), as well as in young children (Aslan & Bäuml, 2010), therefore providing general support for the inhibitory account of RIF (but see Murayama et al., 2014, for a more nuanced discussion on the issue).

1.3.2 RIF in education and testing

Another important applied venue for RIF is the investigation of optimal study, practice, and test formats in educational psychology. In particular, many studies have shown that forgetting of information due to retrieval practice can be modulated by the degree of integration of information occurring at the encoding stage. Therefore, in the experimental context of the RPP, higher integration corresponds to lower RIF (e.g., Anderson & McCulloch, 1999). To identify situations when retrieval may induce forgetting of studied material, instead or along with facilitation of a different subset of the same material (e.g., Chan, McDermott, & Roediger, 2006; Chan, 2009), has the potential to improve best practices in educational psychology and beyond.

In the first study that directly tested a relationship between integration and RIF, Anderson and McCulloch (1999) found that instructing participants to integrate information (i.e., by searching for common/grouping features between the different exemplars of the experimental categories) could reduce RIF. In a subsequent study (Anderson & Bell, 2001) where explicit instructions regarding integration were not provided, participants that later declared to have adopted integration strategies also showed a reduced RIF effect. Other studies employing ecological material more akin to real-life testing situations. For instance, Carroll, Campbell-Ratcliffe, Murnane, and Perfect (2007), asked both a group of novice students and a group of senior students to study two clinical cases from a psychopathology textbook. After that, all the students performed retrieval practice on a subset of the details of one clinical case only, by answering questions related to those specific details, similarly to the practice that often precedes an exam. In the final test phase, the students were asked questions about all the details of both clinical cases. Results showed that novice students exhibited RIF for non-practiced details of the practiced clinical case, whereas senior students did not show RIF. According to the Authors, senior students would have been more effective at integrating the studied material into a pre-existing knowledge schema, thus reducing competition during retrieval practice, which in turn abolished forgetting for non-practiced material. This result strongly suggests that the strategies employed during study and the level of pre-existing expertise on a given type of material/topic may affect memory performance on subsequent tests by reducing the amount of forgetting for non-practiced material.

Taken together, the evidence discussed so far suggest that, within an educational contexts involving competing information (e.g., leaning about the classification of minerals, learning about the mountains and rivers of a certain country; see Little, Storm, & Björk, 2011, and Little, Björk, Björk, & Angello, 2012, for experiments involving similar realistic material) specific attention is warranted toward the format and timing of the study, practice, and test stages of the educational process, in order to avoid excessive interference that could hinder optimal performance.

1.3.3 RIF in legal practice

Beginning with the study by Shaw, Björk, and Handal (1995), RIF entered the court of law as a phenomenon of interest in the context of eyewitness memory. The study moved from the hypothesis that important information acquired by witnesses to a crime scene could be hampered by repeated retrieval of associated information pertaining the very same crime scene, due to repeated questioning of the witness, similarly to what had been shown by Anderson and Colleagues (1994) with simple word pairs on year earlier. In this study, participants first examined a slide show depicting a domestic environment, and characterized by the presence of a series of similar items of two different kinds (i.e., sweatshirts and schoolbooks). Subsequently, participants answered a series of interrogation-style written questions pertaining half the items of either category (e.g., four schoolbooks). Afterwards, participants were tested on all the items presented in the slide show. Shaw and Colleagues (1995) found that this form of incomplete questioning between initial study and final test, mimicking the retrieval practice phase of the RPP, was able to elicit RIF. Importantly, RIF was absent in a second group of participant that did not receive the written interrogation. Therefore, it appears that repeated questioning is able to induce both enhancement of repeated material and forgetting of related unrepeated material, thus manipulating the witness' memory even in the absence of misleading information or ill intentions on behalf of the interrogators.

More recently, García-Bajos, Migueles, and Anderson (2009) demonstrated a similar effect with complex and naturalistic experimental material. In their study, participants were shown a video of a bank robbery where prototypical events that would take place within that context (e.g., bank robbers threatening people at gunpoint) were intertwined with less typical actions (e.g., a robber pointing his gun at a security guard's neck), in order to address the role of typicality in memory performance for this kind of material. Only the latter kind of actions was subject to RIF, whereas high-typicality actions were not affected by forgetting. These results were interpreted in line with the notion that high-typicality material is more easily integrated in pre-existing schemas, which in turn shield the material from the inhibitory mechanisms that lead to RIF (Anderson and McCulloch, 1999; see 1.3.2 above). Because atypical details of witnessed events are often of critical importance for testimony, this line of research provides important information on the reliability (and the fallibility) of eyewitness performance, as well as indications to guide interrogation format in order to prevent loss of essential information.

Another fundamental aspect of RIF that may impact its relevance for eyewitness testimony (as well as educational psychology, see 1.3.2 above) concerns how long lasting the memory impairment may be. Indeed, eyewitnesses may be called into testimony even months later they experienced the event to be recounted in court. If RIF were just a relatively short-lived phenomenon, there would be no relevant implications in an actual testimony. The durability of RIF has been subject to many studies, which produced mixed results that nonetheless suggest a durability exceeding the 24 hours, especially when experimental material other than text is used (see Murayama et al., 2014). More specifically, studies that specifically addressed the duration of RIF in eyewitness-memory paradigms found forgetting up to one week after retrieval practice (García-Bajos et al., 2009), but not two weeks later (Odinot, Wolters, &

Lavender, 2009). However these studies may have been unable to elicit a RIF effect comparable to the real life scenarios they refer to, because eyewitnesses often endure repeated interrogation over several weeks or months, which could produce additional strengthening of practiced memories of the event under scrutiny, at an increasingly greater expense for non-practiced elements of the event. Further research with eyewitness-memory paradigms is warranted to clarify whether this is the case.

1.3.4 RIF in the study of social phenomena

Sharing experiences with other conspecifics is the primary driving force behind both the creation and the transformation of individual and collective memories, and constitutes a fundamental aspect of human societies. An important aspect of this process is how and why some memories are kept, while others are forgotten. Studies on RIF have contributed to this point, highlighting that the very act of sharing some experiences can induce forgetting for other related, but untold, experiences. Importantly, this particular instance of RIF seems to affect both the experiences' narrator and the listener. Cuc, Koppel, and Hirst (2007) first showed the possibility of inducing this peculiar "socially shared RIF" in a group of participants that directly performed only the study and test phase of a RPP, but just assisted and listened to other participants engaging in the retrieval practice phase. Moreover, the Authors found RIF in the listening participants only when they were instructed to monitor the accuracy of the narrator's recall, compared to a different experimental condition when they were instructed to monitor the narrator's fluency instead. This finding has later been replicated with various types of realistic material and contexts (e.g., autobiographical memories, Coman, Manier, & Hirst, 2009; group-membership status, Coman, Stone Castano, & Hirst, 2014; propagation through a social network, Coman & Hirst, 2012; medical information, Coman & Berry, 2015). For example, Coman and colleagues (2009) were able to produce a similar socially shared RIF for autobiographical memories in relationship to the 09/11/2001 terroristic attacks at the World Trade Center, U.S.A. In the study, the Authors replaced the typical retrieval practice phase with either individually tailored structured interviews or free conversation, which both induced RIF in a later recognition test phase, thereby showing that conversations can modify later memory performance for both narrators and listeners, even when the information being shared does not exactly matches the individual experiences (i.e., in the free conversation condition). Interestingly, in a subsequent study, Barber and Mather (2012) found a significant socially shared RIF in their participants only when the speakers were of the same sex of the listeners.

1.3.5 RIF in the study of creative thinking

A recent line of research has established a relationship between the ability to overcome interference in memory and the ability to generate novel ideas. Many of these studies have employed the *Remote Associate Test* (RAT; Mednick, 1962) to investigate such relationship. Participants performing the RAT are asked to generate a word that is semantically associated to three other words that act as cues (e.g., “falling”, “actor”, and “dust”, with “star” being the correct answer). Importantly, in the RAT, the stronger associations for each cue are often unrelated to the other cues, which in turn may induce participants to fixate on the semantic associations pertaining only to a single cue, thereby hampering the production of the correct answer. Therefore, performance at the RAT is assumed to reflect the individual ability to overcome such cognitive fixation and engage in creative thinking.

Storm and Angello (2010) measured the correlation between the individual amount of RIF and performance at the RAT, moving from the hypothesis that inhibitory mechanisms would be essential to overcome fixation, by weakening the task-irrelevant contents of cognitive fixation. Prior to the RAT, the Authors also exposed the participants to distracting associations (i.e., with strong relevance to only one of the available cues) before they confronted the actual RAT problems, thereby manipulating the amount of cognitive fixation experienced by the participants. In fact, the Authors found that the individual amount of RIF was inversely related to the detrimental effects of fixation at the RAT, as the inhibitory account of RIF would predict. The Authors argued that inhibitory mechanisms might contribute to overcoming cognitive fixation, but only when the benefits of such inhibition would surpass the risk of weakening a possible correct answer along with the inappropriate ones (see also Storm & Koppel, 2012). In a following study, Koppel and Storm (2014) further demonstrated that providing participants with an incubation period (i.e., a break between solving attempts) modulated the correlation between RIF and RAT, in a way that suggests that their need for inhibition was reduced by incubation.

Other measures of creativity that have been related to suppression of interference in memory stem from the Alternative Uses Task (AUT; Guilford, 1957). The AUT measures creative and divergent thinking by probing the participants' ability to think about as many possible uses of an object as possible, which are then rated based on the basis of their number (i.e., fluency) or distinctiveness (i.e., originality). It is assumed that good performance in the AUT reflects the individual ability to overcome creative fixation due to their previously established knowledge of the most common uses of each object. In keeping with this line of reasoning, a study. Storm and Patel (2014) combined the logic of the RPP with the AUT to investigate an instance of RIF that they refer to as "thinking induced forgetting". In their study, participants first studied several uses for common objects, in order to increase competition in the subsequent phase, where they had to generate new uses for a subset of the studied objects. In a final cued-recall test phase, the participants were tested for their memory of the studies uses. As hypothesized by the Authors, memory performance was worse for the studied uses that were related to the subset of the objects that participants had to generate new uses for in the AUT (which was basically used in place of the retrieval practice phase). Moreover, the amount of "thinking induced forgetting" was correlated with the individual creative performance at the AUT. In a following study employing a similar approach, Ditta and Storm (2016) demonstrated that even participants' own generated ideas (i.e., objects uses generated by each participant before the AUT) were susceptible to "thinking induced forgetting".

It should be noted that inhibition is not necessarily beneficial to performance in creativity tasks. For example, it could be argued that creative thinking may sometimes require access to mental contents that previously underwent the action of inhibitory control. Related to this point, in a recent study, Gómez-Ariza, del Prete, Prieto del Val., Valle, Bajo, and Fernandez (*in press*), found that words supposed to be suppressed during a retrieval practice phase of the RPP (i.e., the RP- items) were in fact less likely to be generated as solutions in the RAT, relative to baseline words (i.e., the NRP- items).

1.3.6 The ubiquity of RIF in memory

In the previous paragraphs, I have tried to summarize the findings from a large body of literature that investigated a range of important out-of-lab contexts were our knowledge of RIF may prove valuable for appropriate and effective decisions (e.g., education, legal practice, individual differences, problem solving). These diverse but interrelated research lines also suggest that RIF may be the consequence of a domain-general memory mechanism, encompassing all memory systems. This conclusion is also supported by numerous studies that investigated RIF employing a wide range of different materials, manipulations, and test formats.

Particularly important to the notion of a domain-general mechanism, RIF has also been investigated in the context of pure semantic representations in memory, whereas the majority of other works included an episodic component to their behavioural procedures. Johnson and Anderson (2004) investigated RIF with a RPP that excluded a study phase (where episodic associations are established to allow for subsequent practice and test), but tested previously formed associations instead. Specifically, they tested whether retrieving one of the meanings of a homograph (i.e., ”bow”, as in the weapon) would lead to forgetting of the alternative meaning of that homograph (i.e., ”bow”, as in the act of bending as a sign of respect). Because participants practiced the least common meanings of the homographs, the Authors hypothesized that they would have suffered from interference from the dominant meanings during retrieval practice, thereby triggering the need for inhibitory control. As predicted by the Authors, in a later test of the homographs’ meanings, based on free associations, participants showed RIF for non-practice meanings of practiced homographs. This result suggests that, similarly to what is observed in the typical studies of RIF in long-term episodic memory, semantic retrieval may recruit inhibitory mechanisms in order to overcome interference from competing memory representations, thereby reducing their later accessibility (Anderson, 2003).

Turning to a rather different line of research, a number of studies investigated RIF in memory for motor sequences of different complexity. Tempel and Frings (2013) first demonstrated an instance of RIF resulting from overcoming interference between body movements. In their study, participants learned sequential finger movements, six of which involved the right the left hand and the other six the left hand. Subsequently, they performed retrieval practice on half the sequences from either the left or the right hand, followed by a final test phase where they were tested for memory for all the sequences. With this modified RPP, Tempel and Frings (2013) showed that practiced sequences were better recalled than non-practiced ones (i.e., FAC) and, most importantly, non-practiced sequences of a non-practiced hand were better recalled than non-practiced sequences of the practiced hand (i.e., RIF). Results of this study have been conceptually replicated and extended by Reppa, Worth, Greville, and Saunders (2013), and Tempel and Frings (2014a). In addition to that, subsequent studies by Tempel and colleagues demonstrated that RIF for motor programmes is cue independent (Tempel & Frings, 2014b), retrieval specific (Tempel & Frings, 2015), and interference dependent (Tempel, Aslan, & Frings, 2015). Finally, Tempel, Loran, and Frings (2015), found that this peculiar instance of RIF extended to more complex and realistic study material, in the form of dance figures, thereby highlighting the strong applied value of this line of research.

Finally, RIF has also been found for arithmetic facts, employing one-figure multiplications. Theoretical models describe the arithmetic lexicon as stored within an associative network (e.g., Ashcraft, 1992), where numbers are represented as nodes and arithmetic operations as associative links between them. Phenix and Campbell (2004) first demonstrated RIF within this arithmetic associative network. In their experiment, participants were instructed to solve a subset of the classic arithmetic tables (e.g., 6 x 7 = ?). Subsequently, they performed an arithmetic verification task, judging whether the presented answers were correct (e.g., 6 x 7 = 42) or not (e.g., 6 x 7 = 45). Multiplications used in this phase of the procedure belonged to one of three different types: “zero operands” operations, where none of the two operands had been shown in the previous arithmetic-solving task (functioning as NRP- items); “one operand” multiplications, where one of the two operands was used before (functioning as RP- items); “two operands” multiplications, where both operands were seen before (functioning as RP+ exemplars). The results have shown that performance in the correctness judgment was higher for “two operands” multiplications compared to “zero operand” multiplications, thereby mimicking the FAC effect found in the typical RPP. More interestingly, performance for “zero operands” multiplications was higher than for “one operand” multiplications. The Authors interpreted the latter result as the RIF equivalent in the domain of arithmetic facts, arguing that actively retrieving the correct solutions for the multiplications in the practice phase (e.g., 6 x 7 = ?) hinder the subsequent attempt to retrieve multiples of the operands practiced before (e.g., 4 x 7 = 28). Similar results have been observed with slight variations to the procedure described above (e.g., Campbell & Phenix, 2009; Campbell & Thompson, 2012; Galfano, Penolazzi, Fardo, Dhooge, Angrilli, & Umiltà, 2011), further supporting the idea that RIF encompasses associative memory related to arithmetic facts.

1.3.7 RIF as an instance of adaptive forgetting

The bulk of evidence reviewed so far clearly demonstrates not only that RIF is pervasive across memory systems and, subsequently, in out-of-lab contexts, but also highlights a relationship between the ability of overcoming interference in memory and a range of important and highly adaptive functions (e.g., efficient cognitive control and emotion regulation, creative thinking, intact executive functioning). In a recent review, Nørby (2015) has summarized the results from studies that addressed the possible role of forgetting as a regulating mechanism deputed to promote adaptive behaviours. Nørby (2015) argued that forgetting may serve at least three broad purposes: i) it supports emotional regulation, by limiting access to and interference from negative emotions or memories (e.g., Storm & Jobe, 2012); ii) it facilitates acquisition of knowledge; iii) related to the previous point, it promotes “contextual attuning”, i.e., sensitivity to the current status of the surrounding environment in both time and space. This line of reasoning is strikingly counterintuitive with the layman notion of memory retrieval efficiency as indexed by the ability to retrieve as much information as possible, but is strongly supported by the current literature. Instead, retrieval efficiency may be more appropriately described as the ability to selectively retrieve the information with the highest value for the task at hand. This different approach to forgetting conveys a representation of the phenomenon as a mechanism that may serve adaptive purposes, as opposed to popular characterizations of forgetting as a mere failure or limitation of memory systems (e.g., Storm, 2011; Nørby, 2015). For example, RIF has been shown to negatively correlate with the frequency of recall for negative autobiographical memories, so that individuals with greater control over interference in memory recalled significantly less negative memories concerning their personal experiences (Storm & Jobe, 2012). Interestingly, in a different study, Giebl, Storm, Buchli, Björk, and Björk (2015) found that individuals that exhibited higher levels of RIF imagined fewer personal future negative scenarios. Moreover, Groome, Thorne, Grant, & Pipilis (2005) found a significant inverse correlation between RIF and the individual amount of cognitive failures (i.e., forgetfulness) as measured by a self-reported questionnaire, which suggests that individuals displaying a lower ability to control interference in memory may be more susceptible to failures of memory in the everyday life.

In this view, RIF represents the by-product of mechanisms that help maintaining our own well being, as well as shaping our own sense of identity through the modulation of autobiographical memories. Related to this point, Ditta and Storm (2016) also showed that imagining future scenarios could also have detrimental effects on subsequent recall of autobiographical memories that shared similar contexts. Of course, none of the studies described so far suggests that forgetting is always a positive or desired occurrence, but rather that not all instances of forgetting should be regarded as undesirable outcomes.

1.4 Cognitive neuroscience of RIF

In the past ten years, there has been a growing interest in outlining the neural mechanisms underlying RIF. A series of techniques, ranging from event-related potentials (ERPs) to functional Magnetic Resonance Imaging (fMRI), oscillatory brain activity, and animal models, have been used to address a set of question regarding the neural underpinnings of both the retrieval practice and the test phases of the RPP. In the following paragraphs, I review the vast majority of the studies that employed neuroscientific methods in order to further our knowledge about suppression of competing memories, with a focus on the distinct sets of evidence pertaining the retrieval practice and the test phases of the RPP. A separate paragraph is dedicated to two recent studies that provided particularly informative evidence of RIF in animal models. Importantly, each of the studies described in the following paragraphs also contributed to the on-going debate between the inhibitory account of RIF and competing explanatory models. Finally, the last paragraph is devoted to briefly summarize the main contribution of the evidence presented in this section, and provides a link between the existing literature and the set of novel experiments presented in the current work.

1.4.1 Neural correlates of the retrieval-practice phase of the RPP

In the first study that employed EEG to investigate the neural underpinnings of RIF, Johansson, Aslan, Bäuml, Gäbel, and Mecklinger (2007) showed a sustained difference in the amplitude of the electrical activity associated to active retrieval-practice, compared to additional study, localized to the frontal EEG sites. Moreover, this difference predicted the individual magnitude of RIF, but not FAC, observed in the final test phase. The Authors proposed that this pattern might reflect a different executive load associated to the two retrieval practice formats.

Kuhl, Dudukovic, Kahn, and Wagner (2007) instead first used fMRI to shed light on the neural correlates of RIF, employing a RPP with a practice phase characterised by a high number of practice trial repetitions, and found a reduction of the BOLD in lateral PFC regions and anterior cingulate cortex

(ACC) proportional to the number of repetitions. This BOLD decrement was also associated to the individual RIF measured at test. According to the Authors, activity in these cortical areas may reflect the involvement of executive control mechanisms, whose engagement might decrease after the first successful attempts at suppressing interference.

Using fMRI as well, Wimber, Rutschmann, Greenlee, and Bäuml (2009) demonstrated that the activity of medial and lateral PFC regions during the retrieval practice phase of the RPP was negatively correlated with RIF at test, but only during active retrieval practice, compared to passive retrieval practice, suggesting that similarly to Kuhl and Colleagues' findings (2007) a reduced BOLD activity in these areas may signify a reduced demand for inhibitory mechanisms due to interference being successfully overcome within the early practice trials (see also Levy, Kuhl, & Wagner, 2010, for a more comprehensive review on the functional neuroimaging of forgetting).

Differences related to the retrieval practice format have also been investigated in studies that measured electrical oscillatory activity in the brain. For instance, Hanslmayr, Staudigl, Aslan, and Bäuml (2010) examined the time course of the theta rhythm (4-7 Hz) during the retrieval practice phase of the RPP, and found that a competitive retrieval practice was characterized by an increase of this specific oscillatory rhythm, and that this increase was significantly higher than the increase observed in a non-competitive retrieval practice. Moreover, this increment was predictive of RIF (but not FAC) at subsequent test. Staudigl, Hanslmayr, and Bäuml (2010) further clarified the main source of theta activity during retrieval practice, which was localized at the level of the ACC. More recently, Ferreira, Marful, Staudigl, Bajo, and Hanslmayr (2014) also investigated the role of prefrontal theta in RIF. In their study, competitive retrieval practice in the RPP was contrasted with non-competitive retrieval practice, and category cues were presented before the item-specific cues in order to disentangle the interference arising the former with the inhibitory signal associated with the inhibitory mechanisms recruited to weaken the competing memory traces once the target exemplar was revealed. As predicted, the Authors observed RIF in the competitive condition only and, more importantly, higher levels of theta power localized to the ACC within this condition occurred upon presentation of the category cues. Theta power then decreased upon presentation of item-specific cues, and the magnitude of this decrease was associated to that of RIF at later test. Therefore, the results suggest that the time course of theta power during the (competitive) retrieval practice phase of the RPP tightly follows the temporal dynamics of interference.

In keeping with the previous studies that highlighted a prominent role of prefrontal areas in RIF, Wimber, Schott, Wendler, Seidenbecher, Behnisch, Macharadze, anc Colleagues (2011) carried out a combined genetic-fMRI study, aimed at investigating the role of prefrontal dopamine, which is known to support higher cognitive processing and to be involved in many pathological conditions characterized by memory deficits, in long-term memory regulation. In particular, the Authors hypothesized that PFC dopamine availability predicted by the individual catechol-O-methyltransferase (COMT Val108/158Met polymorphism), would have predicted RIF at both the behavioural and the neural level. Results confirmed the role of the PFC dopaminergic system in supporting suppression of interfering memories, by showing that a variation in the gene responsible for PFC dopamine regulation was predictive of the amount of RIF, and of anterior right PFC activation as indexed by BOLD signal in the fMRI. Specifically, Met allele (associated with higher availability of PFC dopamine) carriers displayed the greatest amount of RIF at test, as well as the highest response reduction in right inferior PFC during the retrieval practice phase of the RPP.

In a more recent study, Hellerstedt and Johansson (2014) employed EEG to test the interference dependence tenet of the inhibitory account of RIF, recording and examining ERPs related to reactivation of competing memory traces during the retrieval practice phase of the RPP. The Authors also varied the category-exemplar associative strength of non-practiced items of practiced categories, in order to modulate the amount of competition at retrieval practice. As in the previous study, competitors' reactivation and target retrieval were disentangled by presenting the relevant cues in a two-stage fashion, i.e., presenting the category shortly followed by the target exemplar, as opposed to the typical RPP where the two are presented together within the same display. In line with their hypothesis, the Authors observed more RIF for competitors characterized by stronger category-exemplar association, replicating the typical findings of the RIF literature (e.g., Anderson et al., 1994). Furthermore, a competition-modulated ERP components (i.e., FN400; e.g., Curran & Hancock, 2007) correlated with individual differences in RIF was found in anterior prefrontal sites.

1.4.2 Neural correlates of the test phase of the RPP

Much fewer studies looked into the neural underpinnings of forgetting of competing memories in the final test phase of the RPP where, according to the inhibitory account of RIF, only the after-effects of inhibition can be detected. Nonetheless, research efforts conducted within an inhibitory theoretical framework of memory control have been dedicated to elucidate this aspect of RIF.

Wimber, Bäuml, Bergström, Markopoulos, Heinze, and Richardson-Klavehn (2009) first employed fMRI to investigate the neural correlates of inhibition in the specific phase of the RPP where its effects become manifest at the behavioural level, i.e., within the final test phase. The Authors found that activity in the ventrolateral PFC (VLPFC) and left posterior temporal cortex was correlated to the individual magnitude of RIF, whereas activity in the precuneus and right intraparietal lobule was correlated with the individual magnitude of FAC, thereby demonstrating that the beneficial and detrimental effects of retrieval practice are associated with different neural mechanisms. Importantly, this result is also consistent with pre-existing evidence of similar PFC areas in the retrieval of memory traces weakly tied with their retrieval cues (e.g., Badre & Wagner, 2007).

The electrophysiological correlates of RIF during the final test phase of the RPP have also been investigated (Spitzer, Hanslmayr, Opitz, Mecklinger, & Bäuml, 2009; see also Galfano et al., 2011, in the context of cognitive arithmetic). Spitzer and Colleagues (2009) investigated the ERPs and oscillatory measures associated with recognition of words based on their role (practice vs non-practiced) in the preceding retrieval practice phase of the RPP. The results showed worse recognition performance for non-practiced items relative to control items. Moreover, the former items were associated to reduction in the amplitude of the prefrontal P2 ERP component. Concerning the oscillatory correlates of the test phase, the gamma (60-90 Hz) and theta (4-7 Hz) oscillatory bands were reduced for RP- items compared to control items. Finally, practiced items were found to be associated with a different component and oscillatory signature, originating from different EEG sites as well, pointing to a clear dissociation between the neural signatures of RIF and FAC effects.

1.4.3 Animal models of RIF

In a previous section (see 1.3.6, 1.3.7 above), I have summarized evidence for the ubiquity of RIF across memory systems, as well as the importance of its underlying mechanisms to an optimal functioning of memory systems. Related to this point, few recent studies investigated RIF in animal models. Yamada, Ueno, Takana, and Ichitani (2014) demonstrated that rats could exhibit RIF-like effects in spontaneous object recognition tests. In their study, rats were tested on a modified spontaneous recognition test, consisting of a sample phase, a retrieval or interference phase, and a final test phase. Rats were randomly assigned to a retrieval or interference group. In the sample phase, two different objects (X, Y) were placed in an area that rats were allowed to explore freely. Subsequently, for rats that took part in the retrieval phase, two objects identical to either of the previous ones (e.g., Y, Y) were placed in the area, whereas for rats that took part in the interference phase two identical objects that were novel for the animals (Z, Z). In a final test phase, two different objects (X, W), one of which was identical to one of those presented in the sample phase, were placed in the area. The main dependent variable, collected within the test phase, was the time spent by the rats exploring each object. The Authors found that rats assigned to the interference group spent significantly longer time on the novel object than the familiar object, whereas rats in the retrieval group did not show any difference in exploration time spent between the two objects. Because rats that were assigned to the interference group were better at discriminating the novel object in the test phase, the above result cannot be explained in terms of interference. Importantly, the availability of an animal model of RIF could be exploited to deepen our knowledge of the neural correlates of RIF.

Related to this point, in a different study, Wu, Peters, Rittner, Cleland, and Smith (2014) provided a rodent model of RIF based on a different procedure. In their study, rats were trained on several odour cues associated to rewards, and subsequently half of the rats took part in additional practice on a subset of these cues. On a later memory test employing unrewarded odours, rats exposed to additional practice showed worse memory performance (as indexed by the time spent by the rat into searching for the previously associated reward) for non-practiced odours, compared with memory performance for the same items by the rats that did not receive additional practice. In addition to that, because of the lack of controlled lesion studies in the literature, in the face of many neuroimaging studies highlighting the contribution of the hippocampus (HPC) and the PFC to RIF (see 1.4.1, 1.4.2 above), the Authors carried out an identical procedure with two groups of rats whose HPC or the medial Prefrontal Cortex (mPFC) was temporarily inactivated. As predicted, none of the two groups showed a similar RIF effects as the healthy rats, and the mPFC-inactivated group also showed perseverative responding behaviour, in addition to the lack of RIF. Overall, these results demonstrate that the need for interference resolution in memory may be a common problem across different species, and provide suggestive evidence that these different species might share similar mechanisms that achieve this goal.

1.4.4 Suppression of competing memories and the prefrontal cortex

According to the inhibitory account of RIF, forgetting would arise from inhibitory mechanisms mainly involving PFC that specifically target the competing memory traces during the retrieval practice phase of the RPP, thereby weakening their representational status in memory and thus impairing their later availability for recall (e.g., Anderson, 2003; Levy & Anderson, 2002). However, another (more economical) possibility is that forgetting could be a by-product of PFC-mediated mechanisms that control the retrieval of task-relevant representation in memory (e.g., Miller & Cohen, 2001). For instance, Norman, Newman, and Detre (2007), who first developed a neural network capable of simulating RIF, suggest that competition resulting from co-activation of competing memory traces would be detected by the ACC, which, in turn, would trigger recruitment of PFC regions deputed to resolve this competition by selectively strengthening the task-relevant memory traces. Therefore, according to the Authors' proposal, and in line with Miller and Cohen's model of PFC functioning (2001), RIF would be a by-product of response selection. Instead, according to Kuhl and Wagner (2009; see also Levy et al., 2010), numerous regions within the PFC would be activated in response to arising competition between memory traces, but only a subset of these regions would be responsible for the inhibition of interfering memories, corresponding to the regions primarily associated with RIF in the studies reviewed above, i.e., DLPFC, VLPFC, and ACC. With to the theoretical debate surrounding RIF, as illustrated in the first part of this chapter, the studies reviewed so far that borrowed from neuroscientific techniques to clarify aspects of RIF provided evidence that favour an inhibitory explanation of RIF, as opposed to a response selection model. Importantly to this point, all of the above studies regularly observed a dissociation between the beneficial (i.e., FAC) and the detrimental (i.e., RIF) effects of memory retrieval on subsequent memory tests, which suggests that the two phenomena may be supported by segregated mechanisms, as posited by the inhibitory account of RIF (e.g., Anderson, 2003).

The most recent piece of scientific evidence in favour of the inhibitory account of RIF has been provided by Wimber, Alink, Charest, Kriegeskorte, and Anderson (2015). In this study, the Authors were able to exploit fMRI to quantify the activation and track the time course of retrieval and inhibition dynamics at a single-item level. Therefore, they were able to first show how inhibition resulting from repeated retrieval of target memories among competitors weakened the specific memory traces (i.e., decoded cortical activity patterns) associated to the interfering items. Critically, memory suppression was mediated by PFC regions similar to those engaged in past studies of interference resolution in memory (see Levy et al., 2010), and the magnitude of their involvement predicted the individual amount of RIF at test.

In summary, the majority of the literature reviewed so far speaks in favour of a primary role of the PFC in resolving interference arising from competing memory traces. Future studies should focus on clarifying the specific localization and contribution of PFC areas responsible for RIF, which would provide precious information that could inform the development of new clinical strategies aimed at targeting dysfunctional memory regulation in clinical populations such as patients suffering from posttraumatic stress disorder (see Catarino, Küpper, Werner-Seidler, Dalgleish, & Anderson, 2015), as well as other clinical conditions characterized by impulsivity (see chapters 6 and 7). In this view, the novel studies reported in the present PhD thesis tried to capitalize as much as possible on the wealth of evidence reviewed in this section on the neuroscientific investigations of RIF, where the PFC emerges as the leading force in the control over interference in memory. In particular, in keeping with previous work on the neural underpinnings of RIF, the non-invasive brain stimulation experiments presented here (see chapters 3 and 5) employed transcranial Direct Currenst Stimulation (tDCS) to investigate the possibility of selectively modulating suppression of competing memories in the RPP, and provided the first causal evidence of PFC involvement in this ability. Instead, the experiments involving clinical populations (see chapters 6 and 7) were aimed at providing novel insights into the cognitive profile of the targeted psychiatric disorders, as well as establishing new therapeutic targets for novel treatment strategies involving modulatory techniques such as tDCS to alleviate cognitive symptoms.

2 TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

2.1 A brief history of non-invasive direct current stimulation

The interest toward electrical stimulation as a therapeutic tool is unsuspectedly old. As a matter of fact, almost two thousands year ago, Scribonius Largus, physician at the service of the Roman emperor Claudio (who ruled between 41 and 54 AD), first reported in his *De Compositionibus Medicamentorum* that physicians at that time were using electric fishes on the scalp of patients (1529), grasping the potential effectiveness of electric currents as lenitive techniques, with particular regard to severe headaches. Galen of Pergamon, Greek physician and philosopher, suggested that a similar approach could be also used to treat diseases such as epilepsy, and so did the Roman philosopher and naturalist Pliny the Elder. Later in the 11th century, the physician Ibn-Sidah was among those recommending the application of the electric fish to treat ailments and diseases like headaches, epilepsy, and arthritis (Kellaway, 1946).

The introduction of the electric battery in the 18th century stemmed a series of attempts to stimulate the central nervous system. Charles Le Roy, along with Duchenne de Boulogne, Galvani, Volta, and Aldini, first explored this possibility. For instance, Aldini (Galvani's nephew) authored one of the first detailed reports about the clinical application of galvanic (i.e., continuous) current for the treatment of the so-called *melancholia* (Aldini, 1804). Soon enough the use of low-intensity continuous current, delivered through the muscles or the scalp, spread across and beyond Europe. George (1994) reported that one of Charcot's pupils (the famous French neurologist) used to deliver continuous current stimulation to his patients in Paris, particularly in cases of muscular dystrophies.

However, in the first half of the 20th century and after a series on variable and mostly inconclusive or exaggerated results, this therapeutic approach was gradually abandoned in favour of the more recently introduced psychiatric drugs and other brain stimulation techniques that were deemed more effective, like the electroconvulsive therapy (ECT; high-intensity stimulation, up to 500mA). Therefore, low-intensity electrical stimulation was almost forgotten, with limited exceptions such as the treatment of muscular and bone ailments and neuropathic pain, and electrosleep therapy (i.e., stimulation was delivered during sleep) in Russia (see Gomez & Mikhail, 1978).

At the very beginning of the 21thcentury, as a consequence of the rising interest in magnetic stimulation due to the invention of transcranial magnetic stimulation (TMS; Barker, Jalinous, and Freeston, 1985), other electrical stimulation techniques received renewed attention. Importantly, TMS provided a new approach to explore the effects of low-intensity stimulation techniques on the human brain, as indexed by motor-evoked potentials (MEPs; e.g., Bestmann & Krakauer, 2015). Priori, Berardelli, Rona, Accornero, and Manfredi (1998) first applied low-intensity transcranial Direct (i.e., continuous) Current Stimulation (tDCS) to the human scalp, in order to stimulate the underlying motor cortex, and subsequently employed MEPs to detect changes in cortical activity due to the tDCS. In a subsequent study, Nitsche and Paulus (2000) used a similar approach to detect the effects of weak continuous electric currents applied on the scalp, observing changes in cortical excitability that could last even hours after the stimulation ended, depending on the stimulation parameters and setup. Importantly, they also showed that anodal stimulation enhanced motor cortex excitability, while cathodal stimulation had the opposite effect.

Thanks to these pioneeristic studies, tDCS and related transcranial Electrical Stimulation techniques (tES) are now undergoing a period of extreme popularity, and earned a primary place among other neuroscientific tools, due to their relative simplicity of use, availability, and minimal side effects (within controlled contexts and expert supervision). These features all contribute to make tES a prominent candidate in basic and applied research, with particular regard to the opportunity to develop novel clinical strategies.

In this chapter, I first describe the most commonly used tES devices, with particular regard to tDCS, and I summarize the main findings in the tES literature concerning the most effective montages and parameters, which can be rather different with respect of the intended effects and contexts of application. Secondly, I provide an outline of the putative mechanisms of action of tES, i.e., the neural dynamics and mechanisms that could explain the observed effects of tES. More recently employed tES waveforms (i.e., transcranial alternated current stimulation, tACS, and transcranial random noise stimulation, tRSN) are described as well. Thirdly, I provide a short review of the main findings of the tDCS literature so far, as concerns basic and applied (both clinical and non-clinical) research, with a focus on the studies that investigated scientific hypotheses that more closely match the scope of the present work, i.e., cognitive control in memory and action.

It is worth noting that the burst of enthusiasm for tES and the increasing amount of studies addressing its application in a vast range of domains has also stemmed concern about the quality and reliability of the bulk of results provided so far. Given the pressure to publish outstanding results in the tES literature and to quickly develop therapeutic protocols, healthy scepticism and caution are both warranted and welcomed. Moreover, ethical concerns have been raised in regard to the potential application of tES as a form of “neurodoping”, as well as safety concerns for the growing DYI tES community. The reader may refer to (e.g., Riggal, Forlini, Carter, Hall, Weier, Partridge, et al., 2015; Santarnecchi, Feurra, Galli, Rossi, & Rossi, 2013; Walsh, 2013; Wurzman, Hamilton, Pascual-Leone, & Fox, 2016) for recent discussions of these important points.

2.2 tDCS: Technical and application notes

2.2.1 Device, basic components, and montage

The core component of a tDCS device is a constant current generator, generally powered by a pair of batteries (AA) or a single 9-volt battery. The generator is placed in series with a potentiometer, which allows the user to select the amount of current delivered by the stimulator by modulating its internal resistance. Conductive rubber electrodes (most often a couple) are connected to the generator through cables. The electrodes, i.e., an anodal electrode (positive polarity) and cathodal electrode (negative polarity) are inserted in sponges of varying surface, typically between 16 cm^2 and 100 cm^2, depending on the intended target and current density (i.e., the proportion between the amount of current being delivered and the active area of the electrode). The shape and positioning of the electrode will determine which portion of the brain will be affected by the resulting electric field, and to what extent.

Stimulation intensity is usually set between 0.5 mA and 2 mA, while duration usually ranges between 5 and 30 min. Target site selection is generally achieved in agreement with the 10-20 International System (Jasper, 1958), but alternative methods are used as well (e.g., the non-navigated Beam F3-System and the OLE-system for targeting of the DLPFC; see Seibt, Brunoni, Huang, and Bikson, 2015), and neuronavigation techniques can also be used to assist in the localization of the target area. Once the target areas have been individuated, the electrode-filled sponges are soaked in saline solution and/or a similar medium (e.g., EEG gel) in order to improve conductivity on the scalp (or body, in the case of extra-cephalic setups), and then applied on it through rubber bands or similar, non-conductive headgear. Optimal tightening of the headgear is necessary to prevent drift of the electrodes across the scalp, which could compromise the effectiveness of the protocol, undermine reliability and replicability of results, and favour dispersion of the conductive medium (e.g., because of sponge squeezing under the rubber bands) that could lead to unintended stimulation or sensations at near-target sites, or even complete failure of the stimulation protocol (e.g., due to higher impedances on the scalp). The reader can find more thorough practical advices on performing a stable tDCS setup in a recent work by Woods, Bryant, Sacchetti, Gervits, and Hamilton, (2015).

2.2.2 The electrodes

Several studies investigated how different tDCS electrodes' shape and size affect the resulting electric field in the brain, the behavioural outcomes of tDCS, and the cutaneous sensations due to stimulation (e.g., Minhas, Datta, & Bikson, 2011). Moreover, Datta, Elwassif, Battaglia, and Bikson 2008) e Datta, Bansal, Diaz, Patel, Reato, and Bikson (2008) found that a shorter distance between the electrodes increased the degree of shunting through the scalp (i.e., the loss of current due to high resistivity of the skull), with the consequence that higher current is needed to produce an equivalent electric field on the cortex. However, there also seems to be a negative correlation between the inter-electrode distance and the duration and magnitude of tDCS after-effects (Moliadze, Antal, & Paulus, 2010). Therefore, one should deliver higher stimulation intensity for setups with large inter-electrode distances, as it is often the case with montages employing an extra-cephalic reference (see also Nasseri, Nitsche, & Ekhtiari, 2015, for a categorization and description of the various tDCS montages).

It should be noted that modelling studies on the tDCS-induced electric field (e.g., Neuling, Wagner, Wolters, Zahele, & Herrmann, 2012; Miranda, Lomarev, & Hallett, 2006) showed that the stimulation affects areas of the scalp and brain that can be far removed from the intended target site. Moreover, current density on the scalp appears to be at its highest at the edges of the electrodes, whereas in the brain the highest current density is achieved in the area immediately under the electrode.

Along with the shape and size of the electrodes, excessive saturation of the electrode or sponges with the conductive medium can alter the distribution and flow of the current on the scalp and the resulting electric field in the brain, as well as worsen cutaneous sensations typically associated with tDCS (e.g., Minhas et al., 2011). According to Dundas, Thickbroo, and Mastaglia (2007), the optimal medium concentration of NaCL to minimize discomfort during stimulation with tDCS ranges from 15 to 140 mM.

2.2.3 Focality

The lack of focality of tDCS is often considered the Achilles' heel of the technique, although few expedients can be used to ensure maximal stimulation of the target site while reducing current spreading. For instance, it has been suggested that reducing the size of the electrode that is placed on the target area, and increasing the size of the reference electrode, can increase focality under the target electrode site if current density is kept constant (e.g., DaSilva, Volz, Bikson, & Fregni, 2011; Nitsche, Doemkes, Karakose, Antal, Liebetanz, Lang, et al., 2007). This is also important if one considers that the reference electrode in the context of tDCS is most often a functionally active one, and thus effects at the reference site, as well as combined effects of both electrodes, need to be taken into account when making inferences about observed outcomes of tDCS. This is especially true for bipolar montages (i.e., with both anodal and cathodal electrodes on the scalp). In this view, increasing the size of the active reference electrode represents a useful expedient to at least partially address the issue. Some authors have also proposed the use individually tailored electrodes with personalized size and shape (e.g., Santi, Cancelli, Cottone, Carducci, & Tecchio, 2016). However, this approach might actually yield additional sources of inter-subject variability while minimizing others, as it could reasonably lead to different current flow, physiological effects, and sensations, between individuals. Moreover, increasing current intensity might be necessary to adjust for over-proportional decrease in the current flow into the brain due to when reducing electrodes size.

Finally, a new type of putatively focal tDCS called "high definition tDCS" has also been proposed (HD tDCS; e.g., Kuo, Bikson, Datta, Minhas, Paulus, Kuo, et al., 2013), but the extent of its actual benefits and differences with respect to "standard" tDCS devices and protocols is currently under scrutiny. In any case, it should be noted that the lack of focality of the vast majority of tDCS protocols is not necessary a weakness of the technique. Instead, depending on the context, initial hypothesis, and desired outcomes, more widespread effects of tDCS could be a desired feature (e.g., in specific therapeutic applications).

2.2.4 Intensity, duration, timing, and polarity

Concerning current intensity, higher densities generally induced stronger effects (e.g., Iyer, Mattu, Grafman, Lomarev, Sato, & Wasserman, 2005; Nitsche & Paulus, 2000). However, it is worth noting that higher currents would not necessarily yield either better behavioural outcomes (e.g., Hoy, Emonson, Arnold, Thomson, Daskalakis, & Fitzgerald, 2013) in terms of magnitude, direction, and duration, of the effects of interest, or larger changes in cortical excitability. For instance, Batsikadze, Moliadze, Paulus, Kuo, and Nitsche (2013) applied tDCS at varying intensities to healthy participants, and observed significant effects (in the same direction) of both anodal and cathodal stimulation over the left primary motor cortex at 2 mA in the MEPs amplitude (i.e., corticospinal excitability). On the contrary, MEPs amplitude was reduced after 1 mA cathodal tDCS, pointing to an intensity-dependent, rather than polarity-dependent, stimulation effects. It is worth noting that, depending on the stimulation site, somatosensory-evoked potentials (SEPs; e.g., Sehm, Hoff, Gundlach, Taubert, Conde, Villringer, et al., 2013) and visual evoked potentials (VEPs; e.g., Accornero, Li Voti, La Riccia, & Gregori, 2007) have been used as well to asses the effects of tDCS.

Regarding the duration of tDCS effects, longer stimulation protocols are more often associated to longer lasting effects (up to several hours), but only for cathodal stimulation (Paulus, 2011). Studies addressing the modulation of MEPs with a frontopolar montage (e.g., Nitsche & Paulus, 2000, 2001; Nitsche, Nitsche, Klein, Tergau, Rothwell, & Paulus, 2003) found that a few seconds of tDCS at moderate intensity could induced temporary acute excitability alterations, which did not result in after-effects, whereas short-lived after-effects (up to 10 min) were achieved by stimulating for a few minutes (up to 7). Stimulation exceeding 10 min induced after-effect that lasted approximately 1 h. Related to this point, Stagg and Nitsche (2011) provided an outline of the physiological basis underlying after-effects of tDCS. It is also important to consider that longer stimulation, may have the counterintuitive outcome of inverting the direction of stimulation effects (i.e., the direction that we would expect to observe at lower parameters; see Batsikadze et al., 2013; Monte-Silva, Kuo, Hessenthaler, Fresnoza, Liebetanz, Paulus, et al., 2013), similarly to what is observed for increases in stimulation intensity. Importantly, it is still unclear whether the known stimulation effects in the motor cortex domain can be generalized to other cortical areas. This is particularly challenging, as we do not currently have objective indexes such as MEPs for the main targets of interest in tDCS research. To this end, co-registration (i.e., employing neuroimaging techniques alongside stimulation) may help better clarifying the neural consequences of stimulation parameters.

Polarity of the electrode(s) over the target area is also critical feature of the tDCS setup. It is often assumed that anodal current enhances cortical excitability, along with the behavioral performance that reflects the cognitive mechanisms associated with the stimulated region, whereas cathodal stimulation would yield the opposite effect, i.e., decreased cortical excitability and related performance at the behavioral level (see also 2.3). However, this anodal-excitatory / cathodal-inhibitory model stems from a line of research on tDCS that begun with the first studies that investigated modulation of the motor cortex excitability with electrical stimulation (e.g., Nitsche & Paulus, 2000; 2001; Priori et al., 1998), but that by no means pretended to inform the whole range of potential applications of the technique. Eventually, researchers soon realized that results from studies where brain regions other than the motor cortex were stimulated with tDCS rarely fitted this model. A recent review and meta-analysis by Jacobson, Koslowsky, and Lavidor (2012c) suggests that this is clearly the case. In fact, while anodal and cathodal stimulation showed consistent direction of the tDCS outcoms in studies addressing motor cortex excitability, a much more nuanced scenario emerged from research that employed stimulation to investigate high-order cognitive processes, where anodal stimulation behaves similarly to motor studies, but cathodal stimulation rarely induce increased inhibition. Sometimes even inverse polarity effects can be observed: For example, Accornero and Colleagues (2007) reported a reduction of VEPs after anodal tDCS, and an increase in the same neurophysiological measure after cathodal stimulation. In any case, whenever a study is designed to demonstrate specific effects of polarity of tDCS, delivering the opposite polarity as well (while keeping the other parameters constant) is an optimal choice of control condition.

In addition to all of the above setup parameters, timing of the stimulation (i.e., when to stimulate) is also important depending on the desired outcomes and the research hypotheses being tested. Both off-line (i.e., before data collection) and online (i.e., during data collection) tDCS have been employed, with different outcomes depending on the context and dependent variables (e.g., MEPs, behavioural measures). Interestingly, when administering multiple tDCS sessions, the duration of the inter-session interval (which could vary from few minutes to several hours or days, depending on the study) seems to significantly modulate the regulation of cortical excitability in terms of duration of the after-effects of stimulation as indexed by MEPs (Monte-Silva, Kuo, Paulus, & Nitsche, 2008).

2.2.5 Target areas and target functions

Almost every tDCS application, in either basic or clinical research, moves from the hypothesis that a certain area of the brain is involved in a cognitive process, and that successful modulation of that particular area may allow for enhancement or impairment in the associated cognitive process of interest. Similarly, we may hypothesize that a brain region is involved in specific symptoms and dysfunctional mechanisms associated to a clinical condition, and we may want to investigate the possibility of using tDCS to normalise a compromised function or alleviate certain symptoms. Therefore, establishing the right target is a primary concern when devising a tDCS experiment. Subsequently, one can explore the large space of the possible combinations of the parameters described above, aiming to find an optimal combination according to the intended outcomes, while taking into account the boundaries of the stimulation protocol according to the safety regulations of tDCS, as well as past works that investigated the modulation of identical or similar brain areas and underlying cognitive processes.

Apart from studies that applied tDCS to modulate motor cortex excitability (e.g., Nitsche & Paulus, 2000, 2001), electrical stimulation has already been used in a broad range of different applications, spanning almost every research domain within the cognitive sciences. In particular, a wealth of studies have been devoted to the application of tDCS to modulate important high-order cognitive functions such as attention, language, memory, and executive functions. For instance, left prefrontal stimulation delivered at the F3 site (corresponding to the left DLPFC) of the 10-20 EEG electrodes placement system (Jasper, 1958), has been shown to increase performance at naming facilitation and verbal fluency tasks (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Iyer et al., 2005). The same site has been stimulated in numerous studies employing tDCS to modulate working memory (WM) as indexed by the *n*-back task (e.g., Fregni, Boggio, Nitsche, Bermpohl, Antal, Feredoes, et al., 2005; Ohn, Park, Yoo, Ko, Choi, Kim, et al., 2008). Turning to the investigation of tDCS effects on learning, Meinzner, Jähnigen, Copland, Darkow, Grittner, Avirame, and Colleagues (2014) found that repeated sessions of tDCS (over multiple days) applied to the left posterior temporo-parietal junction induced an improvement in learning and maintenance of newly acquired words. Stimulation of sensory cortices and related perceptual processes has been investigated as well: For instance, Costa, Hamer, Nagy, Barboni, Gualtieri, Boggio, and Colleagues (2015) were able to selectively modulate different processing channels in the visual cortex with tDCS over OZ in the 10-20 EEG system, whereas Reinhart, Xiao, McClenahan, and Woodman (2016) stimulated either the P1 (i.e., left visual cortex) or the P2 (i.e., right visual cortex) site of the 10-20 system, and found an immediate beneficial effect on visual acuity in the contralateral visual field. Regarding the auditory cortex, for example, Heimrat, Kuehne, Heinze, and Zaehle (2014) applied tDCS over either the C3 or the C4 10-20 sites, corresponding to the left and right auditory cortices respectively, and observed an impairment in the perception of rapidly changing acoustic information specific for C3 stimulation, thereby suggesting a left hemisphere dominance for this specific process. Related to the cognitive domain of perception, there is also evidence of tDCS-induced modulation of cross-modal effects (e.g., disruption of the McGurk illusion with tDCS over the T3 and T4 10-20 sites, corresponding to superior temporal sulcus; Marques, Lapenta, Merabet, Bolognini, & Boggio, 2014).

A few years after the inception of tDCS into the field of cognitive neuroscience, some researchers begun applying electrical stimulation to the cerebellum as well, a procedure that has been termed “cerebellar tDCS” (cTDCS), in order to investigate the involvement of this under-studied brain structure in many cognitive processes, and to explore new possibilities for novel therapeutic interventions (e.g., Ferrucci, Marceglia, Vergari, Cogiamanian, Mrakic-Sposta, Mameli, et al., 2008, for a study on WM; see Ferrucci, Cortese, & Priori, 2014, for review and practical recommendations).

As a general rule, experiments designed to provide evidence for the causal involvement of a particular brain region on a certain cognitive process or behaviour should employ control conditions where additional unrelated brain regions are stimulated. Moreover, a double-dissociation design can be implemented in tDCS studies as well in order to allow for even stronger inferences on the results.

As I mentioned before, previous studies with similar or overlapping rationales are the most valuable source of information regarding which tDCS setup to use in one’s own study. However, it should be kept in mind that the majority of works on tDCS so far, with particular regard to the first seminal studies that investigated the most effective parameters to induce cortical excitability, have been carried out on the primary motor cortex, which cannot be assumed as a model of the whole cortex’s response to tDCS. More generally, anatomical differences between portions of the cortex, state-dependency (i.e., the current status of the cortex while receiving tDCS, due to on-going tasks or additional manipulations), and other factors as well, all speak against direct transferability of tDCS outcomes from one context of application to another (e.g., Gill, Shah-Basak, & Hamilton, 2015; Kessler, Turkeltaub, Benson, Hamilton 2012; Nitsche & Paulus, 2000). In addition to that, the complexity of the brain hinders accurate predictions of stimulation effects, thereby requiring a more nuanced approach where, for each stimulation protocol, specific predictions are advanced on the basis of the functional and structural features of the target area, its connections to other brain regions, and the functional networks it partakes into. Hypotheses will also be shaped according to the behavioural and physiological measures that will be implemented in the protocol. Coupled with the considerable inter-individual differences often observed in tDCS outcomes (López-Alonso, Cheeran, Rodríguez, & Fernández-del-Olmo, 2014; Wiethoff, Hamada, & Rothwell, 2014), related to age, gender, and genetic characteristics of the stimulated individual, among many other factors (e.g., Chaieb, Antal, & Paulus, 2008; Fritsch, Reis, Martinowich, Schambra, Ji, Cohen, et al., 2010; Suppa & Cheeran, 2015) these considerations call for caution against over-generalisation but also for exploration of the optimal parameter space with respect to the peculiar research questions under scrutiny, especially when no precedent has been established for a particular application of the technique (e.g., Iyer et al., 2005).

2.2.6 Sham stimulation: Achieving blinding in tDCS research

2.2.6.1 Blinding the participants

A common and important feature of tDCS devices is the option to deliver of a simulated stimulation, i.e., “sham” stimulation, which allows for the inclusion of control groups blinded (or even double-blinded), which is often essential to make sense of results from studies employing this kind of modulatory approach. Sham stimulation generally consists of a very brief stimulation, ramped up for a few seconds at the beginning of the tDCS protocol, aimed at generating sensations that are quite common in the very first stage of electrical stimulation of the scalp, and usually fade after a short habituation period. At the beginning of stimulation, participants often report an itching or tingling sensation, however the extremely short stimulation is not able to induce after-effects. Several studies found this protocol to induce sensations that were undistinguishable from those experienced by groups of participants receiving real stimulation, especially when the participants did not have previous experience of tDCS (e.g., Ambrus, Al-Moyed, Chaieb, Sarp, Antal, & Paulus, 2012; Gandiga, Hummel, &

Cohen, 2006; Palm, Reisinger, Keeser, Kuo, Pogarell, Leicht, et al., 2013; see also O'Connell, Cossar, Marston, Wand,Bunce,Moseley, et al., 2012, for potential concerns regarding effective blinding at intensities of 2 mA). It should be noted that higher currents may lead to increased sensations, thus potentially compromising blinding of the stimulation procedure, in particular with repeated measure (i.e., multiple within-participant stimulation protocols) experimental designs (O'Connell et al., 2012; Palm et al., 2013), whereas this issue might be irrelevant for studies employing a parallel experimental design (i.e., between-group comparison of stimulation protocols). Related to this point, it is important to monitor and record sensation due to tDCS at the end of the protocol (see Fertonani, Ferrari, & Miniussi, 2015, for a standardized sensations questionnaire), which may contribute to establishing effectiveness of the blinding procedures across sessions/stimulation groups, as well as ensuring that the stimulation protocol is well-tolerated by participants or patients, depending on the context of usage (see Poreisz, Boros, Antal, & Paulus, 2007, and Fertonani et al., 2015, for surveys of the potential adverse effects of tDCS). Another approache to blinding of participants in tDCS experiment consists of the application of topical anaesthetics (Guleyupoglu et al., 2014) to abolish sensations on the skin.

2.2.6.2 Blinding the experimenter

Achieving double blinding of tDCS experiments requires the device operator to be as unaware as the participants regarding the specifics of the protocol. This is generally accomplished thanks to options available to several tDCS devices, where codes for a specific setup are inputted on the device that would subsequently deliver stimulation according to the parameters associated to that particular setup, without further programming on behalf of the operator. However, it should be noted that the operator would necessarily be aware of the gross features of the montage (i.e., targeted areas), which could be used to infer part of the experimental hypotheses and predictions underlying the stimulation protocol. In addition to that, the possible stimulation-induced skin erythema due to vasodilation could be exploited as well to correctly guess whether participant is being stimulated or not (Durand et al, 2002; Ezquerro et al., 2016).

In summary, ensuring efficient blinding in tDCS experiments is essential to test the specificity of the stimulation setup in producing a set of observed outcomes.

2.2.7 Safety and tolerability

A safe and tolerable tDCS administration is based on four prerequisites: Firstly, a careful selection of volunteers or patients based on exclusion criteria related to the interaction between electrical currents to the head/brain and their interactions with pre-existing medical conditions, medications, and symptoms. Typical exclusion criteria include but are not limited to history of head trauma, convulsions or seizures, faint spells or syncope, metal implants, cochlear implants, metal fragments or apparatus, medications, cardiac pacemaker. Depending on the class, objectives, setting, and tDCS parameters, which characterize a particular study, certain criteria may be relapsed (e.g., excluding individuals with history of seizures, if the study is aimed at reducing their occurrence), or else, additional constraints may apply (see Rossi, Hallett, Rossini, & Pascual-Leone, 2011, for a set of screening questions for TMS safety that can be easily adapted for use with tDCS). Secondly, the experimenters should be aware of, monitor, and record, the typical sensations associated with tDCS, and the modulation of their magnitude depending on the montage parameters (i.e., intensity, density, target area, electrodes, duration). Recently Fertonani, Ferrari, and Miniussi (2015) provided a review on sensations induced by electrical stimulation, as well as a useful questionnaire for participants to report which sensations were experienced and how intensely. The most typical sensations associated with tDCS are mild itching, burning, or tingling, under the electrodes. Apart for physical sensations not associated with tissue damage (with few exceptions, e.g., Wang, Wei, Wen, & Li, 2014), potential cognitive and neurobiological side-effects have been hypothesized as well, even though none of them have been observed so far within the range of the stimulation parameters recommended by safety guidelines (e.g., Ardolino, Scelzo, Cogiamanian, Bonara, Nozza, & Rosa, 2014, on the effects of tDCS on circulating lymphocytes). For obvious reason, the main concern with electrical stimulation pertains the risk of inducing seizures, with particular regards to healthy volunteers. However, so far, none have been reported. A thorough report on tDCS safety has recently been published by Bikson, Grossman, Thomas, Zannou, Jiang, Adnan, and Colleagues (2016) (see also Krishan, Santos, Peterson, & Ehinger, 2015, for a report on tDCS safety in children and adolescents). Thirdly, as mentioned above, stimulation parameters in human experimentations should strictly adhere to the recommended values in the literature (e.g., Bikson et al., 2016; Bikson, Datta, & Elwassif, 2009). Last, but not least, it is essential that tDCS operators be comprehensively trained in the foundational aspects of electrical stimulation: theoretical background, rationale of use, safety and screening guidelines, determination of parameters, montage and setup, emergency conducts, and monitoring and reporting of adverse events (Woods, Antal, Bikson, Boggio, Brunoni, Celnik, et al., 2016).

2.2.8 Other tES waveforms

The majority of devices used to administer tDCS can also deliver different waveforms. The most common waveforms besides tDCS are transcranial Alternated Current Stimulation (tACS; Antal, Boros, Poreisz, Chaieb, Terney, & Paulus, 2008), and transcranial Random Noise Stimulation (tRNS; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). The following paragraphs provide a brief outline of these two waveforms. The reader is referred to Paulus, Nitsche, and Antal (2016) for a comprehensive review of the three main tES waveforms (i.e., tDCS, tACS, tRNS).

2.2.8.1 transcranial Alternated Current Stimulation (tACS)

Transcranial Alternated Current stimulation (tACS) consists of sinusoidal waves (most often, but other waveforms are possible) of bidirectional, biphasic current, which can be applied at different intensities and frequencies (see also Chaieb, Antal, Pisoni, Saiote, Opitz, Ambrus, et al., 2014, for a report on tACS safety). Ideally, tACS in the EEG range or in the so-called “ripple” range (e.g., Moliadze et al., 2010) allows interfering with the oscillatory brain activity by enhancing their amplitude or entraining them (Helfrich, Schneider, Rach, Trautmann-Lengsfeld, Engel, & Hermann, 2014) by stimulating at the corresponding frequency. Therefore, it has been proposed that application of tACS may yield promising results in disorders characterized by abnormal oscillatory activity in the brain, by restoring optimal oscillatory patterns. Phase-locking of endogenous EEG could also be accomplished with tACS, which also enables modulation of phase coherence between different brain areas. In the kHz range, instead, tACS could affect more selectively the neuronal membrane's excitability. These effects could be exploited to modulate behavioral, cognitive, and neurophysiological mechanisms, known to be associated to the target frequency. Frequency, intensity, and phase of stimulation, are the main parameters of a tACS protocol, and contribute in shaping the outcomes of the stimulation. Duration could reasonably be important as well, but it has not been systematically investigated yet, and evidence provided by studies with tDCS may not directly translate to tACS. Similarly to tDCS, the first studies to employ tACS investigated the modulation of the motor cortex, providing mixed results with respect to neurophysiological effects (e.g., Antal et al., 2008; Feurra, Blanco, Santarnecchi, Del Testa, Rossi, & Rossi, 2011; Moliadze et al., 2010; Pogosyan, Gaynor, Eusebio, & Brown, 2009; Zaghi, de Freitas Rezende, de Oliveira, El-Nazer, Menning, Tadini, et al., 2010).

A critical aspect of tACS is the setup and interpretation of different electrodes, because when tACS is applied they will keep switching between anodal and cathodal current at each half cycle of oscillation, whereas in tDCS the anode and cathode maintain the same function throughout the whole stimulation session. Therefore, during tACS, all target areas will receive similar stimulation. This particular feature of oscillating electrical stimulation also implies a different rational when planning a study, compared to tDCS experiments: Identifying the oscillatory signature and its specific parameters whose modulation may shape the cognitive process of interest. Moreover, cross-frequency effects should be taken into account; Indeed, it has been shown that delivering tACS at a certain frequency can induce changes in "antagonistic" frequencies as well (e.g., Helfrich, Knepper, Nolte, Strüber, Rach, Hermann, et al., 2014, for gamma-alpha cross-frequency effects).

A relevant phenomenon associated with tACS is the observation that stimulation protocols close to the retina or targeting the visual cortex can induce retinal or cortical phosphenes, respectively, but not in the “ripple” range. It should be noted that retinal phosphenes might also appear with tDCS close to the eyes, and therefore their occurrence is one of the reasons why tDCS protocols are delivered with a fade-in and a fade-out of current intensity. Because of the occurrence of phosphenes in tACS protocols, the potential for blinding in tACS studies has been questioned (e.g., Raco, Bauer, Olenik, Brkic, & Gharabaghi, 2014; Schutter & Hortensius, 2010), and effective strategies should be developed by future research, with particular regard to stimulation protocols within the alpha and gamma ranges.

2.2.8.2 transcranial Random Noise Stimulation (tRNS)

Among the three main waveforms that can be delivered with regular tES equipment, transcranial Random Noise Stimulation (tRNS) is the most recent, as well as the one we know the least about. This electrical stimulation method may be regarded as a special case of tACS, consisting of a bidirectional biphasic current that randomly oscillates within a spectrum of pre-defined frequencies and is not sensitive to the direction of the current flow, and it has been first introduced by Terney et al., (2008). Terney and Colleagues found that weak tRNS in the high-frequency spectrum (between 100 and 640 Hz) applied on the motor cortex for 10 min enhanced corticospinal excitability both online and offline with respect to the stimulation session. In general, delivering tRNS to the motor cortex enhances cortical excitability, but the stimulation effects could be dependent on current intensity (Moliadze, Atalay, Antal, & Paulus, 2012). The effects of tACS are likely dependent on the task performed during stimulation and the ongoing baseline oscillatory activity (Neuling, Rach, & Hermann, 2013). For instance, Ambrus, Zimmer, Kincses, Harza, Kovacs, Paulus, and Colleagues (2011) found that tRNS over the DLPFC induced more mistakes in a probabilistic classification task, whereas Mulquiney, Hoy, Daskalakis, and Fitzgerald (2011) did not observe any effects of tRNS on an *n*-back task when stimulating on the same site. In other studies, tRNS over the visual cortex enhanced neuroplasticity in a perceptual learning paradigm (Fertonani, Pirulli, & Miniussi, 2011), but only when stimulation was delivered concurrently with the task (Pirulli, Fertonani, & Miniussi, 2013).

Concerning safety of stimulation, tRNS seems to yield even smaller side effects and unpleasant sensations than tDCS, to the point of being almost unnoticeable and painless to many volunteers, thereby granting this stimulation technique with unparalleled blinding potential compared to other tES protocols. If tRNS will prove effective at modulating pathological oscillatory activity, in addition to brain rhythms in the healthy brain, it could provide great economical and practical advantages in clinical settings, compared to other stimulation techniques such as repeated TMS (rTMS) that are used with a similar rationale (i.e., inducing or disrupting brain plasticity).

2.3 Putative mechanisms of action

Several mechanisms of action underlying the effects of tDCS have been proposed. Importantly, as opposed to TMS, the weak electric fields (0.5-2 mA) employed in tDCS are not able to induce action potential, but act at a sub-threshold level instead. Consequently, tDCS is usually referred to as a neuromodulation technique, compared to other neurostimulation methods that are known to eliicit action potentials. At the neural level, it has been suggested that tDCS might be able to induce a polarity-dependent shift in the resting membrane potential. Therefore, for instance, anodal tDCS would depolarize the neuronal membranes within the target area, thus making spontaneous neuronal firing more likely to occur, whereas cathodal tDCS should have the opposite effect, through hyperpolarization of the neuronal membranes (but see 2.2.4 for a less clear-cut distinction between the two polarities of tDCS).

The two polarities of tDCS seem to be dissociable in their neurochemical effects as well. Indeed, pharmacological studies reported that administering drugs that induced blockage of Na^+ (i.e., carbamazepine) and Ca^+ (i.e., flunarizine) channels impaired the excitatory after-effects typically associated with anodal current, whereas cathodal stimulation was unaffected by the pharmacological manipulation (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Liebetanz, Lang, Antal, Tergau, & Paulus, 2003).

These evidences are in line with the hypothesis that tDCS is able to modulate the neuronal resting membrane potential in a polarity-dependent fashion. Moreover, they suggest that tDCS could be modulated by the concurrent administration of drugs affecting the central nervous system. This could be an important venue for future studies, because it could both provide new combined therapeutic strategies and inform the use of tDCS in clinical populations that are already receiving prescription drugs.

Because tDCS induces effects that outlast the stimulation window, it is unlikely that the underlying neural mechanisms that mediate such effects can be solely attributed to changes in the baseline neuronal resting membrane potential. Indeed, besides direct polarizing effects, tDCS can also induced indirect functional and structural modifications in cortical and subcortical areas that may be even far removed from the target site, through alterations of connectivity between the areas (e.g., Boros, Poreisz, Münchau, Paulus, & Nitsche, 2008). Studies that employed fMRI revealed that, even though tDCS seems to exert its strongest effect at the target site (e.g. Kwon, Ko, Ahn, Kim, Song, Lee, et al., 2008), stimulation could induce diffuse and sustained modifications in other regions as well (Lang, Siebner, Ward, Lee, Nitsche, Paulus, et al., 2005). EEG studies also provided evidence in favour of long-range tDCS effects, showing that stimulation was able to induce widespread and synchronized changes of the oscillatory activity in the brain (e.g., Ardolino, Bossi, Barbieri, & Priori, 2005; Marshall, Molle, Hallschmid, & Born, 2004).

Modification of the synaptic environment induced by tDCS has also been observed, at the level of both receptors and neurotransmitters (e.g., Nitsche et al., 2003; Liebetanz et al., 2002; Stagg, Best, Stephenson, O'Shea, Wylezinska, Kincses, et al., 2009). In addition to that, animal studies (e.g., Fritsch et al., 2010; see Jackson, Rahman, Lafon, Kronberg, Ling, Parra, et al., 2016, for a thorough review of the contribution of animal studies to the comprehension of tES) suggest that stimulation effects may be related to *long-term potentiation* (LTP). Related to this point, tDCS also induced changes in synaptic plasticity dependent from secretion of the neurotrophic factor in the mouse brain (BDNF; Fritsch, et al., 2010).

Recently, it has been proposed that tDCS may work in an altogether different way, that is, by affecting glial cells, rather than neurons (see Roth, 2012, and Ruohonen & Karhu, 2012; see also Monai, Ohkura, Tanaka, Oe, Konno, Hirai, et al., 2016, for a study of calcium imaging in the mouse brain). Although this hypothesis is still in need of thorough investigation, it has sparkled a great interest in the literature, as it may address several concerns related to the current assumptions underlying tDCS effects, such as the fact that neuronal membrane polarization could happen under electric fields as low as those produced by tDCS, especially when current dispersion due to intervening tissues (e.g., skin and bones) are taken into account.

In any case, it should be noted that neurophysiological markers of tDCS such as those presented above do not necessarily translate into effects of stimulation that could be relevant for investigating or shaping human behaviour, with particular regard to the clinical setting. The interested reader may refer to Medeiros, de Souza, Vidor, de Souza, Deitos, Volz, and Colleagues (2012), for a review on the neurobiological mechanisms underlying tDCS.

Turning to tRNS (2.2.8.2), the effects of oscillating currents have been explained in terms of temporal summation of neural activity mediated by repeated opening of the Na^+ channels, as suggested as well by a recent study showing inhibited MEPs after concurrent administration of tRNS and carbamazepine (Chaieb et al., 2015). Alternatively, the concept of stochastic resonance has been proposed as an explanatory framework for tRNS. Stochastic resonance refers to the phenomenon that a signal too weak to overcome a threshold can be amplified by adding random noise (see Cappelletti, Gessaroli, Hithersay, Mitolo, Didino, & Kanai, 2015; Fertonani & Miniussi, 2016; Miniussi, Harris, & Ruzzoli, 2013). Therefore, effects of tRNS would be task-dependent (i.e., the on-going task would establish the need for exceeding the threshold to discharge). Another possibility is that tRNS may prevent homeostasis of the stimulate system, compared to other tES techniques, due to its unpredictable and varying nature (Fertonani et al., 2011). All these proposals could very well coexist into shaping the observed effects of tRNS in the literature. For comprehensive reviews on the physiological bases and the proposed mechanisms of actions of tES, the reader may refer to Stagg and Nitsche (2011), and Fertonani and Miniussi (2016), respectively.

2.4 Neuromodulation and treatment of cognitive control

One of the main objectives of tDCS is to effectively influence behavioural performance associated to cognitive processes that are supposed to be modulated by stimulation of their neural underpinnings. This, in turn, would allow to use tDCS and related stimulation techniques to enhance behavioural performance in healthy individuals, and more importantly, to repair impaired performance in patients suffering from a wide range of clinical conditions. So far, a wealth of studies employed tDCS on a broad variety of cognitive tasks addressing hypotheses stemming from the principal domains of the cognitive sciences (i.e., attention, emotion, language, memory, perception), in both healthy volunteers and patients. In this regard, tDCS has provided mixed evidence of effectiveness. However, several important points should be considered when evaluating or comparing outcomes of tDCS research.

To begin with, tDCS has been usually coupled with typical cognitive and neuropsychological tasks, which are not necessarily sensitive enough to reflect the effects of electrical stimulation that neurophysiology studies suggest to be very subtle. Moreover, different stimulation protocols and tasks are used by different authors that work on the same research questions, which may lead to diverging results due to even minimal changes between experimental procedures (see also 2.2), or between different study samples (especially when they are rather small, as it is often the case with tDCS studies). Electrical stimulation may also interact with the behavioural tasks being performed during the stimulation session, but at the moment there is minimal knowledge about the characteristic of such interaction, and how to beneficially exploit it.

In the following paragraphs (2.4.1, 2.4.2), I focus on past studies that investigate the modulation of the core cognitive process that ties together all the original experiments presented here, i.e., cognitive control, in a broad range of behavioural instances (2.4.1) and across different clinical populations suffering from impulsivity and impairment in this fundamental ability (2.4.2).

2.4.1 Modulation of cognitive control in healthy volunteers

tDCS has been widely used in basic research applications aimed at disentangling the neural underpinnings of several behavioural tasks often used to probe cognitive control. For instance Beeli, Casutt, Baumgartner, and Jäncke (2008) found that tDCS to the rDLPFC impaired performance in a go/no-go task, where participants respond to the majority of the stimuli as fast as they can, but also have to refrain from responding when a smaller subset (typically ¼) of the stimuli is presented, with cathodal stimulation having the strongest impact on false alarm rates.

The stop-signal task (SST; e.g., Logan & Cowan 1984), which puts the participants in a situation where they are sometimes required to outright stop their motor response, allows to measure the covert latency of the inhibitory process responsible for successful stopping, and it has been extensively employed to test the effects of tDCS on inhibitory control of motor action, as well as to demonstrate the causal involvement of right prefrontal areas in this ability. The bulk of evidence on this specific domain of tDCS research is of particular importance with respect to the scope of the present thesis, because of the putative relationship between selection and inhibition of motor action and episodic memory retrieval (e.g., Levy & Anderson, 2002; Schilling et al., 2014). Jacobson, Javitt, and Lavidor (2011) first applied tDCS to the rIFG before a SST, and observed an improvement of the stopping process only for the anodal tDCS stimulation. Subsequent studies confirmed and extended this right PFC inhibitory enhancement induced by anodal tDCS, with few mixed results (e.g., Cai, Li, Liu, Li, Feng, Wang, et al., 2016; Cunillera, Brignani, Cucurell, Fuentemilla, & Miniussi, 2015; Cunillera, Fuentemilla, Brignani, Cucurell, & Miniussi, 2014; Ditye, Jacobson, Walsh, & Lavidor, 2012; see also Castro-

Meneses, Johnson, & Sowman, 2015, for a study that included also vocal response inhibition task, and Hogeveen, Grafman, Aboseria, David, Bikson, & Hauner, 2016, for a study that employed HD-tDCS). Liang, Lo, Yang, Peng, Cheng, Tseng, and Colleagues (2014) also investigated the neural correlates of response inhibition improvement by tDCS, and found an increase in a measure of complexity of the EEG signal associated to improvement in motor stopping in participants that initially (i.e., without stimulation) showed poorer performance. However, they adopted a different tDCS montage compared to the studies discussed above, which was identical to the one implemented by Hsu, Tseng, Yu, Kuo, Hung, Tzeng, and Colleagues (2011; but see Berryhill, Peterson, Jones, and Stephens, 2014, for a failure to replicate Hsu et al., 2011, and related discussion).

Turning on instances of cognitive control other than motor stopping, tDCS seems to yield the potential to improve performance in risk-taking tasks such as the Balloon Analog Risk Task, by promoting more cautious decision making (e.g., Fecteau, Pascual-Leone, Zald, Liguori, Théoret, Boggio et al., 2007; see also Fecteau, Knoch, Fregni, Sultani, Boggio, & Pascual-Leone, 2007, for similar results with a different task involving gambling). In particular, a recent study has shown detrimental effects of cathodal tDCS on performance in list-method directed forgetting, a task that probes the voluntary ability to control interfering memories (Silas & Brandt, 2016). In a different study, Oldrati, Patricelli, Colombo, and Antonietti (2016) also found a detrimental effect of prefrontal cathodal tDCS on inhibitory performance, as indexed by incorrect impulsive responses at the cognitive reflection test, which probes the ability to overcome cognitive conflict.

Different results have been observed in a study employing the Hayling Task (Metzuyanim-Gorlick, & Mashal, 2016), which requires participants to complete sentences with compatible words in the initiation condition, and on the contrary to generate incompatible and unrelated words in the suppress condition (Burgess & Shallice, 1997). In this study, left anodal/right cathodal stimulation significantly improved inhibition of irrelevant responses, compared to a sham control group. However, the use of a bilateral montage, as opposed to the two studies above that employed fronto-polar montages (Oldrati et al., 2016; Silas & Brandt, 2016), does not lend to a straightforward comparison of this result with the evidence presented so far. Finally, Herrmann, Beier, Simons, and Polak (2016) were able to attenuate skin conductance response to unpredictable threatening stimuli by the means of anodal tDCS to the rIFG, thus providing evidence in favour of a role of this area in emotional regulation, which could be regarded as a specific instance of cognitive control.

In general, tDCS seems to be a promising technique for the manipulation and enhancement of cognitive control (for extensive reviews, see Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016, and Sarkis, Kaur, & Camprodon, 2014). However, it should be noted that electrical stimulation effects are far from being consistent across different studies. Related to this point, Berryhill and Colleagues (2014) discussed possible sources of variability in tDCS outcomes as concerns modulation of performance in similar tasks.

2.4.2 Modulation of cognitive control in clinical populations

Many studies have already investigated the use of tDCS to ameliorate a wide range of pathological conditions, as concerns both psychiatric, neuropsychological, and neurological disorders (for recent reviews, see Kuo, Paulus, & Nitsche, 2014, Cappon, Jahanshahi, & Bisiacchi, 2016, and Convento, Russo, Zigiotto, & Bolognini, 2016, respectively). In particular, relevant to the present work, tDCS yields promising results in the reduction of symptoms pertaining to impulsivity, craving, and lack of control, in both healthy individuals and patients with psychiatric diagnoses.

For instance, a recent study by Kekic, McClelland, Campbell, Nestler, Rubia, David, and Colleagues (2014) suggests that prefrontal tDCS may be effective at temporarily lowering food craving in healthy women suffering from frequent occurrences of this particular symptom. Other studies found beneficial effects of administering tDCS to the DLPFC on craving (e.g., Boggio, Sultani, Fecteau, Merabet, Mecca, Pascual-Leone, et al., 2008, on alcohol craving; Fregni, Orsati, Pedrosa, Fecteau, Tome, Nitsche, et al., 2008, on food craving) The neural underpinnings that may mediate these effects have been subsequently investigated, by Lapenta, Di Sierve, Coutinho de Macedo, Fregni, and Boggio (2014), which found a significant modulation of ERP components typically associated with inhibitory control (i.e., N2 and P3a). Moreover, a recent review by Sauvaget, Trojak, Bulteau, Jiménez-Murcia, Fernández-Aranda, Wolz, and Colleagues (2015) suggests that tDCS may be effective as a treatment strategy for food and behavioural addiction, and in particular the Authors recommend additional efforts into the investigation the neuromodulatory effects of tDCS on the latter symptom, which appears to be under-studied with respect to the former (see also Ljubisavljevic, Maxood, Bjekic, Oommen, & Nagelkerke, 2016). There is also compelling evidence of reduced smoking behaviour as a consequence of prefrontal tDCS (Fecteau, Agosta, Hone-Blanchet, Fregni, Boggio, Ciraulo, et al., 2014).

Apart from addiction, the use of prefrontal tDCS to ameliorate inhibitory control has been investigated in other clinical populations with inhibitory disregulation and undiagnosed individuals with impulsivity-related traits. For instance, Soltaninejad, Nejati, and Ekhtiari (2016) delivered tDCS to the left DLPFC of adolescents suffering from ADHD symptoms, and observed an improvement of inhibition of prepotent response in a go/no-go task following cathodal tDCS. Taken together, results from the literature discussed above not only suggest a central role of the DLPFC in cognitive control, but also highlight an ideal target for neuromodulatory attempts aimed at manipulating this ability.

3 TDCS OVER THE RIGHT DORSOLATERAL PREFRONTAL CORTEX (RDLPFC) ABOLISHES RIF

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Retrieving information from long-term memory can result in the episodic forgetting of related material. One influential account states that this retrieval-induced forgetting (RIF) phenomenon reflects inhibitory mechanisms called into play to decrease retrieval competition. Recent neuroimaging studies suggested that the prefrontal cortex, which is critically engaged in inhibitory processing, is also involved in retrieval competition situations. Here, we used transcranial direct current stimulation (tDCS) to address whether inhibitory processes could be causally linked to RIF. tDCS was administered over the right dorsolateral prefrontal cortex during the retrieval- practice phase in a standard retrieval-practice paradigm. Sixty human participants were randomly assigned to anodal, cathodal, or sham-control groups. The groups showed comparable benefits for practiced items. In contrast, unlike both the sham and anodal groups, the cathodal group exhibited no RIF. This pattern is interpreted as evidence for a causal role of inhibitory mechanisms in episodic retrieval and forgetting.

3.1 Introduction

Retrieving information from long-term memory is known to elicit two well-established phenomena. On the one hand, processing of the retrieved items is enhanced, an effect known as retrieval-induced facilitation (FAC). On the other hand, how- ever, processing of items related to those that have been retrieved is impaired, resulting in a phenomenon called retrieval-induced forgetting (RIF; Anderson et al., 1994). These effects have typically been studied with the retrieval-practice paradigm (Levy & Anderson, 2002), in which participants first learn several category–exemplar pairs from several categories (study phase) and then actively retrieve some of the studied exemplars of half categories only (retrieval-practice phase). The final phase (test phase) consists of a recall test involving all learned exemplars. Typically, the FAC effect consists of a better recall of practiced items over un- practiced items from non-practiced categories (i.e., control items), whereas the RIF effect consists of a better recall of control items over non-practiced items from practiced categories.

RIF has proved a robust effect and has been replicated in a variety of domains (Galfano et al., 2011; Johnson & Anderson, 2004). According to an influential class of models, RIF would reflect inhibitory mechanisms actively engaged by retrieval processing during the practice phase, aimed to maximize the retrieval of the to-be-practiced items (Anderson, 2003; for a review, see Storm & Levy, 2012). Crucially, according to inhibitory accounts, facilitation of practiced items is functionally independent from forgetting of non-practiced, related competitors, whereas, according to non-inhibitory accounts, RIF and FAC are function- ally related, because forgetting of non-practiced, related items is attributable to the strengthening of practiced items. Neuroimaging studies suggested that a broad prefrontal neural network, involved in executive control, is engaged during retrieval practice, and some of the activated areas within this network [i.e., anterior cingulate cortex, anterior ventrolateral prefrontal cortex, dorsolateral prefrontal cortex (DLPFC)] seem to be directly linked to forgetting of competitors, because their activation predicts the amount of RIF but not that of FAC (Kuhl et al., 2007; Wimber, Bäuml, Bergström, Markopoulos, Heinze, & Richardson-Klavehn, 2008). Nevertheless, these data are correlative in nature.

The present study aimed to establish a causal relationship between prefrontal areas and the specific cognitive mechanisms underlying RIF using transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique (Dayan, Censor, Ruch, Sandrini, & Cohen, 2013). We targeted the DLPFC because fMRI data suggest that its activation correlates with the amount of RIF (Wimber et al., 2009) and is engaged in direct suppression of unwanted thoughts (Benoit & Anderson, 2012; Gagnepain, Henson, & Anderson, 2014). Based on previous neuromodulation studies investigating inhibitory control (Juan & Muggleton, 2012), active stimulation was delivered over the right hemisphere. tDCS was administered during the practice phase of a standard retrieval-practice paradigm, because inhibitory processes would act specifically during this phase according to inhibitory accounts (Anderson, 2003). If the right DLPFC plays a causal role in RIF and inhibition is a critical mechanism underlying such phenomenon, then we would expect no alterations of FAC but a significant, stimulation-dependent, alteration of RIF.

3.2 Methods

3.2.1 Participants

Sixty students (10 males; mean 23.4, SD, 2.1 years), who met the inclusion criteria for participating in brain stimulation studies, gave their written informed consent to take part in the experiment, performed in accordance with the principles of the Declaration of Helsinki. The local ethical committee approved the study, which adopted the safety procedures of non-invasive brain stimulation. Sample size for each group was determined a priori on the basis of both previous neuroimaging studies addressing RIF (Wimber et al., 2009) and neuromodulation studies implementing between-participants designs (Penolazzi, Pastore, & Mondini, 2013). A single blind, sham-controlled, between-group design was used: Participants were randomly assigned to one of three stimulation conditions (two active stimulations and one sham-placebo stimulation), without being informed about the kind of stimulation they received.

3.2.2 Retrieval Practice Paradigm (RPP)

RIF was assessed using a standard RPP (Anderson et al., 1994). Stimuli were 96 Italian nouns of exemplars belonging to eight semantic categories selected from the category production norms for Italian language (Boccardi & Cappa, 1997). Criteria for stimuli selection were those generally used for this paradigm: (1) categories were relatively unrelated; (2) semantic associations between items of different categories were kept to a minimum; (3) only at least five letter items were included; and (4) within each category, each item had a unique first letter. In all categories, 7 of 12 items were strong exemplars (i.e., they were generated with a high frequency according to the production norms; mean number of produced exemplars, 73.7; range, 39.43–102.4), whereas the other five items were weak exemplars (i.e., they were generated with a low frequency according to the production norms; mean number of produced exemplars, 6.1; range, 1–16). Because weak exemplars suffer significantly less RIF than strong exemplars do (Anderson et al., 1994), to maximize the probability of eliciting the effect, weak exemplars served as to-be-practiced items, whereas strong exemplars served as non-practiced, related items.

As shown in Figure 3.1 and Figure 3.2, in the first phase of the paradigm (study phase), participants studied the 96 category-exemplars pairs randomly presented in a categorized blocked order. Each trial started with a fixation cross for 0.5 s, followed by a blank lasting 0.5 s, and a category-exemplar pair for 2.5 s. The inter-trial interval consisted of a blank lasting 0.5 s. In the second phase (retrieval-practice phase), participants retrieved only weak exemplars from half of the studied categories through a cued-recall test. Specifically, items were randomly presented four times each, in the form category-plus-three-letter-stem (e.g., FRUIT-pru__). This allowed to distinguish items as follows: (1) practiced items from practiced categories (RP+; corresponding to weak exemplars); (2) non-practiced items from practiced categories (RP-; corresponding to strong exemplars); and (3) control items, i.e., non-practiced items from non-practiced categories [in turn, distinguished in weak exemplars (NRP+) acting as control for RP+ items and strong exemplars (NRP-) acting as control for RP- items]. Each trial started with a fixation cross for 1 s, followed by a blank lasting 1 s, and an item for 4 s. The inter-trial interval lasted 1 s. In the third phase (test phase), participants performed a cued-recall task (items in the form category-plus-one-letter-stem, e.g., FRUIT-p__), including all items studied in the first phase. Each trial started with a fixation cross lasting 0.5 s, followed by a blank screen lasting 0.5 s, and an item for 4 s. The inter-trial interval lasted 1 s. To ensure that RIF was not caused by output interference (i.e., interference exerted by RP+ items, which tend to be recalled first), RP- items were always tested before RP+, NRP+, and NRP- items, which appeared in random order. Although this presentation order might have caused NRP- items to undergo more interference than RP- items, such bias was held constant across participants and hence is unlikely to have influenced the results as a function of stimulation. Four balanced lists differing in the subgroups of categories acting as either to-be-practiced categories or control categories were built and randomly assigned to participants.

3.2.3 tDCS

tDCS was delivered through a battery-driven current stimulator (BrainStim; EMS), using a pair of surface saline-soaked sponge electrodes (16 cm2). A constant current of 1.5 mA was applied for 20 min(fade-in/fade-out time, 60 s) in both the active stimulation conditions. In the anodal group, the anode was positioned over the right DLPFC (F4 siteof the 10 –20 EEG system), whereas the cathode was positioned over the left supraorbital area, a commonly used site for the reference electrode. Although other regions are also known to be involved in RIF (Wimber et al., 2009), we focused on DLPFC for two critical reasons. First, DLPFC is critically engaged in inhibitory processing (Knoch, Gianotti, Pascual-Leone, Treyer, Regard, Hohmann et al., 2006; De Neys, Vartanian, & Goel, 2008) and thought suppression (Benoit and Anderson, 2012). Second, DLPFC is more consistently identified as underlying a specific site of the 10–20 EEG system compared with other areas (e.g., ventrolateral prefrontal cortex). We focused on the right hemisphere because brain stimulation studies addressing motor inhibition highlighted its key rolein inhibitory control (for a review, see Juan and Muggleton, 2012). Furthermore, given the linguistic nature of our stimuli, we preferred to minimize the possible modulation of areas involved in linguistic processing. In the cathodal group, electrode positioning was reversed with respect to the anodal group. In the sham group, a 1.5 mA current was applied for 15 s at the beginning and 15 s at the end of the stimulation period.

To rule out alternative accounts of tDCS effects, a self-report questionnaire measuring mood and arousal was administered at both the beginning and the end of the experiment. In addition, to detect possible differences in the sensations experienced during the different stimulation conditions, at the end of the experiment, participants were asked to complete a five-point-scale questionnaire (Fertonani et al., 2010).

Stimulation was delivered during the retrieval-practice phase, in which inhibitory processes are assumed to operate according to inhibitory accounts. Because the retrieval-practice phase lasted less than the stimulation period, when the former finished, participants were asked to complete unrelated filler questionnaires until the end of the stimulation. When the stimulation finished, the test phase started.

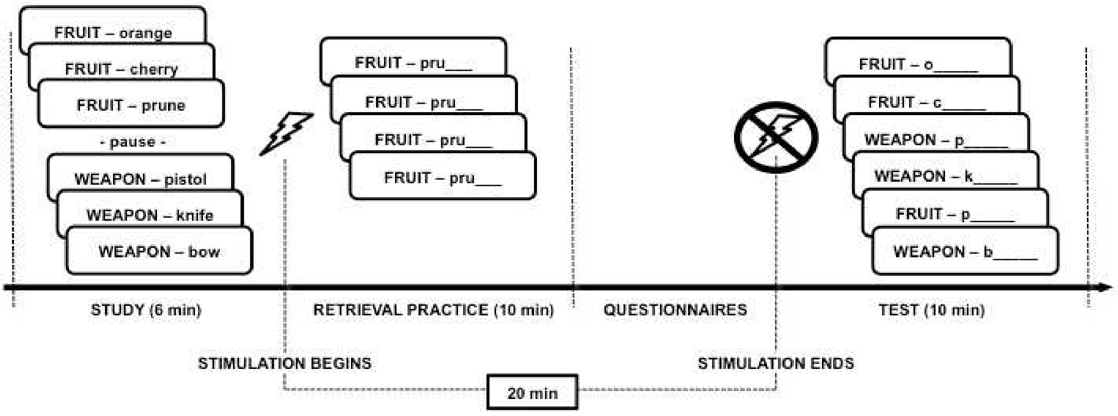

Figure 3.1 Schematic illustration of the experimental procedure. A standard retrieval-practice paradigm (RPP) was employed. Stimulation was administered during the phase whereby inhibitory processes are assumed to occur according to inhibitory accounts, and lasted 20 min. Between the practice and test phases, participants completed filler questionnaires unrelated to the present research. The test phase was performed immediately after the end of the stimulation but after a brief delay with respect to the practice phase, in line with the typical RPP.

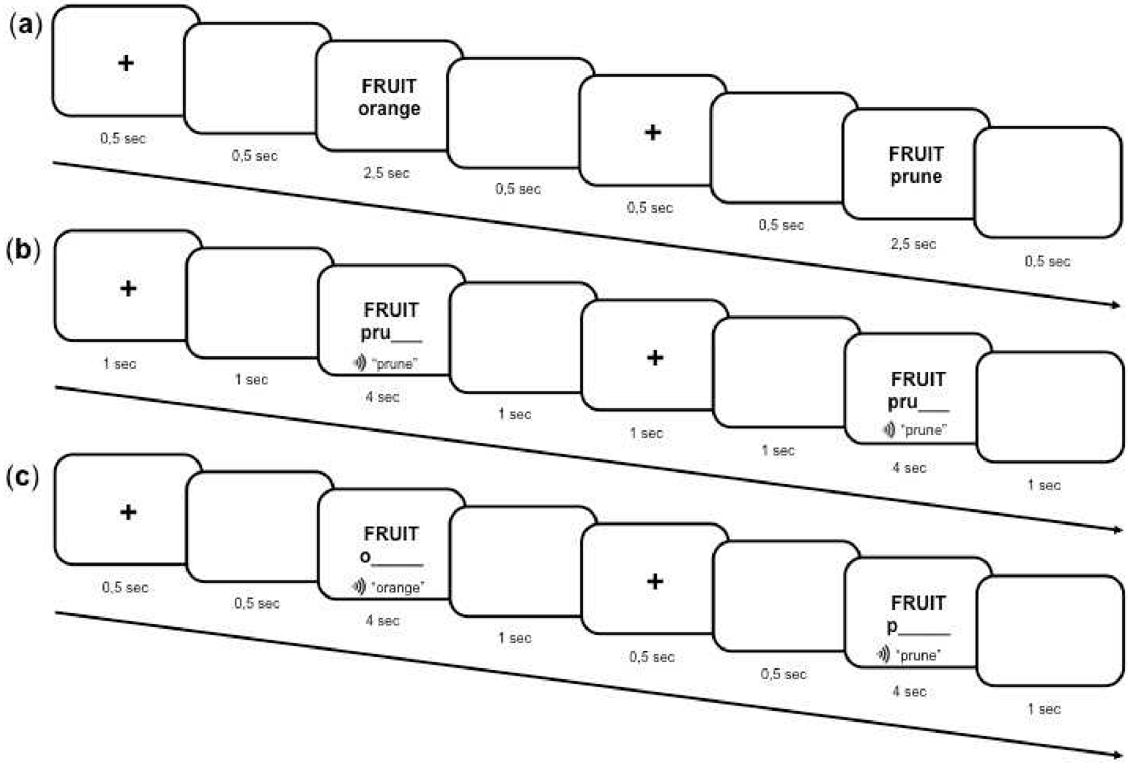

Figure 3.2 Schematic representation of trial structure across the three phases of the RPP: (a) study phase; (b) practice phase; (c) test phase. (b&c) Participants responded by recalling the name of the exemplar associated to the cue provided on screen aloud (sound waves symbol).

3.2.4 Analysis

A one-way ANOVA with group (anodal, cathodal, sham) as the between-participant factor was conducted on the percentage of correctly recalled items in the retrieval-practice phase. However, the crucial analyses to test our experimental hypothesis were related to the percentage of correctly retrieved items in the test phase. In this regard, a mixed-design ANOVA was performed for FAC, with group as a between-participant factor and item type (RP+, NRP+) as a within-participant factor. An analogue ANOVA was performed for RIF, with group as a between-participant factor and item type (NRP-, RP-) as a within-participant factor. For significant interactions, Bayesian analyses were used to disentangle which model (null vs alternative hypothesis) was more strongly supported by the available data. Specifically, the Bayesian information criterion (BIC) was computed to test the presence of the investigated effects (FAC and RIF) in each group (Masson, 2011). Within this framing, the posterior probability that the data favor the alternative hypothesis, i.e., $p_{\mathrm{BIC}}(H_1 \mathrm{I} D)$, ranges from 0 to 1 and is just the complement of the posterior probability that the data favour the null hypothesis. Thus, $p_{\mathrm{BIC}}(H_1 \mathrm{I} D)$ higher than 0.50 indicate that there is more evidence for the alternative than for the null hypothesis, whereas values lower than 0.50 indicate the opposite. Finally, Pearson's correlations between FAC (i.e., RP+ and NRP+) and RIF (i.e., NRP- and RP-), for both the entire sample and the three groups, were performed to further test the hypothesis of their independency, with positive correlations indicating that RIF increases as FAC increases.

3.3 Results

Retrieval Practice Paradigm (RPP)

Table 3.1 shows the mean percentage of correct recall during the test phase as a function of both Item Type and Stimulation Group. As for the FAC effect (i.e., difference in correct recall between RP+ and NRP+ items), the ANOVA only revealed a significant main effect of *Item type,* $F(1,57) = 285.93$, $p < .001$, $\eta^2_p = .83$, indicating that RP+ items were recalled better than NRP+ items, irrespective of the Stimulation Group ($M_{RP+} = 59.42\%$, $95\%CI_{RP+} = 55.24/63.59$ and $M_{NRP+} = 22.92\%$, $95\%CI_{NRP+} = 20.08/25.75$). Neither the main effect of *Stimulation Group,* $F(2,57) = .25$, $p = .778$, $\eta^2_p = .01$, nor the *Stimulation Group × Item type* interaction, $F(2,57) = 1.84$, $p = .168$, $\eta^2_p = .06$, were significant (see Figure 3.3). As regards RIF (i.e., difference in correct recall between NRP- and RP- items), the ANOVA showed a non-significant main effect of *Item type,* $F(1,57) = 3.35$, $p = .073$, $\eta^2_p = .05$ and a significant main effect of *Stimulation Group,* $F(2,57) = 4.11$, $p = .022$, $\eta^2_p = .13$ ($M_{Sham} = 34.20\%$, $95\%CI_{Sham} = 30.00/38.39$; M_{Anodal}=29.64%, $95\%\ CI_{Anodal}$=25.45/33.84; $M_{Cathodal} = 25.71\%$, $95\%CI_{Cathodal} = 21.52/29.91$). Critical for the purpose of the study, the *Group × Item type* interaction was also significant $F(2,57) = 4.98$, $p = .01$, $\eta^2_p = .15$, (see Figure 3.3). Bayesian analyses showed that the posterior probability favouring the alternative hypothesis (presence of RIF, that is NRP- items recalled better than RP- items) in the Sham group was $p_{BIC}(H_1|D) = 0.823$, which, according to the conventional categorization of degrees of evidence (see Masson, 2011), constitutes a positive evidence for the presence of RIF in this group. As regards the Anodal group, the posterior probability favouring the alternative hypothesis was $p_{BIC}(H_1|D) = 0.660$, which constitute a weak evidence for the presence of RIF in this group. Crucially, the posterior probability favouring the alternative hypothesis in the Cathodal group was $p_{BIC}(H_1|D) = 0.338$, indicating that no RIF was present for this group. Correlations between FAC and RIF scores performed for both the entire sample and each of the three groups separately were not significant (highest $r = -0.39$).

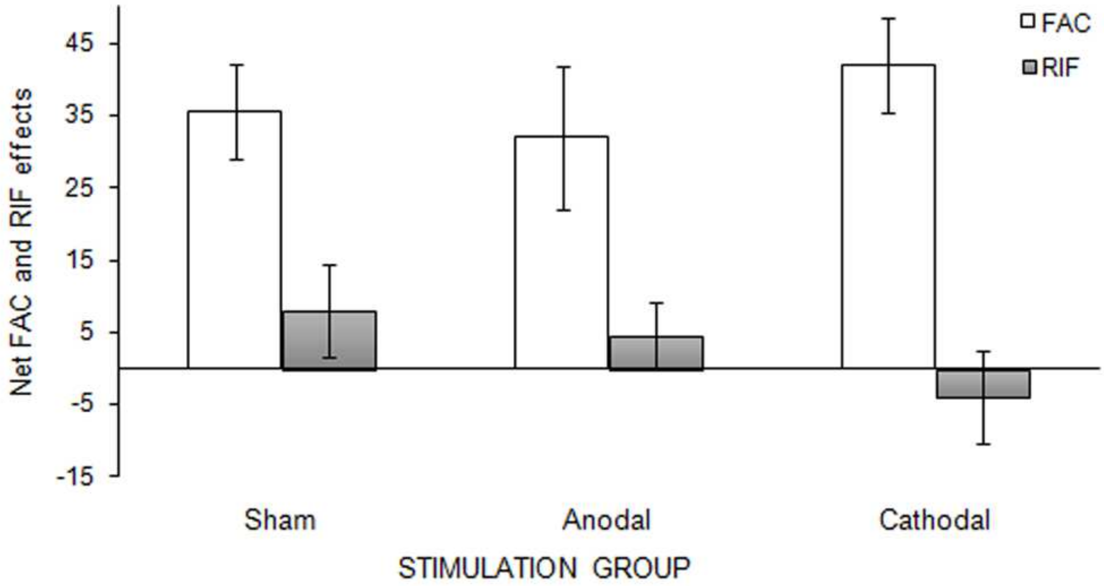

Figure 3.3 Recall data from the final test phase in the three groups. FAC is computed as follows: FAC = (%RP+) - (%NRP+). RIF is computed as follows: RIF = (%NRP-) - (%RP-). Bars represent 95% CIs.

Table 3.1 Mean percentage of recall in the retrieval-practice phase and in the final test phase as a function of both item type and stimulation group.

	Retrieval Practice Phase	Final Test Phase			
	Item Type	Item Type			
Stimulation Group	RP+	RP+	NRP+	RP-	NRP-
Sham	74.61 (69.44/79.79)	59.75 (52.94/66.56)	24.25 (19.26/29.24)	30.18 (24.80/35.56)	38.21 (32.73/43.69)
Anodal	75.12 (69.95/80.29)	55.75 (47.49/64.01)	23.75 (17.78/29.72)	27.32 (23.04/31.60)	31.96 (26.45/37.48)
Cathodal	77.50 (72.33/82.67)	62.75 (55.22/70.28)	20.75 (16.44/25.06)	27.68 (22.07/33.28)	23.75 (18.63/28.87)

3.3.1 Questionnaires

Analyses of the self-report questionnaire measuring mood and arousal revealed no significant differences in any of the items as a function of stimulation conditions. With regard to the self-report questionnaire assessing the sensations experienced during the stimulation, sham and active protocols were found to be indiscernible, because none of the assessed sensations significantly varied as a function of group.

3.4 Discussion

In the present study, we tested whether RIF could be modulated by tDCS over the right DLPFC by administering stimulation during the retrieval-practice phase of a standard retrieval-practice paradigm. Retrieval-practice data showed that perturbing the practice phase by administering tDCS did not affect accuracy. Although this result might seem surprising, past work has shown that dividing attention with a concurrent task during retrieval practice does not impair retrieval success while disrupting inhibitory processes (Román et al., 2009). Regarding the data of the final test phase, FAC (i.e., the classic practice effect) was present in all stimulation groups, as practiced items were recalled better than control items regardless of group. Concerning RIF, sham and anodal stimulations induced a similar effect (although stronger for the sham group): non-practiced items from practiced categories were recalled significantly worse than control items. In sharp contrast, cathodal stimulation abolished RIF.

3.4.1 Causal evidence for rDLPFC involvement in RIF

Several fMRI studies (e.g., Wimber et al., 2009) suggested that DLPFC, among the many prefrontal regions engaged in competitive retrieval practice, could have an active role in determining RIF, given that its recruitment during the practice phase predicted the amount of subsequent forgetting in the test phase. The present study, overcoming a correlational approach, provided the first data supporting a causal involvement of the right DLPFC in the functional genesis of RIF. However, this does not necessarily mean that this is the only area causally involved in the phenomenon. Similarly, given that tDCS electrode size is relatively large and transynaptic effects are also possible, one cannot rule out the possibility that the present electrode montage also resulted in influencing other areas, adjacent to the DLPFC, also involved in the neural circuitry underlying RIF. However, the critical point here is that the present results attest that the right DLPFC has a key role within the network involved in the suppression of un- wanted episodic memories, as suggested by recent fMRI data (Benoit & Anderson, 2012). Importantly, a growing literature focusing on encoding, retrieval, and reconsolidation mechanisms showed that right lateral prefrontal cortex plays a pivotal role in episodic memory (Manenti, Cotelli, Robertson, & Miniussi, 2012; Sandrini, Censor, Mishoe, & Cohen, 2013). The present findings extend this body of evidence by showing that such a region is also relevant for episodic forgetting.

Besides providing topographical information concerning the neural network underpinning RIF, the present findings are also crucial for evaluating current theoretical perspectives concerning the functional mechanisms that allow us to overcome interference from competing memories. At the functional level, RIF has been interpreted as reflecting two possible mechanisms (Storm & Levy, 2012) based on either inhibitory or non-inhibitory processes (the latter being often referred to as associative interference accounts). Inhibitory accounts (Anderson, 2003) assume that inhibitory mechanisms are actively engaged during the practice phase to resolve retrieval competition by decreasing activation of the items related to those that have been practiced, in such a way that they would be less available with respect to control items in the test phase. In contrast, associative–interference accounts assume that the only mechanism active in the retrieval-practice phase is the strengthening of the category–item associations for items to be practiced. This reinforcement would block or weaken access to non-practiced, related competitors in the subsequent test phase, thus determining their retrieval disadvantage as a mere side effect. Crucially, according to inhibitory accounts, facilitation of practiced items is functionally independent from forgetting of non-practiced, related items, whereas, according to non-inhibitory accounts, RIF and FAC are functionally related, because forgetting of non-practiced items is attributable to the strengthening of practiced items. In this regard, our results, obtained by stimulating the right DLPFC when inhibitory mechanisms are assumed to act on interfering memories (Anderson, 2003), strongly support inhibitory accounts based on two arguments. First, stimulation-induced effects were obtained by perturbing an area of the right prefrontal cortex that is known to play an important role in inhibitory control according to studies addressing different cognitive domains (Knoch et al., 2006; De Neys et al., 2008). Second, the modulation of RIF in the absence of a concomitant modulation of FAC indicates a clear dissociation between the cortical key areas causally involved in these phenomena and, in turn, a dissociation between the underlying cognitive mechanisms. These dissociations are only consistent with inhibitory accounts, because associative interference accounts postulate a direct relationship between the extents to which non-practiced, related items are forgotten and the extent to which practiced items are strengthened (Mensink & Raaijmakers, 1988). In this regard, our findings not only fail to confirm the positive correlation predicted by associative interference accounts but, in line with previous evidence (Weller et al., 2013), seem to go significantly against it, because the correlation between RIF and FAC, albeit not statistically significant, was inverse. This is consistent with evidence showing that the two phenomena are not only differentially sensitive to manipulations aimed to overload executive control processes (with only RIF being selectively affected by stress and dual-task requirements; Koessler et l., 2009, and Román et al., 2009, respectively) but also linked to different neurotransmitters (Wimber et al., 2011).

Although one may have expected a reduction in RIF as a result of better recall of RP- items for the active stimulation groups than for the sham group, it is important to note that we used a between-participant design, and because active stimulation groups were not tested for RIF before receiving tDCS, we cannot rule out the possibility that the three groups were different in their baseline. Therefore, when referring to this type of design, it is safer to rely on comparisons involving differential (i.e., relative) rather than absolute scores, that is to focus on relative variations in the performance on the two key item types necessary to assess RIF and FAC within each group, and compare such effects. Although the combined use of brain stimulation and retrieval- practice paradigm may be difficult to implement in a within-participant design, future studies adopting such experimental logic may address this issue in a more straightforward manner.

3.4.2 Effects of anodal and cathodal tDCS on RIF

Concerning the effects exerted by the two types of active stimulation used here, we did not find opposite behavioural effects of anode and cathode. Such a pattern might have been expected based on the fact that cortical excitability is increased by anodal stimulation and decreased by cathodal stimulation. However, these dual-polarity effects have not been reported consistently, especially in the cognitive domain (Penolazzi, Di Domenico, Marzoli, Mammarella, Fairfield, Franciotti, et al, 2010; Jacobson et al., 2012c). Interestingly, the only study addressing motor inhibition processes indexed by the number of false alarms in a go/no-go task (Beeli et al., 2008) and delivering stimulation over the right DLPFC showed that, consistent with our findings, cathodal stimulation decreased inhibition, whereas anodal stimulation did not. This suggests that excitatory and inhibitory effects of anodal and cathodal stimulations may emerge by complex interactions between the stimulated areas and the task used to assess the behavioural effects of inhibitory control. The observed asymmetrical effect of anodal and cathodal stimulation does not change the meaning of the present results, which indicate that altering neural activity of the right DLPFC by administering tDCS during the retrieval practice of some items does not affect their subsequent retrieval but only the forgetting of non-practiced, related items.

3.4.3 Conclusions

The stimulation-induced abolishment of RIF observed here is likely dependent on active inhibition of competitor items and emphasizes the need for incorporating inhibitory mechanisms in general theories of episodic retrieval and forgetting at both behavioural and neural levels. Future studies should address the role of other areas potentially relevant for memory control and inhibitory processing (e.g., ventrolateral prefrontal cortex and the left DLPFC), whose involvement was demonstrated in fMRI studies addressing RIF-related phenomena (Wimber et al., 2009; Benoit & Anderson, 2012; Hanslmayr, Volberg, Wimber, Oehler, Staudigl, Harmann, et al., 2012). The combined use of tDCS and neuroimaging techniques might provide additional critical insights for understanding the functional dynamics underlying the interplay between these areas in orchestrating episodic memory processes (Venkatakrishnan & Sandrini, 2012).

4 A COMPARISON OF tDCS MONTAGES FOR MOTOR INHIBITION

This chapter has been published in **Stramaccia, D. F.**, Penolazzi, B., Sartori, G., Braga, M., Mondini, M., & Galfano, G. (2015). Assessing the effects of tDCS over a delayed response inhibition task by targeting the right inferior frontal gyrus and right dorsolateral prefrontal cortex. *Experimental brain research*, *233*(8), 2283-2290.

Many situations in our everyday life call for a mechanism deputed to outright stop an on-going course of action. This behavioural inhibition ability, known as response stopping, is often impaired in psychiatric conditions characterized by impulsivity and poor inhibitory control. Transcranial direct current stimulation (tDCS) has recently been proposed as a tool for modulating response stopping in such clinical populations, and previous studies in healthy humans have already shown that this non-invasive brain stimulation technique is effectively able to improve response stopping, as measured in a stop-signal task (SST) administered immediately after the stimulation. So far, the right inferior frontal gyrus (rIFG) has been the main focus of these attempts to modulate response stopping by the means of non-invasive brain stimulation. However, other cortical areas such as the right dorsolateral prefrontal cortex (rDLPFC) have been implicated in inhibitory control with other paradigms. In order to provide new insight about the involvement of these areas in response stopping, in the present study, tDCS was delivered to 115 healthy subjects, using five

stimulation setups that differed in terms of target area (rIFG or rDLPFC) and polarity of stimulation (anodal, cathodal, or sham). The SST was performed 15 min after the offset of the stimulation. Consistently with previous studies, only anodal stimulation over rIFG induced a reliable, although weak, improvement in the SST, which was specific for response stopping, as it was not mirrored in more general reaction time measures.

4.1 Introduction

On many occasions in our everyday life, we face situations that require suddenly stopping an on-going course of action. Often, this ability is essential to ensure ours or others' safety. For example, if while cooking we accidentally drop a boiling pot, we could instinctively try to catch it, as we often do when an object we are currently using falls toward the floor. However, this would probably result in getting burnt; hence, a process for outright stopping of an overlearned response to a situation which is similar, but not identical, to the one where such behaviour would have been appropriate is needed.

There is now a growing amount of evidence from neuroimaging studies (e.g., Aron, Behrens, Smith, Frank, & Poldrack, 2007; Chevrier, Noseworthy, & Schachar, 2007; Li, Huang, Constable, & Sinha, 2006) that response stopping is associated with activation in prefrontal areas, such as the inferior frontal gyrus (IFG), the dorsolateral prefrontal cortex (DLPFC), and the medial frontal gyrus, as well as in the basal ganglia. Among these areas, the right portion of the IFG (rIFG) has been proposed as the core component of a prefrontal-basal ganglia network selectively deputed to response stopping (e.g., Aron, Robbins, & Poldrack, 2014; but see Swick & Chatham, 2014, for a different viewpoint).

The involvement of rIFG in response stopping processes is also supported by lesion (e.g., Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003), and brain stimulation studies including both transcranial direct current stimulation (tDCS; Ditye et al. 2012; Jacobson et al. 2011) and Transcranial Magnetic Stimulation, (TMS, Chambers, Bellgrove, Stokes, Henderson, Garavan, Robertson, et al. 2006). Recently, non-invasive brain stimulation techniques (NIBS) such as tDCS and TMS have gained credit as promising tools for investigating and modulating the neural substrates of high-level cognitive functions (e.g., Vannorsdall et al. 2012; Metuki, Sela, & Lavidor, 2012; Penolazzi et al. 2010, 2013; see also Jacobson, Goren, Lavidor, & Levy, 2012b) and inhibitory control processes (Juan and Muggleton 2012). Indeed, the same techniques are being tested for use as therapeutic tools to improve symptoms in many psychiatric disorders, with a particular attention to tDCS, given its relative inexpensiveness and ease of use (e.g., Brunoni, Shiozawa, Truong, Javitt, Elkis, Fregni, et al. 2014; Feil & Zangen, 2010; Krause & Cohen Kadosh, 2013). Since inhibitory deficits have been implicated in many psychiatric conditions, inhibitory processes are among the favoured cognitive processes targeted in brain stimulation studies (see Juan and Muggleton 2012, for a review on both tDCS and TMS studies).

As regards response stopping, for instance, a recent study by Jacobson et al. (2011) has shown that anodal tDCS could be effectively used to modulate performance in a commonly used behavioural inhibitory task called stop- signal task (SST) (e.g., Logan & Cowan 1984). This modulation was obtained by targeting the rIFG. A subsequent study (Jacobson et al. 2012a) with EEG recordings provided supporting evidence for the efficacy of a rIFG direct current stimulation, showing a selective theta band reduction over the rIFG after anodal tDCS administration. On a later study, Ditye et al. (2012) found that combining anodal tDCS over the rIFG with training in a SST yielded a better improvement in response stopping than training alone, but only after the third session of four combined training and stimulation sessions.

Remarkably, different stimulation loci have been shown to successfully modulate performance in other inhibitory tasks. For example, Beeli et al. (2008) found an increase in false alarms in a go/no-go task that followed cathodal stimulation of the right prefrontal region. In the same vein, Penolazzi, Stramaccia, Braga, Mondini, & Galfano (2014) showed that cathodal tDCS over the right dorsolateral prefrontal cortex (rDLPFC) during a retrieval-practice task induced a reduction in retrieval- induced forgetting, a measure of forgetting which is thought to reflect the intervention of an inhibitory process deputed to selective retrieval from competing memories (Anderson, 2003).

In the present study, we aimed to address two main questions related to the literature discussed above. Firstly, we aimed to address the persistence of the modulatory effects of tDCS in response stopping reported in previous studies that delivered electrical stimulation over the prefrontal cortex (Ditye et al. 2012; Jacobson et al. 2011). To this end, we adopted a tDCS protocol where participants were asked to perform a standard SST 15 min after the offset of the stimulation (delayed task).

The SST probes inhibitory motor control by requiring participants to withhold a response that has already been triggered. In a typical SST, participants take part in a choice RT task (e.g., a shape judgment task) and are instructed to withdraw their response whenever they hear a stop signal (e.g., a sound), which can be presented shortly after the target stimulus has appeared. Trials that include the stop signal are usually quite infrequent (e.g., 25 %) compared to trials where participants must respond (go trials). This is assumed to elicit a bias in the participants, who are somehow “pushed” into responding. According to the horse- race model of response inhibition in the SST (e.g., Logan & Cowan 1984; Osman, Kornblum, & Meyer, 1986), during a stop trial, the inhibitory process triggered by the stop signal races against the on-going response process triggered by the tar- get. Response inhibition is therefore successful whenever the former process acts faster, leading to inhibition of the initiated response. Critically, the individual probability of successful inhibition in a given stop trial is a function of the stop-signal delay (SSD), i.e., the time elapsed between the target stimulus and the stop-signal in that particular trial. Indeed, longer SSD mean that the response process will be closer to execution when the competing inhibitory process is triggered. Inhibitory performance in the SST is typically measured with the stop-signal reaction time (SSRT) index, which is computed as the difference between mean RT in the go trials (no-signal RT, NSRT) and the mean SSD in the trials where they must interrupt response. SSRT is interpreted as the covert latency of the response stopping process, so that shorter SSRTs indicate a more efficient response inhibition. The task is often kept challenging by using an adaptive staircase procedure which adjusts the SSD in a trial-wise fashion. This procedure is intended to keep the probability of effectively inhibiting response at ~0.5. Previous work has shown that SSRT could also yield clinical relevance, since high SSRTs had been associated with several psychiatric conditions such as attention-deficit hyperactivity disorder (Depue, Burgess, Willcutt, Ruzic, & Banich, 2010), eating disorders (Wu, Giel, Skunde, Schag, Rudofsky, de Zwaan, et al., 2013a), obsessive–compulsive disorder (Boisseau, Thompson-Brenner, Caldwell-Harris, Pratt, Farchione, & Harrison Barlow, 2012), schizophrenia (Enticott, Ogloff, & Bradshaw, 2008), and substance abuse disorder (Fillmore and Rush 2002).

In the context of our study, we decided not to administer the SST both immediately after tDCS and after this short delay, because we did not want to make the experimental session too demanding for our participants (which, in turn, also allowed us to test a reasonably larger sample com- pared to standard tDCS studies). As for the effects observed immediately after tDCS, we relied on the pattern observed in previously published reports attesting that stimulation over both the right IFG and right DLPFC is effective in modulating inhibitory processing (Beeli et al. 2008; Jacobson et al. 2011, 2012a; see Juan and Muggleton 2012, for a review). In addition, we decided to test participants after 15 min because this time delay seemed a good compromise between our aim of estimating the short-term effects of single session tDCS and the need to keep the duration of the experimental session not too long for our participants. In this regard, assessing the persistence of tDCS-induced effects on behaviour is particularly relevant. Indeed, on the one hand, many studies have shown that, depending on stimulation parameters and montage, tDCS is able affect cortical excitability up to several hours after the current has been delivered (Batsikadze et al. 2013). However, on the other hand, much less effort has been devoted to assess whether measures of behavioural performance mirror this long-lasting effects. Hence, although some recent studies have already suggested tDCS effects on delayed cognitive tasks related to high-level cognitive processes (Falcone, Coffman, Clark, & Parasuraman, 2012; Penolazzi et al. 2010, 2013), the durability of stimulation effects is in need of further investigation. The second aim of the present study was to clarify the role of areas other than the rIFG in response stopping. To this purpose, anodal, cathodal, or sham stimulations were delivered to either the rIFG or the rDLPFC in five groups of human participants. We targeted the rDLPFC to probe the involvement of this area in response stopping, thus contributing to the debate about the specificity of the neural underpinnings of inhibitory processes. Assuming that our tDCS protocol was capable of inducing long-lasting neuromodulatory effects, and in light of pre-existing evidence of the association between anodal tDCS and faster SSRT (i.e., more effective response inhibition; Ditye et al. 2012; Jacobson et al. 2011), our main prediction was to observe beneficial effects in inhibitory performance—if any—in the experimental group that received anodal stimulation over the rIFG. In light of the findings reported by Beeli and Colleagues (2008) and Penolazzi and Colleagues (2014), we expected to observe also a possible modulation of SSRT when administering tDCS over rDLPFC.

4.2 Methods

4.2.1 Participants

One hundred and fifteen undergraduate students participated in the study (29 males, *M* = 23.37, SD = 2). All participants met the inclusion criteria for taking part in brain stimulation protocols (Bikson et al. 2009; Nitsche et al. 2003), had normal or corrected-to-normal vision, and did not suffer from hearing impairment. All participants gave a written informed consent before taking part in the study, which was performed in accordance with the principles of the Declaration of Helsinki and approved by the local ethical committee. Participants were randomly assigned to one of four experimental groups or to a control group and were naïve to the purpose of the experiment.

4.2.2 Stop-Signal Task (SST)

We administered the SST provided within the STOP-IT software (Verbruggen,, Logan, & Stevens, 2008). The task consisted of two experimental blocks of 64 trials each (128 total), and a shorter practice block (32 trials) at the beginning to ensure that participants understood the instructions. The primary task engaged participants in a choice reaction time test, where they had to respond as fast and accurately as possible. Each trial began with a 250-ms central fixation (+), followed by a visual stimulus (either a square or a circle) that stayed centrally on screen until participants responded or 1.250 ms had elapsed. Both fixation and stimuli were presented in a white font on a black background. The ISI was 2000 ms and was independent of RTs. Participants used the keyboard to respond, and they had to press “A” for squares or “L” for circles. On 25 % of the trials, shortly after stimulus onset, a sound (750 Hz, 75 ms) was presented through loudspeakers as a stop-signal. When the stop-signal was presented, participants had to hold back their response. The task began with a stop-signal delay of 250 ms, which then increased or decreased by 50 ms after each successful or unsuccessful stopping trial, respectively. Under this tracking procedure, participants correctly stopped half the responses, which is required by the method used to calculate SSRT. According to the horse-race model (Logan and Cowan 1984; Osman et al. 1986), SSRT is calculated as the difference between mean RT in the trials where participants must respond and mean SSD in the trials where they must withhold response.

The SST used here is schematically represented in Figure 4.1.

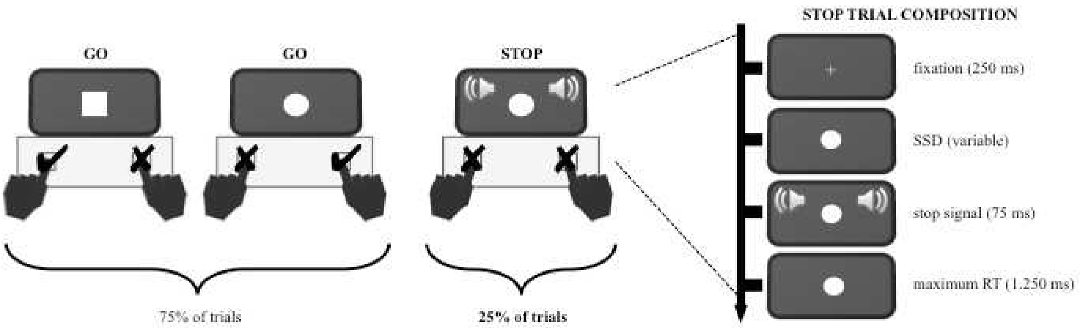

Figure 4.1 Illustration of the different trial types in the stop-signal task (SST) and sequence of events in a stop trial.

4.2.3 tDCS

The study adopted the procedures for safe administration of NIBS (Bikson et al. 2009; Nitsche et al. 2003). In the active stimulation conditions, we delivered a 1.5 mA direct current for 20 min (fade-in/fade-out time: 60 s) with a battery-driven current stimulator (BrainStim, EMS, Italy), wired to a pair of surface saline-soaked sponge electrodes (16 cm2, resulting in a current density of 0.094 mA/cm2). In the sham (i.e., control) condition, instead, we delivered a 1.5 mA direct current for 15 s at the beginning and 15 s at the end of the stimulation time. We choose to stimulate with parameters that lead to a higher current density (i.e., intensity/electrode size) than previous studies (Ditye et al. 2012; Jacobson et al. 2011), in order to increase the spatial focality of tDCS effects (Nitsche, M. A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, et al., 2007).

We used a single blind, between-group design: Depending on the random assignment to conditions, participants could receive either anodal stimulation over the right IFG (*N* = 20; 6 males, *M* = 23.95, SD = 2.26), cathodal stimulation over the right IFG (*N* = 20; 8 males, 23.35, SD = 1.53), anodal stimulation over the right DLPFC (*N* = 20; 3 males, *M* = 23.65, SD = 2.08), cathodal stimulation over the right DLPFC (*N* = 20; 3 males, 23.10, SD = 2.57), or sham stimulation on either right DLPFC or right IFG (*N* = 35; 9 males, *M* = 23.06, SD = 1.61). In all conditions, electrode placement followed the 10–20 EEG system (Jasper 1958). The rIFG was identified as the area underlying the crossing point between T4-Fz and F8-Cz (Jacobson et al. 2011), the rDLPFC was identified as the area underlying F4, and the reference electrode was positioned above the left supraorbital area in all groups. An overview of the different tDCS montages used here is shown in Figure 4.1 (see both Panel A and B). As anticipated earlier, we choose the right IFG as a stimulation site because we sought to extend previous findings on SST targeting this area with tDCS. Furthermore, we stimulated the right DLPFC, since previous studies suggest its involvement in several tasks probing response stopping (Hughes, Budd, Fulham, Lancaster, Woods, Rossell, et al. 2014) as well as other inhibition-related phenomena (Beeli et al. 2008; Bermpohl, Fregni, Boggio, Thut, Northoff, Otachi, et al., 2006;

Penolazzi et al. 2014). Both at the beginning and at the end of the procedure, participants completed a self-report questionnaire about arousal and mood as further control to rule out alternative accounts of tDCS effects on response stopping. At the very end of the experiment, participants completed a self-report questionnaire (Fertonani et al. 2010) dealing with unpleasant sensations (if any) due to tDCS stimulation.

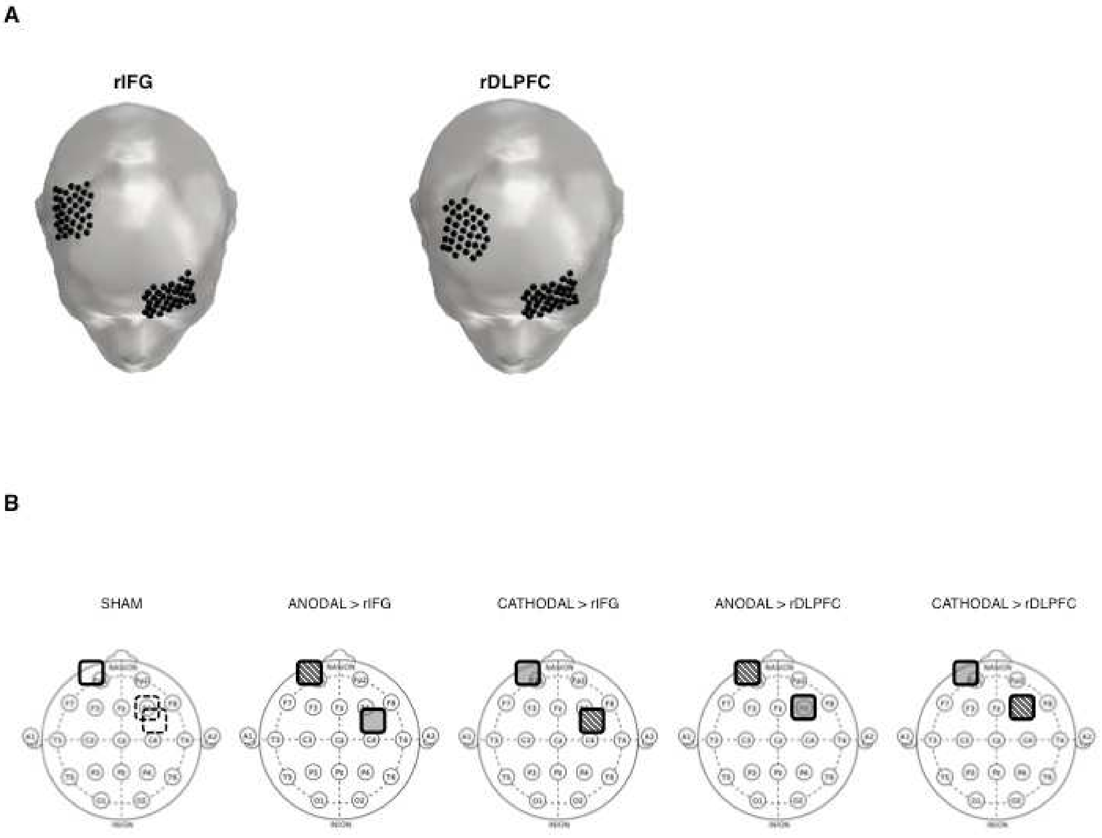

Figure 4.2 A) Schematic illustration of the tDCS montages used in the study. Anodal electrodes are *gray*, cathodal electrodes have an *oblique texture*, inactive electrodes are *transparent*. *Dotted lines* in the Sham group indicate that for half participants the montage involved the rIFG, whereas for the remaining participants it included the rDLPFC. Electrodes are not drawn to scale. B) Modeled image of the human head schematically showing the position of the electrodes in the two montages aimed at targeting the rIFG (on the left side) and the rDLPFC, displayed on the left and right sides respectively (rendered with the COMETS toolbox in MATLAB; Jung et al. 2013).

4.2.4 Procedure

The experiment began with a 20-min tDCS session. About 15 min after the end of the stimulation, participants performed the SST. During the stimulation and the 15-min interval prior to the SST, participants performed filler tasks (i.e., they were required to learn word-pairs and to fill paper-and-pencil questionnaires) aimed at delaying SST administration but unrelated to motor inhibition processes.

4.3 Analysis and Results

Data from one participant of the Cathodal rIFG Group were lost due to a technical failure of the software. In order to investigate whether tDCS effectively and selectively modulated inhibitory performance in the SST, we first calculated SSRT and NSRT separately for each participant using the ANALYZE-IT software (Verbruggen et al. 2008), which comes as companion software to STOP-IT. To calculate individual SSRT, ANALYZE-IT first computes the mean RTs for all trials without a stop signal and then subtracts the mean stop-signal delay from this value (Verbruggen et al. 2008). First, we performed a between-participant ANOVA with Group as factor. Subsequently, we performed a series of independent samples *t* tests to compare SSRT of each experimental group with SSRT of the control, sham stimulation group. Independent samples *t* tests on NSRT were also carried out to assess any effect of the stimulation on RTs in go trials, which, if found, could be attributed to mechanisms different from those responsible of SSRT, thus undermining the selective effect of tDCS on response stopping. To minimize the occurrence of type II error while controlling for type I error, we adjusted the α level for the number of comparisons according to the False Discovery Rate procedure for multiple testing (Benjamini and Hochberg 1995). This latter approach is well established (e.g., Betta, Galfano, & Turatto, 2007; Galfano, Betta, & Turatto, 2004; Stefan, Cohen, Duque, Mazzocchio, Celnik, Sawaki, et al. 2005) and is particularly suited and powerful for analyzing RT data, as shown by Montecarlo studies (Pastore, Nucci, & Galfano, 2008).

The tracking procedure was effective in keeping the overall probability (respond/signal) at about 0.5 for all participants. The main effect of Group in the

ANOVA approached significance, F (4,114) = 2,221, p = 0.07. The FDR-corrected t tests revealed that only the comparison between SSRT of anodal rIFG group and control group showed a significant difference, $t(53) = 2.281$, $p < 0.02$, with lower SSRT (indicating better inhibitory performance) for the anodal right IFG group compared to the control group (Figure 4.3 ; Table 4.1). No significant differences between groups emerged on NSRT (Figure 4.4).

Analyses of questionnaires revealed no effect of stimulation on any of the items (i.e., mood/arousal and sensations perceived during stimulation) for participants assigned to sham and real stimulation groups. No differences in the percentage of correctly recalled word pairs (filler task) emerged as a function of group.

Table 4.1 Mean percentage and 95 % confidence intervals of SSRT and NSRT as a function of stimulation group.

Stimulation Group	SSRT	NSRT
Sham	291,18 (276.97/305.38)	568.66 (521.97/615.35)
Anodal rIFG	264.02 (243.24/284.80)	583.86 (511.25/656.46)
Cathodal rIFG	272.57 (254.15/291.00)	587.43 (503.47/671.40)
Anodal rDLPFC	291.38 (277.03/305.72)	525.66 (484.91/566.38)
Cathodal rDLPFC	287.58 (270.61/304.54)	590.05 (527.04/653.05)

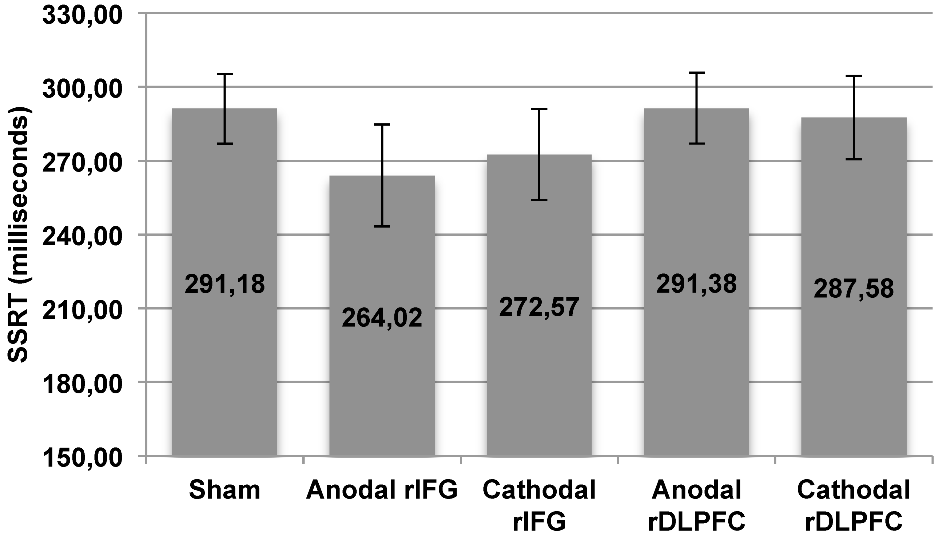

Figure 4.3 Mean (95 % confidence intervals in *brackets*) SSRT values for each stimulation group.

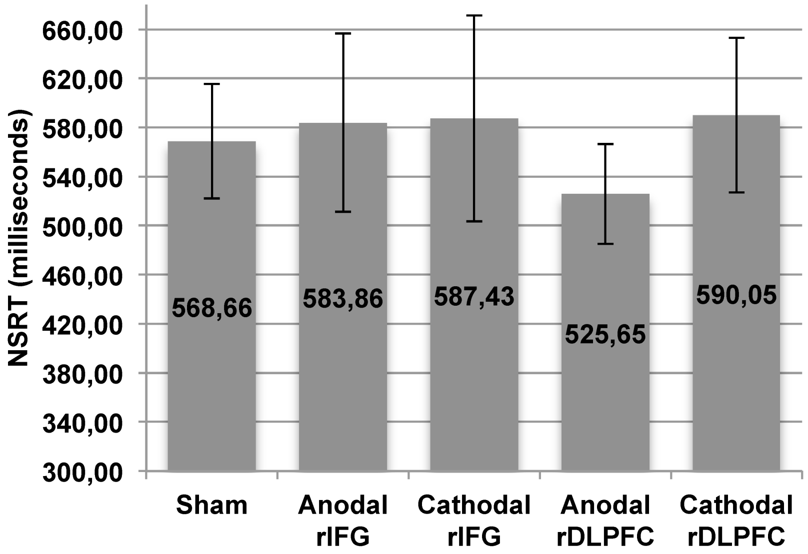

Figure 4.4 Mean (95 % confidence intervals in *brackets*) NSRT values for each stimulation group.

4.4 Discussion

Previous research has shown that delivering tDCS to the right prefrontal cortex can improve the ability to outright stop an initiated course of action (Jacobson et al. 2011), an inhibitory process often termed response stopping, which is recruited whenever a change in the context occurs and an overlearned, prepotent, behavioural response needs to be suppressed because inappropriate to the updated environment.

For the purpose of extending previous findings on the modulation of the response stopping ability, the present study tested the hypothesis that tDCS to the rIFG could improve SSRT even on a delayed SST, whereas in previous studies (Ditye et al. 2012; Jacobson et al. 2011) participants engaged in the SST immediately following tDCS application. Overall, the observed results confirmed this hypothesis, as SSRTs were lower for participants assigned to the rIFG anodal tDCS condition compared to those assigned to the control group. Interestingly, the magnitude of such improvement was similar to that reported in previous studies (Ditye et al. 2012; Jacobson et al. 2011). This finding indicates that, in the domain explored by the pre- sent study, at least for brief post-stimulation periods (i.e., about 15 min), the magnitude of behavioural effects induced by tDCS does not seem to diminish. It is worth noting that this response stopping improvement is unlikely to result from a general cognitive enhancement. Indeed, it is more likely to reflect a specific effect on a process selectively deployed during stop trials, because NSRT analysis failed to show any significant between-group difference.

In sharp contrast, delivering tDCS to the rDLPFC did not affect response stopping. This is remarkable if one considers that the stimulation sites were closely contiguous (but see Penolazzi et al. 2013, for similar results with partially overlapping tDCS montages), and that tDCS is generally described as characterized by a low spatial resolution (especially when compared to other, more invasive, neurostimulation techniques such as TMS). This finding might be prone to several interpretations. One possibility is that rDLPFC may be not involved in the process of response stopping as measured in the SST. Notably, however, this would not necessarily imply that rDLPFC plays no role in inhibitory processing, given that this area is known to be involved in other tasks that probe this cognitive function (e.g., Beeli et al. 2008; Penolazzi et al. 2014). Another possibility is that the stimulation-induced engagement of rDLPFC is short lasting and hence not evident in the pre- sent (delayed) protocol.

Alternatively, tDCS parameters implemented in the protocol adopted in the present study, which were higher in both intensity and duration compared to previous studies (Ditye et al. 2012; Jacobson et al. 2011), could have been sub-optimal to produce an effective modulation of the rDLPFC. Likely, all the different factors illustrated above played some role in accounting for the absence of tDCS-induced modulations when targeting the rDLPFC. Further studies focusing on the manipulation of both tDCS parameters (e.g., density and duration) and stimulation-task delay will possibly shed light on the relative weight of the different alternatives illustrated above.

One may wonder whether the present findings may reflect a different engagement of the rIFG and rDLPFC networks by the filler tasks used during stimulation to delay the SST administration. We discard this alternative account based on neuroimaging evidence (e.g., Kuhl et al. 2007) revealing that both the rIFG and the rDLPFC are critically involved in the cognitive processes called into play by our filler memory tasks as parts of a broad prefrontal network considered to support cognitive control.

4.4.1 Different roles for rIFG and rDLPFC in response stopping

Recently, Hughes et al. (2014) have proposed that performance in the SST would be supported by two dissociable networks, one including the rIFG responsible for phasic, transiently activated, response stopping and the other comprising the rDLPFC involved in tonically maintaining the stopping rule (see also Chikazoe, Jimura, Hirose, Yamashita, Miyashita, & Konishi, 2009). Within this perspective, it could be well possible that perturbing the neural underpinnings of either process would produce different effects on response stopping, as the two processes could be not only differently sensitive to disruption or enhancement by means of tDCS, but even differently related to behavioural performance in the SST. The version of the SST implemented in the present experiment was more apt to probe the phasic, reactive, component of response inhibition. In this regard, a recent study by Cunillera and Colleagues (2014) used a hybrid response-stopping task which allowed investigating both the tonic and the phasic components of response inhibition. Stimulating the rIFG modulated both components. Using a similar task by targeting both the rIFG and the rDLPFC might represent a promising avenue to disentangle the specific contribution of these areas in the two types of response stopping.

Research so far suggests a role of the rIFG in response stopping. However, there is far from unanimous agreement on whether this inhibitory process is critically orchestrated by the IFG and mainly dependent on the right hemisphere (Aron et al. 2014; Banich & Depue 2015), or else results from the combined action of a more widespread network of areas (Schall & Godlove 2012; Swick, Ashley, & Turken, 2011). Moreover, studies addressing the role of areas other than the rIFG in response stopping obtained mixed results. For example, Hsu et al. (2011) modulated inhibition as measured by non-cancelled rates in a SST by delivering tDCS over the pre- supplementary motor area, but failed to observe a significant effect on SSRT. Finally, Berryhill et al. (2014) failed to find any effect of a stimulation protocol similar to the one used by Hsu et al. (2011) on response inhibition in a go/no-go task (Swick et al., 2011).

As a final remark, given the importance of the reference electrode in determining the current flow distribution, it is worth noting that, in tDCS studies, findings should generally be ascribed to the combined effect of the active and the reference electrodes than to the effect of stimulated target areas in isolation. Therefore, our results are more likely to reflect the joint effect of stimulation of the rDLPFC and left frontal pole on the one hand, and stimulation of the rIFG and left frontal pole on the other hand. Nevertheless, it is important to note that, although the same reference was used, stimulation of two close but distinct areas resulted in different behavioural effects related to the phenomenon under investigation that, in turn, highlights that these two areas contributed to the investigated process to a different extent.

4.4.2 Conclusions

In summary, the results obtained in the present study support the notion that tDCS-induced effects can be relatively long lasting by exploring a different cognitive domain with respect to those already investigated in the literature (Falcone et al. 2012; Penolazzi et al. 2010, 2013). Interestingly, the present findings add to the growing amount of evidence that the rIFG is critically involved in response stopping. In our opinion, the current state of the literature suggests that the rIFG is the most reliable target for brain stimulation studies aimed to modulate response stopping in the SST, and perhaps favoured target for clinical investigations interested in developing therapeutic proto- cols based on NIBS (especially tDCS) with regard to clinical populations that suffer from lack of inhibitory control.

5 tDCS MODULATION OF MEMORY CONTROL AND MOTOR STOPPING

This chapter is in preparation for submission as **Stramaccia, D. F.**, Penolazzi, B., Altoè, G., & Galfano, G. Cathodal tDCS to the rIFG Disrupts Control over Interference in Memory Retrieval.

In a previous study, we demonstrated that tDCS over the right PFC can modulate performance in suppression of competing memories during selective retrieval. Specifically, cathodal stimulation to the right DLPFC abolished the detrimental effects of selective memory retrieval, whereas the beneficial effects of repeated practice were unaffected. Here, we turn to the modulation of a different brain area of the right PFC, i.e., the right IFC. To this end, we delivered tDCS over the right IFG during the retrieval-practice phase in a standard retrieval-practice paradigm. In Experiment 1, fifty-three healthy volunteers were randomly assigned to anodal, cathodal, or sham-control groups. In Experiment 2, we tried to further clarify the effects of tDCS over the right IFG, and also tested modulation of motor stopping performance in the SST. Across the two experiments, the groups showed comparable benefits for practiced items. In contrast, with particular regard to Experiment 2, the anodal and cathodal group exhibited no RIF, compared to the sham control group. Importantly, influence analyses on the semantic categories employed here revealed diverging patterns of results in different subsets of the experimental material. In contrast, we did not find any evidence of modulation of motor stopping performance.

5.1 Introduction

Cognitive control refers to a set of essential abilities that allow us to maintain an adaptive behaviour within an ever-changing environment. From abruptly stopping a course of action that is not optimal anymore (Verbruggen & Logan, 2008), to suppressing unwanted or irrelevant memories from coming to mind (Anderson & Hanslmayr, 2014; Storm & Levy, 2012), cognitive control is constantly recruited in our everyday life. According to some Authors, the inferior frontal gyrus (IFG) orchestrates inhibitory control across cognitive domains via top-down regulation of other cortical and subcortical areas depending on the task at hand (e.g., Aron et al., 2014). In this view, the IFG represents a key node for the neural networks deputed to both motor stopping and memory suppression. The two abilities, in turn, may constitute different but interrelated instances of inhibitory control. Levy and Anderson (2002) also described a similar perspective. In their model, response selection in both action and memory might be supported by inhibitory mechanisms that share similar neural substrates mainly located in the prefrontal cortices. In particular, the Authors pointed to the dorsolateral prefrontal cortex (DLPFC) as a putative central hub for the cognitive processes mediating inhibitory control in both domains, whereas the anterior cingulate cortex (ACC) would be deputed to the role of conflict detector and signaller to the DLPFC.

In respect to cognitive control over memory retrieval, neuroimaging evidence suggests a role for both the DLPFC and the IFG during selective retrieval from episodic memory in the face of interference arising from competing memory traces (Wimber et al., 2008, 2009, 2015; see also 1.4.4). Moreover, these studies suggested a greater contribution of right prefrontal areas, similar to what as been reported in other work on related domains (e.g., Benoit & Anderson, 2012, in voluntary forgetting, and Goghari & MacDonald III, 2009, in the go/no-go task).

Because we have already investigated the role of right DLPFC (rDLPFC) in resolving interference from competing memory traces, the present study focused on testing the involvement of the right IFG (rIFG) instead. We hypothesized that interfering with the activity of this particular brain region during a task that putatively relies on the ability to suppress interfering memories would affect later recall of these memories. To this end, we targeted the rIFG with transcranial Direct Current Stimulation (tDCS) in healthy volunteers performing a retrieval practice paradigm (RPP; Anderson et al., 1994; see Murayama et al., 2014, for a recent meta-analytical review), which is commonly used to assess the individual ability to overcome interference in memory.

In the RPP, participants first study a series of category-exemplar word pairs (e.g., “FRUIT-CHERRY”). Immediately after that, they repeatedly perform active retrieval practice on half the exemplars from half the categories (e.g., “FRUIT-CHE____”). Finally, participants’ memory for all the experimental material is tested (e.g., “FRUIT-C____”). The RPP allows measuring two distinct effects. On the one hand, the well-known superiority of memory performance on subsequent recall of study material that underwent additional practice, compared to different study material that was unrehearsed, typically referred to as facilitation (FAC) effect in the context of the RPP. On the other hand, the observation that selectively practicing retrieval of certain exemplars leads to impairment of unrehearsed exemplars that share the same category cue (e.g., FRUIT-), compared to unrehearsed exemplars belonging to different categories (e.g., WEAPONS-). The latter phenomenon has been called retrieval-induced forgetting (RIF), to highlight the fact that the very act of selectively retrieving memory traces is responsible for the later inaccessibility of related memory traces. According to an influential model in the RIF literature (Anderson, 2003) during selective retrieval practice on a subset of the study material, inhibitory mechanisms would be implicitly recruited to overcome interference from related exemplars by weakening the memory traces associated to them, thereby promoting retrieval of the cued exemplars. Therefore, in the final test phase of the RPP, the inhibited exemplars would be less available to recall from memory.

The reasons for employing tDCS as a method to modulate the cognitive processes underlying RIF are twofold. Firstly, in a previous study from our group (Penolazzi et al., 2014), we used a similar approach to provide the first causal evidence for the involvement of DLPFC in control over interfering memories, as indexed by RIF. Specifically, RIF was gradually reduced in two stimulation groups, which received anodal and cathodal tDCS respectively, compared to a sham control group. In particular, on average, participants receiving cathodal tDCS, which is thought to inhibit endogenous activation in the target area, showed the least amount of RIF, to the point of observing a reversed effect, compared to a sham stimulation (i.e., control) group, where a significant effect was observed. Moreover, our manipulation did not affect the amount of FAC in any of the experimental groups.

The second reason to for using tDCS is that a great interest has recently developed into investigating strategies and techniques that could allow modulating or even enhancing cognitive control in healthy individuals, as well as potentiating recovery of normal control abilities in people suffering from a range of psychiatric and neuropsychological conditions characterized by impairments in this ability. To this end, transcranial electrical stimulation (tES) techniques may offer a unique opportunity to provide a feasible and economical modulation strategy. In particular, many studies already employed transcranial direct current stimulation (tDCS) to modulate performance in behavioural tasks related to inhibitory control, with overall promising results (e.g., Ditye et al., 2012; Jacobson, Javitt, & Lavidor, 2011; Metzuyanim-Gorlick & Mashal, 2016; Penolazzi et al., 2014; Stramaccia, Penolazzi, Sartori, Braga, Mondini, & Galfano, 2015). In addition to that, tDCS has proven to be relatively safe and tolerable (Bikson et al., 2016), and easily manageable for autonomous use (Charvet, Kasschau, Datta, Knotkova, Stevens, Alonzo, et al., 2015; Kasschau, Reisner, Sherman, Bikson, Datta, & Charvet, 2016). Finally, within the specific context of the RPP, tDCS allows for modulation of performance without excessive disruption of the typical experimental procedure, and with minimal discomfort for the participants as well.

In the present work, we delivered anodal, cathodal, or sham stimulation, to three groups of healthy participants performing an RPP that was identical to that employed in our previous study (Penolazzi et al., 2014). If rIFG plays an important role in RIF, we may expect to observe a pattern similar to our previous study, with cathodal stimulation showing the greatest impact on the behavioural index of successful inhibition. On the contrary, the absence of major group differences could signify that rIFG is not primarily involved in this internally directed instance of cognitive control, compared to the well-established contribution of the rDLPFC (Penolazzi et al., 2014; Wimber et al., 2008, 2009, 2015). Moreover, in keeping with the inhibitory account of RIF, we did not expect to observe any stimulation effects on FAC, as the two phenomena would rely on different neural substrates and, different cognitive processes. For the same reason, we looked at the correlation between RIF and FAC in the three groups, expecting not to find evidence of an association between the measures, as posited by the strength independence assumption of the inhibitory account of RIF (Anderson, 2003; Storm & Levy, 2012; see also 1.2.4).

5.2 Experiment 1

5.2.1 Methods

5.2.1.1 Participants

The ethical committee for psychological research of the University of Padua approved the study, which was performed in accordance with the principles of the Declaration of Helsinki. All participants underwent an eligibility screening for the tDCS procedure, and provided an informed consent prior to their participation and a final consent at the end of the experimental procedure. 53 healthy volunteers (18 males) aged between 21 and 27 years (*mean age* = 23.30, *SD* = 1.70; *mean years of education* = 17.43, *SD* = 1.64) took part in the experiment. All participants were Italian native speakers with no history of neurological disease, psychiatric disorders, heart conditions, severe head injury, seizures (personal or in first degree relatives), recurring syncope, or learning disability. Additional exclusion criteria included pregnancy, presence of metal in the face or the head (other than dental work), presence of skin conditions on the scalp or history of severe dermatitis, on-going or recent use of medical prescriptions other than contraceptives, and excessive use of alcohol on the day prior to the stimulation session.

5.2.1.2 Retrieval Practice Paradigm (RPP)

We used the RIF effect as an index of memory suppression (Anderson et al., 1994; Storm & Levy, 2012), and we administered a typical three-phase RPP in order to obtain an individual measure of the effect. The RPP employed here was identical to that used in our previous work (Penolazzi et al., 2014). Our paradigm included 96 category-exemplar word pairs (e.g. “FRUIT-CHERRY”), divided by 8 semantic categories, with twelve exemplars for each category. We selected and adapted all the material from the categorical productions norm for the Italian language by Boccardi and Cappa (1997), according to the following criteria: (i) within each category, we included seven exemplars with high taxonomic strength (strong exemplars) and five with low taxonomic strength (weak exemplars), according to the production norms; (ii) words within the same category always had a different initial letter; (iii) we tried to keep semantic associations between and within categories to a minimum, to avoid semantic integration (Goodmon & Anderson, 2011); (iv) we included only words that were no longer than ten or no shorter than four letters; v) we chose only unambiguous, non-compound words for both exemplars and categories.

It is worth noticing that participants were completely naïve to the procedure: participation to previous studies using this behavioural paradigm constituted an additional exclusion criterion. The RPP used here is schematically represented in Figure 3.1.

In the study phase, we instructed the participants to memorize all of the 96 category-exemplar word pairs, by relating each exemplar to its category. We also informed them that they would have been tested later on the exemplars. Study trials began with a brief fixation (500 ms), followed by a blank screen (500 ms); subsequently, one category-exemplar word pair was presented on screen (2500 ms), followed by a blank screen (500 ms). We delivered the stimuli in a randomized blocked-by-category order, where each block contained one exemplar from each semantic category, with the additional constraint that two items from the same category could not be presented one after another.

In the practice phase, participants repeatedly practiced the weak exemplars of half the semantic categories (four repetitions of 30 exemplars, 72 trials in total). In the practice trials, we provided the category and the first three letters of each exemplar (e.g. “FRUIT-CHE___”) to the participants, and we instructed them to answer vocally with the name of the specific exemplar associated to the particular cue in full (4000 ms). Presentation of practice stimuli was randomized, and each practice item was preceded by a fixation cross for 1 s, followed by a blank screen lasting 1 s. The intertrial interval consisted of a blank screen lasting 1 s. We labelled the practiced weak exemplars as RP+ items, the non-practiced strong items from practiced categories as RP- items, the weak non-practiced items from non-practiced categories NRP+ items, and the strong non-practiced items NRP-. NRP+ and NRP- items served as controls for RP+ and RP- items, respectively. Importantly, practicing weak exemplars only should boost the RIF effect due to increased competition from the remaining strong exemplars (Anderson, 2003). We used four lists of categories to fully counterbalance the practiced categories across groups. As a result, all semantic categories contributed equally to all four types of items. We presented the stimuli in a similar order to the previous phase.

In the final test phase, we presented again all the stimuli from the initial study phase (96 trials). Presentation format and timing, response modality, and instructions, were the same as above, the only difference being that we provided the participants with the category plus the first letter of an exemplar only (e.g. “FRUIT-C____”). We presented the stimuli in a similar order to the previous phases, with the additional constraint that all RP- items were presented before all the NRP-, RP+, and NRP+ items, in order to control for output interference at test, which is known to inflate the RIF effect (Anderson, 2003).

5.2.1.3 transcranial Direct Current Stimulation (tDCS)

We used a battery-driven Direct Current stimulator (BrainStim, EMS, Italy) wired to pair of surface 4 cm × 4 cm conductive rubber electrodes inserted in saline-soaked sponges, and secured to the scalp with rubber bands. We delivered anodal, cathodal, or sham tDCS over the rIFG at 1.5 mA (current density of 0.09 mA/cm^2). We located the target area at the FC4 position in the EEG 10-20 system (Jasper, 1958) as the crossing point between T4-Fz and F8-Cz (e.g., Jacobson et al., 2011), and we placed the (active) reference electrode (anode, cathode, or sham according to stimulation group) on the left supraorbital area (see Figure 4.2, panel B, left side). We selected the stimulation parameters according to our previous work (Penolazzi et al., 2014). We used a single blind, between group design: Participants were randomly assigned to anodal (N = 17, 6 males, *mean age* = 23.65, *SD* = 1.80), cathodal (N = 16, 6 males, *mean age* = 23.25, *SD* = 1.34), or sham tDCS (N = 20, 6 males, *mean age* = 23.05, *SD* = 1.90). Stimulation begun prior to the practice phase of the RPP, and it lasted 20 minutes in total for all three groups, covering the entire practice phase. In the active tDCS conditions, we ramped up the stimulation to 1.5 mA over 30 s, maintained it for 20 minutes, and ramped it down over 30 s again at the end to minimize unpleasant sensations. In the Sham stimulation group, we ramped up and then immediately ramped down stimulation over 15 s at both the beginning and end of the protocol, an approach that is commonly used to blind participants in tDCS experiments (e.g., Gandiga et al., 2006; Brunoni, Nitsche, Bolognini, Bikson, Wagner, Merabet, et al., 2012).

5.2.2 Procedure

As soon as participants completed the screening process for tDCS and gave written consent, we prepared the montage for the tDCS, without starting the stimulation. Participants first performed the study phase of the RPP. After that, we checked the integrity of the montage, and turned the stimulation on. As soon as the participants felt comfortable with the stimulation (always within moment from the initial ramp up period), they performed the retrieval practice phase of the RPP, followed by filler questionnaires whose contents were unrelated to the experimental material. Stimulation ended shortly before completion of the questionnaires, and we removed the montage before proceeding with the final test phase of the RPP. Upon completion of the experimental procedure, participants also filled out a self-report questionnaire about unpleasant sensations related to tDCS (Fertonani et al., 2010).

Figure 3.1 and Figure 3.2 show a schematic representation of the RPP and overall experimental procedure used here.

5.2.3 Analysis

We analysed recall accuracy in the test phase of the RPP as the main dependent variable. Exact answers only were considered as correct, with the exception of occasional and obvious spelling mistakes. In keeping with the typical approach in the RIF literature, we analysed FAC-relevant items (RP+ and NRP+) separately from RIF-relevant items (RP- and NRP-). We analysed the data with R (R Core Team, 2016), and fitted generalized linear (logistic) mixed models using the glmer procedure in the lme4 package (Bates, Maechler, Bolker, & Walker, 2015), which is more appropriate to examine accuracy data with respect to repeated measures ANOVA (e.g., Jaeger, 2008).

Following Baayen, Davidson, and Bates (2008), we entered item type, stimulation group, and the possible interaction term, as fixed effects, and subject and category as random intercept terms, in order to account for both subject- and item-related variability. In particular, we entered category in the model as a random factor to counter the well-known *language-as-fixed-effect* fallacy (e.g., Clark, 1973), while keeping the stability of the model (i.e., avoiding convergence issues due to the relatively small number of observations per single item) and the experimental grouping of the stimuli within categories in mind. We used the Akaike's information criterion (AIC; Akaike et al., 1973) transformed to conditional probabilities for each model, i.e., AIC weights (Wagenmakers & Farrell, 2004) to select the models that more appropriately described our data throughout the whole data analysis. Indeed, AIC weights improve the interpretation and the accessibility of results for further analyses, provide a deeper insight on the features of the competing models, and quantify conclusions based on AIC (Wagenmakers & Farrell, 2004). We employed the "qpcR" package (Spiess, 2014) to compute AIC weights. Post-hoc contrasts for selected models were then computed with the "testInteraction" function in the "phia" package (De Rosario-Martinez, 2015). Moreover, "effects" package (Fox, 2003, Fox & Hong, 2009) was used to display effects, and the "stargazer" package (Marek, 2015) was used to create the tables reporting model comparisons.

Finally, we performed correlational analyses to assess whether RIF and FAC were uncorrelated, as posited by the strength independence tenet of the inhibitory account of RIF (Anderson, 2003).

5.2.4 Results

Mean proportions of recall in the final test phase for each item type and FAC/RIF effects are reported in Table 5.1).

Table 5.1 Mean proportion of recall in the final test phase as a function of item type/effect and stimulation group.

	Final Test Phase					
	Item Type					
Stimulation Group	RP+	NRP+	RP-	NRP-	FAC	RIF
Sham	0.538 (±0.174)	0.212 (±0.142)	0.246 (±0.131)	0.279 (±0.139)	0.325 (±0.169)	0.032 (±0.098)
Anodal	0.626 (±0.134)	0.241 (±0.119)	0.313 (±0.118)	0.296 (±0.147)	0.385 (±0.140)	-0.017 (±0.084)
Cathodal	0.566 (±0.141)	0.250 (±0.108)	0.292 (±0.122)	0.261 (±0.092)	0.316 (±0.133)	-0.031 (±0.161)

For the FAC effect, the model including only the main effect of item type best fit the data, as showed by the available evidence ($AICw_{(type*group)}$ = 0.087,

$AICw_{(type+group)} = 0.287$, $AICw_{(type)} = 0.626$; see also Table 5.2). In line with our predictions, the FAC effect was significant in each group:

```
Chisq Test:
P-value adjustment method: holm
        Value Df   Chisq Pr(>Chisq)
group1 0.17037  1  90.747  < 2.2e-16 ***
group2 0.14434  1 101.240  < 2.2e-16 ***
group3 0.18754  1  67.372  2.249e-16 ***

“group1”=Sham tDCS; “group2”=Anodal tDCS; “group3”=Cathodal tDCS.
```

Concerning the RIF effect, in contrast with our predictions, the winning model was again the one that included only the main effect of item type ($AICw_{(type*group)} = 0.096$, $AICw_{(type+group)} = 0.195$, $AICw_{(type)} = 0.709$; see also Table 5.2). Furthermore, post-hoc contrasts did not reveal a significant RIF in any of the three stimulation groups (Figure 5.1):

```
Chisq Test:
P-value adjustment method: holm
        Value Df  Chisq Pr(>Chisq)
group1 0.54510  1 1.6580     0.5936
group2 0.48426  1 0.1873     0.7656
group3 0.46675  1 0.7616     0.7656

“group1”=Sham tDCS; “group2”=Anodal tDCS; “group3”=Cathodal tDCS.
```

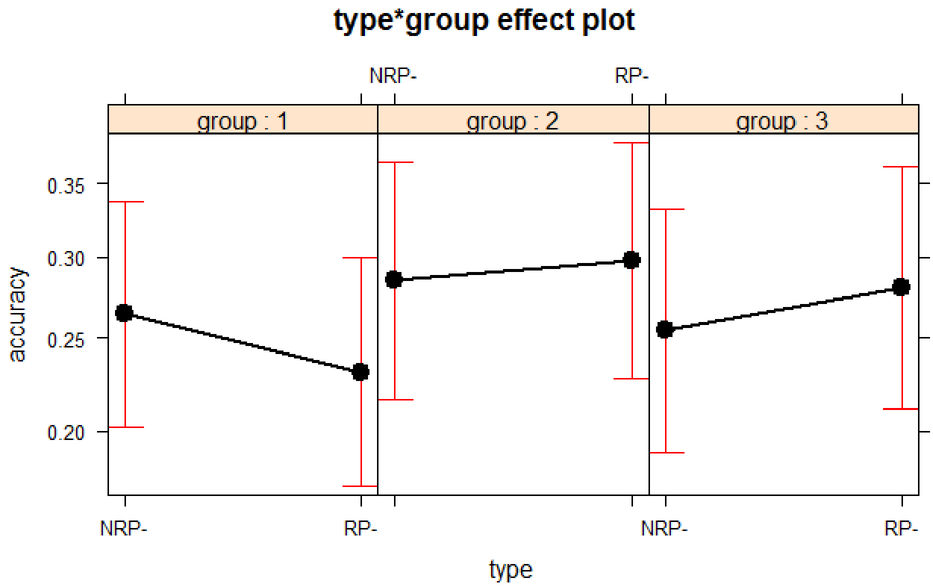

Figure 5.1 Interaction plot for each stimulation group separately. “group1”=Sham tDCS; “group2”=Anodal tDCS; “group3”=Cathodal tDCS. Sham tDCS shows a numerically larger difference between NRP- and RP-, compared to Anodal and Cathodal tDCS.

Table 5.2 Model comparisons for the FAC effect in Experiment 1. 95% CI are reported in parentheses.

FAC model comparison

	Memory performance		
	Accuracy		
	full	main effects	type
RP+	1.583^{***}	1.611^{***}	1.611^{***}
	(1.257, 1.909)	(1.412, 1.810)	(1.412, 1.810)
Anodal tDCS	0.189	0.300	
	(-0.275, 0.653)	(-0.076, 0.675)	
Cathodal tDCS	0.239	0.174	
	(-0.230, 0.709)	(-0.208, 0.556)	
RP+:Anodal tDCS	0.197		
	(-0.276, 0.669)		
RP+:Cathodal tDCS	-0.117		
	(-0.592, 0.358)		
Constant	-1.414^{***}	-1.431^{***}	-1.282^{***}
	(-1.835, -0.994)	(-1.823, -1.039)	(-1.618, -0.946)
Observations	2,120	2,120	2,120
Log Likelihood	-1,255.849	-1,256.658	-1,257.876
Akaike Inf. Crit.	2,527.698	2,525.316	2,523.752
Bayesian Inf. Crit.	2,572.971	2,559.271	2,546.389
Note:	$^{*}p<0.1$; $^{**}p<0.05$; $^{***}p<0.01$		

Table 5.3 Model comparisons for the RIF effect in Experiment 1. 95% CI are reported in parentheses.

RIF model comparison

	Memory performance		
	Accuracy		
	full	main effects	type
RP-	-0.181	-0.003	-0.003
	(-0.456, 0.094)	(-0.169, 0.162)	(-0.169, 0.162)
Anodal tDCS	0.103	0.223	
	(-0.312, 0.518)	(-0.142, 0.588)	
Cathodal tDCS	-0.053	0.104	
	(-0.477, 0.371)	(-0.268, 0.476)	
RP-:Anodal tDCS	0.244		
	(-0.153, 0.640)		
RP-:Cathodal tDCS	0.314		
	(-0.092, 0.721)		
Constant	-1.022^{***}	-1.109^{***}	-1.006^{***}
	(-1.373, -0.671)	(-1.445, -0.773)	(-1.278, -0.734)
Observations	2,968	2,968	2,968
Log Likelihood	-1,709.865	-1,711.160	-1,711.869
Akaike Inf. Crit.	3,435.731	3,434.320	3,431.737
Bayesian Inf. Crit.	3,483.696	3,470.294	3,455.720
Note:	$^{*}p<0.1$; $^{**}p<0.05$; $^{***}p<0.01$		

Finally, as predicted, correlational analysis did not show any evidence of a correlation between FAC and RIF effects across the whole sample (*r* = -0.13;Figure 5.2).

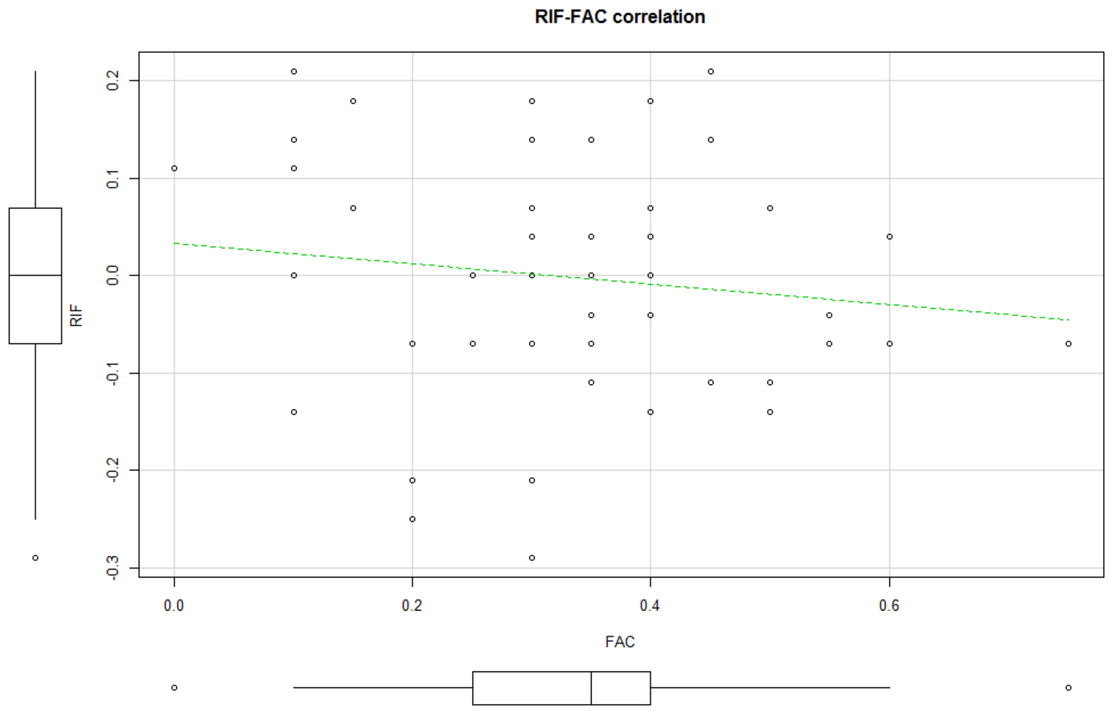

Figure 5.2 Scatterplot of the correlation between the RIF and FAC effects.

5.2.5 Discussion

The results concerning the beneficial effect of retrieval practice were in line with our predictions, with a reliable FAC observed in all the experimental groups and no interaction with our tDCS protocol. Turning to RIF, the results observed in this first experiment were quite unexpected. As a matter of fact, in light of our previous work, upon which the present experiment capitalized, we were not surprised about the lack of RIF in the two real stimulation groups, in particular regarding the cathodal stimulation group. However, the absence of an interaction between item type and stimulation group, coupled with the lack of a significant RIF effect in the control group, does not allow either supporting or completely rejecting our initial hypotheses. Therefore, results from this first experiment appeared to be inconclusive on whether interfering with rIFG during a RPP has any effects on inhibitory performance as indexed by RIF.

It is important to note that the RPP variant used in this experiment suffered from a few limitations, which also affected and were partially addressed in our previous work (Penolazzi et al., 2014), and which could have influenced the current results nonetheless: i) We employed a blocked-by-category study format that could have facilitated encoding strategies based on grouping the exemplars together under the category label, thus favouring integration in our participants, which is known to reduce RIF (Anderson & McCulloch, 1999); ii) The study material consisted of a standard number of categories (eight) compared to the literature on RIF (e.g., Anderson et al., 1994), but quite a large number of exemplars (twelve) by the same standards, therefore we hypothesized that interference during retrieval practice in our paradigm may have been more diluted among the many competing items (seven), thus potentially limiting the inhibitory demands, and/or the subsequent inhibitory effort may have been less effective at reducing the competing items' representation in memory to a point that later recall would suffer from such impairment; iii) While the test format allowed to rule out output interference on RP- items (Anderson, 2003), it could have caused NRP- items to undergo more interference than the RP- items, since the former items were mixed together with the RP+ and NRP+ items (It is worth mentioning that such bias was held constant across participants and hence is unlikely to have influenced the results as a function of stimulation (see also Penolazzi et al., 2014). In addition to these points, variability in our sample's performance due to individual characteristics and their interaction with the aforementioned issues in the study design, even though the current experiment's control group was very similar to the one that took part in our previous study (Penolazzi et al., 2014), in terms of age, education, gender, and cultural background. In consideration of all these critical points, and because results provided by this experiment did not lend themselves to a clear interpretation, we carried out a second experiment in which we employed a similar rationale and improved upon the behavioural procedure, neuromodulation parameters, and sample size.

This new experiment was not just a refined replication of the previous one, but included also an important element of novelty. In fact, we took the chance to replace the filler questionnaires acting as a buffer between the retrieval practice and test phases of the RPP with an additional task aimed at measuring the individual ability to override an initiated course of action. Specifically, we employed a stop-signal task (SST; Verbruggen & Logan, 2008) that participants performed immediately after the retrieval practice phase, while tDCS was still active. In the SST, participants perform a choice RT task and withhold response when a stop signal is presented shortly after the target stimulus. In order to push participants into committing mistakes, trials that require stopping are infrequent (often 25%) compared to go trials, and the delay between the target and stop signal (stop-signal delay, SSD) is adaptively adjusted by a staircase procedure aimed at keeping participants' accuracy at about 50%. The horse-race model of inhibition in the SST (e.g., Logan & Cowan 1984; Osman et al., 1986) posits that whenever a stop trial occurs, the inhibitory process triggered by the stop signal competes with the response process elicited by the target. Consequently, longer SSDs make for harder stop trials, as the response process will be closer to translate into action and further "out of reach" for the inhibitory process. The main index of the efficiency of inhibitory performance in the SST at the individual level is the stop-signal reaction time (SSRT), which can be computed as the difference between mean RTs in the go trials (no-signal RTs, NSRTs) and the mean SSD in the stop-trials, for a given participant. Given that the SSRT is interpreted as the covert latency of the inhibitory process that overrides motor action, shorter SSRTs indicate a more efficient stopping process.

Many tDCS studies have shown that stimulation of prefrontal areas significantly modulates control abilities in different tasks spanning both memory and action; however, they all investigated a single inhibitory measure at a time (see Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016, for a review on PFC involvement in inhibitory control as revealed by non invasive brain stimulation). Moreover, although a few works have investigated the relationship between motor inhibition and suppression of competing memories (e.g., Schilling et al., 2014; Storm & Bui, 2016), none of them has implemented tES as a method of concurrent modulations of the two mechanisms, and correlational results have been inconsistent (see also Noreen & MacLeod, 2015). Hence, to further our understanding of tDCS effects over memory and action control, as well as the relationship between the two cognitive mechanisms, in the second experiment we first combined multiple behavioural methods typically used for measuring inhibitory control in episodic memory and motor action within a PFC-tDCS study. We predicted that active tDCS over the rIFG would modulate suppression of competing memories, i.e., RIF, compared to sham stimulation, but also affect the ability to override a prepotent motor response, as indexed by SSRTs, because of the importance of this brain region for motor stopping (e.g., Aron et al., 2014; Stramaccia et al., 2015). Concerning the latter hypothesis, in particular, we predicted a better inhibitory performance in the anodal stimulation group, compared to the sham and cathodal stimulation groups, based on results from previous work that investigated the effects of tDCS to the rIFG in the SST (e.g., Jacobson et al., 2011; Ditye et al., 2012; Stramaccia et al., 2015). Finally, we sought to explore the relationship between measures of motor stopping and memory suppression.

5.3 Experiment 2

5.3.1 Methods

5.3.1.1 Participants

The ethical committee for psychological research of the University of Padua approved the study, which was performed in accordance with the principles of the Declaration of Helsinki. All participants, none of which had taken part in the previous experiment, underwent an eligibility screening for the tDCS procedure, and provided an informed consent prior to their participation and a final consent at the end of the experimental procedure. With respect to the previous experiment, sample size was increased to 72 healthy volunteers (28 males) aged between 20 and 40 years (*mean age* = 23.57, *SD* = 2.86; *mean years of education* = 17.43, *SD* = 1.28). All participants were screened for possible exclusion criteria that were identical to Experiment 1 (5.2.1.1).

5.3.1.2 Retrieval Practice Paradigm (RPP)

As for Experiment 1, we used the RIF effect as an index of memory suppression and we administered a typical three-phase RPP (Anderson et al., 1994) in order to obtain an individual measure of the effect. However, there were several changes in our paradigm with respect to the previous experiment, concerning both the stimuli and some features of the three phases. Our revised paradigm included 84 category-exemplar word pairs (e.g. “FRUIT-PRUNE”), divided by 12 semantic categories, with seven exemplars for each category. We reasoned that to observe a stronger RIF in the control group, it would have been better to include more semantic categories with fewer exemplars each, rather than relatively few categories with many exemplars each, because competition under the latter circumstances could be more diluted among the exemplars, and subsequent inhibitory efforts less effective. Moreover, having more exemplars in each category increased the risk of unwanted semantic associations (Goodmon & Anderson, 2011). We selected and adapted all the material from the categorical production norm for the Italian language by Boccardi and Cappa (1997), according to the same criteria used for the first experiment, with the exception that in all categories, four out of seven items were strong exemplars, whereas the other three items were weak exemplars. All participants were completely naïve to the procedure. The RPP used here is schematically represented in Figure 5.3.

In the study phase, we instructed the participants to memorize all of the 84 category-exemplar word pairs, by relating each exemplar to its category. We also informed them that they would have been tested later on the exemplars, but not about the specific format, duration, or repetition (both the practice and the test phases are testing instances) of such testing. Study trials began with a brief fixation (500ms), followed by a blank screen (500ms); subsequently, one category-exemplar word pair was presented on screen (3500ms), followed by a blank screen (500ms). In order to discourage integration strategies, which may hamper RIF (Anderson & McCulloch, 1999), we delivered the stimuli in a randomized blocked order, in which each block contained one exemplar from each semantic category, with the additional constraint that two items from the same category could not be presented one after another.

In the practice phase, participants repeatedly practiced the weak exemplars of half the semantic categories (three repetitions of 18 exemplars, 72 trials in total). Practicing weak exemplars only should boost the RIF effect due to increased competition from the remaining strong exemplars (Anderson, 2003). In the practice trials, we provided the category and the first two letters of each exemplar (e.g. "FRUIT-PR____") to the participants, and we instructed them to answer with the name of the specific exemplar associated to the particular cue in full (8000ms). We labelled the practiced weak exemplars as RP+ items, the non-practiced strong items from practiced categories as RP- items, the weak non-practiced items from non-practiced categories NRP+ items, and the strong non-practiced items NRP-. NRP+ and NRP- items served as controls for RP+ and RP- items, respectively. We used four lists of categories to fully counterbalance the practiced categories across groups. As a result, all semantic categories contributed equally to all four types of items. We presented the stimuli in a similar order to the previous phase.

In the final test phase, we presented again all the stimuli from the initial study phase (84 trials). Format, response modality, and instructions were the same as above, however now we provided the participants with the category plus the first letter of an exemplar only (e.g. "FRUIT-P____") We presented the stimuli in a similar order to the previous phases, with the additional constraint that all RP- and NRP- items came before all the RP+ and NRP+ items, in order to control for output interference at test, which could inflate the RIF effect (Anderson, 2003). This particular order was also different from that of Experiment 1 (5.2.1.2). In fact, as mentioned before (3.4) the test format implemented in Experiment 1 might have lead to an imbalance in the amount of interference received by NRP- items, compared to RP- items, thus reducing the chances to observe RIF.

5.3.1.3 Stop-Signal Task (SST)

Between the retrieval practice phase and the test phase of the RPP, participants performed the SST provided within the STOP-IT software

(Verbruggen et al., 2008), which probes the individual efficiency of the covert motor stopping process (i.e., SSRTs). The task begun with a short practice block (32 trials) allowing the participants to familiarize with the task, followed by two experimental blocks of 64 trials each (128 total trials). In the primary task, participants performed a choice reaction time test, with the instruction to prioritize both speed and accuracy of responses. Each trial began with a 250-ms central fixation (+), followed by a visual stimulus (either a circle or a square) that stayed centrally on screen until the participants responded, with the constraint that participants had up to 1.250 ms to respond. The central fixation and stimuli were presented in white on a black background. The ISI was 2000 ms, independently of RTs. The participants used a keyboard to respond, and they had to press “A” for squares or “L” for circles. On 25 % of the trials, shortly after stimulus onset, a sound (750 Hz, 75 ms) signalling to hold back the response (i.e., a stop-signal) was presented through loudspeakers. The stop-signal delay was 250 ms at the beginning of the task, and subsequently increased or decreased by 50 ms after each successful or unsuccessful stopping trial, respectively. Under this tracking procedure, participants correctly withheld approximately half the responses, meeting the requirements of the method used to calculate SSRT. According to the horse-race model (Logan & Cowan 1984; Osman et al. 1986), SSRT is calculated as the difference between mean RT in the trials where participants must respond and mean SSD in the trials where they must hold back the response. A schematic representation of the task is displayed in Figure 4.1.

5.3.1.4 transcranial Direct Current Stimulation (tDCS)

The stimulation parameters, montages, and overall procedure, were identical to the first experiment (see Figure 4.2, panel B, left side). We used a single blind, between group design: We randomly assigned the participants to anodal (*N*=24, 9 males, *mean age* 23.96, *SD* 3.74), cathodal (*N*=24, 12 males, *mean age* 23.33, *SD* 2.28), or sham stimulation (*N*=24, 7 males, *mean age* 23.42, *SD* 2.43). Stimulation begun prior to the practice phase of the RPP, and it lasted 20 minutes in total for all three groups, covering the entire practice phase and the subsequent SST. In the active tDCS conditions, we ramped up the stimulation to

1.5 mA over 30 s, maintained it for 19 minutes, and ramped it down over 30 s again at the end to minimize unpleasant sensations. In the Sham stimulation group, we ramped up and then immediately ramped down stimulation over 60s at both the beginning and end of the protocol.

5.3.2 Procedure

We received the participants in a sound-attenuated testing room, and sat them at the computer. We prepared the montage for the tDCS, without starting the stimulation. Participants first performed the study phase of the RPP. After that, we checked the integrity of the montage, and turned the stimulation on. As soon as the participants felt comfortable with the stimulation (always within moment from the initial ramp up period), they performed the retrieval practice phase of the RPP, followed by the SST. Stimulation ended shortly before completion of the SST, and we removed the montage before proceeding with the final test phase of the RPP. In keeping with Experiment 1 (5.2.2), we also administered a sensation questionnaire (Fertonani et al., 2010) at the end of the whole procedure.

See Figure 5.3 below for a schematic representation of the experimental procedure.

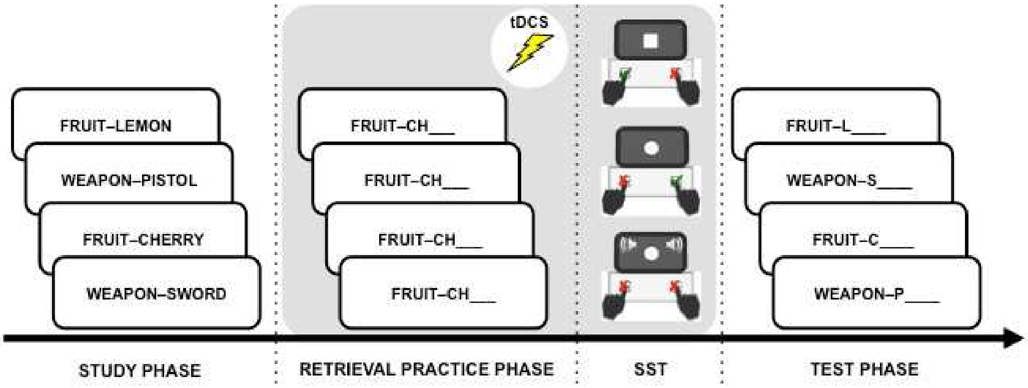

Figure 5.3 Schematic representation of the experimental procedure employed in Experiment 2. The SST is embedded between the retrieval practice and test the test phases of the RPP.

5.3.3 Analysis

We performed identical treatment and subsequent analysis of RPP data with respect to Experiment 1 (5.2.3).

Concerning the SST, we discarded data from one participant in the cathodal rIFG Group due to a technical failure. To assess whether tDCS selectively modulated motor stopping, we calculated individual SSRTs and NSRTs using the ANALYZE-IT software (Verbruggen et al. 2008). With respect to individual SSRTs, ANALYZE-IT computes the mean RTs for all successful go trials and then subtracts the mean stop-signal delay from this value (Verbruggen et al. 2008).

5.3.4 Results

5.3.4.1 Retrieval Practice Paradigm (RPP)

Mean proportions of recall in the final test phase for each item type and FAC/RIF effects are reported in Table 5.4 below.

Table 5.4 Mean proportion of recall in the final test phase as a function of item type/effect and stimulation group.

	Final Test Phase					
	Item Type					
Stimulation Group	RP+	NRP+	RP-	NRP-	FAC	RIF
Sham	0.449 (±0.149)	0.213 (±0.144)	0.354 (±0.117)	0.436 (±0.110)	0.236 (±0.167)	0.082 (±0.169)
Anodal	0.447 (±0.163)	0.227 (±0.133)	0.385 (±0.154)	0.408 (±0.101)	0.220 (±0.118)	0.023 (±0.140)
Cathodal	0.396 (±0.173)	0.227 (±0.096)	0.354 (±0.120)	0.366 (±0.099)	0.211 (±0.142)	0.012 (±0.128)

Note. Standard deviations are reported in parentheses.

For the FAC effect, the model including only the main effect of item type best fitted the data ($AICw_{(type*group)} = 0.037$, $AICw_{(type+group)} = 0.264$, $AICw_{(type)} = 0.698$; Table 5.5). The FAC effect was significant in each group, and numerically lower than that observed in both Experiment 1 and Penolazzi and Colleagues’ work (2014; compare Table 5.4, Table 5.1, and Table 3.1):

```
Chisq Test:
P-value adjustment method: holm
         Value Df  Chisq Pr(>Chisq)
group1 0.23463  1 55.710  2.520e-13 ***
group2 0.24684  1 50.106  2.912e-12 ***
group3 0.24249  1 48.127  3.994e-12 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

“group1”=Sham tDCS; “group2”=Anodal tDCS; “group3”=Cathodal tDCS.
```

As for the RIF effect, in contrast with our predictions, the best fitting model was again the one that included only the main effect of item type ($AICw_{(type*group)} = 0.193$, $AICw_{(type+group)} = 0.253$, $AICw_{(type)} = 0.554$; Table 5.6). Post-hoc contrasts driven by our initial hypothesis revealed a significant RIF in the Sham tDCS group only (Figure 5.4), whose magnitude was numerically similar to that observed in our previous study (in chapter 3; compare Table 5.4 and Table 3.1):

```
Chisq Test:
P-value adjustment method: holm
         Value Df  Chisq Pr(>Chisq)
group1 0.58807  1 8.3178    0.01178 *
group2 0.52470  1 0.6447    0.84401
group3 0.51361  1 0.1892    0.84401

“group1”=Sham tDCS; “group2”=Anodal tDCS; “group3”=Cathodal tDCS.
```

As for the correlational analysis, we did not find any evidence for a correlation between FAC and RIF effects across the whole sample ($r < -0.01$; see Figure 5.5).

Table 5.5 Model comparisons for the FAC effect in Experiment 2. 95% CI are reported in parentheses.

FAC model comparison

	Memory performance		
	Accuracy		
	full	main effects	type
RP+	1.182^{***}	1.146^{***}	1.146^{***}
	(0.872, 1.493)	(0.964, 1.328)	(0.964, 1.328)
Anodal tDCS	0.059	0.019	
	(-0.390, 0.508)	(-0.349, 0.388)	
Cathodal tDCS	-0.201	-0.227	
	(-0.659, 0.256)	(-0.598, 0.144)	
RP+:Anodal tDCS	-0.067		
	(-0.504, 0.370)		
RP+:Cathodal tDCS	-0.043		
	(-0.489, 0.403)		
Constant	-1.412^{***}	-1.391^{***}	-1.460^{***}
	(-1.809, -1.015)	(-1.759, -1.022)	(-1.762, -1.157)
Observations	2,592	2,592	2,592
Log Likelihood	-1,493.640	-1,493.686	-1,494.714
Akaike Inf. Crit.	3,003.280	2,999.372	2,997.429
Bayesian Inf. Crit.	3,050.162	3,034.533	3,020.870
Note:	$^{*}p<0.1$; $^{**}p<0.05$; $^{***}p<0.01$		

Table 5.6 Model comparisons for the RIF effect in Experiment 2. 95% CI are reported in parentheses.

RIF model comparison

	Memory performance		
	Accuracy		
	full	main effects	type
RP-	-0.356^{***}	-0.171^{**}	-0.171^{**}
	(-0.598, -0.114)	(-0.311, -0.031)	(-0.311, -0.031)
Anodal tDCS	-0.120	0.006	
	(-0.401, 0.161)	(-0.220, 0.232)	
Cathodal tDCS	-0.303^{**}	-0.155	
	(-0.586, -0.020)	(-0.382, 0.072)	
RP-:Anodal tDCS	0.257		
	(-0.085, 0.599)		
RP-:Cathodal tDCS	0.302^{*}		
	(-0.043, 0.646)		
Constant	-0.269^{*}	-0.359^{***}	-0.409^{***}
	(-0.546, 0.008)	(-0.619, -0.099)	(-0.635, -0.183)
Observations	3,456	3,456	3,456
Log Likelihood	-2,256.578	-2,258.306	-2,259.524
Akaike Inf. Crit.	4,529.156	4,528.613	4,527.049
Bayesian Inf. Crit.	4,578.339	4,565.500	4,551.640
Note:	$^{*}p<0.1$; $^{**}p<0.05$; $^{***}p<0.01$		

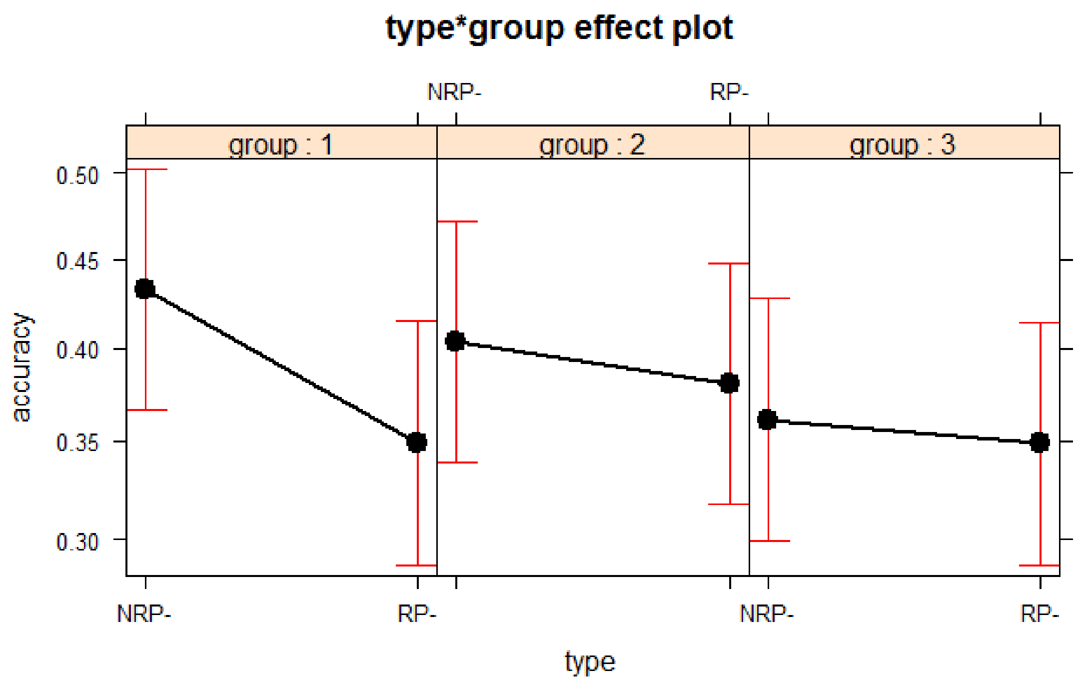

Figure 5.4 Interaction plot for each stimulation group separately. "group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS. Altough the interaction is not significant, Sham tDCS exhibits a significant RIF effect.

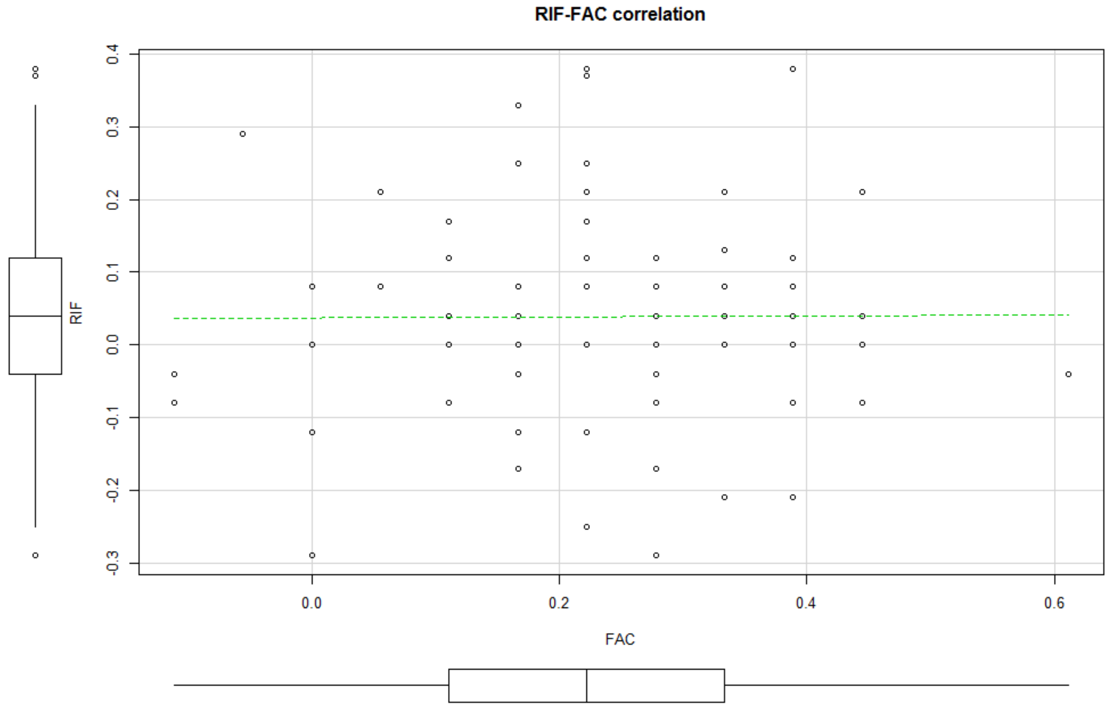

Figure 5.5 Scatterplot of the correlation between the RIF and FAC effects.

At a first glance, these results seemed to merely suggest a similar pattern with respect to our previous work (Penolazzi et al., 2014), though with little statistical support behind it. At the same time, it should be noted that, when compared directly, the interaction model and the main effects model did not show a large difference in AICw. Interestingly, further visual inspection of the data suggested large differences in the amount of RIF elicited by the different semantic categories employed here. To shed light on the contribution of the individual categories to the overall results, we analysed the amount of evidence in favour of a main effect of item type within each category taken separately, and for the sham (control) group alone (to rule out additional effects due to the neuromodulatory manipulations).

This procedure revealed that few categories showed a particularly weak or reversed RIF effect in the control group (i.e., “BIDS”, “FLOWERS”, “FRUITS”, “SPORTS”). Because of that, we performed new model comparisons between the full model (type * group) and the model without interaction (type + group), gradually excluding the categories that showed the least support for the presence of RIF in the control group, in order to assess whether the inability of these categories to elicit RIF in the control group was related to the lack of evidence in support of the interaction model. Surprisingly, removing the two categories that showed the least amount of even reversed RIF in the control group (i.e., “SPORTS” and “BIRDS”, respectively) improved the amount of RIF in the control group to a magnitude that was unparalleled in the experimental groups, resulting in the new analysis now largely favouring the full model over the model with fixed effects only ($AICw_{(type*group)} = 0.773$, $AICw_{(type+group)} = 0.227$; Figure 5.6):

```
Chisq Test:
P-value adjustment method: holm
         Value Df   Chisq Pr(>Chisq)
group1 0.61516  1 11.8524   0.001728 **
group2 0.52775  1  0.6721   0.824635
group3 0.49995  1  0.0000   0.998747

"group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.
```

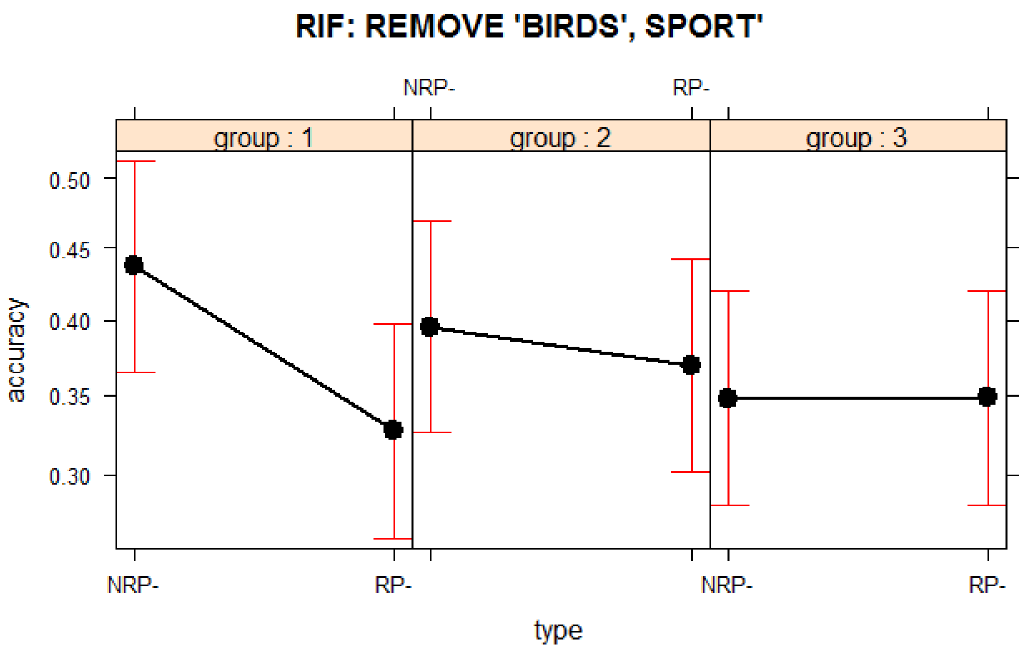

Figure 5.6 Interaction plot for each stimulation group separately, after removal of "BIRDS" and "SPORTS" categories from Experiment 2 data. "group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.

Further removal of the two additional "negative" categories (i.e., "FLOWERS" and "FRUITS") resulted in an even stronger change in the amount of evidence in favour of the interaction model ($AICw_{(type*group)} = 0.931$, $AICw_{(type+group)} = 0.069$; Figure 5.7):

```
Chisq Test:
P-value adjustment method: holm
          Value Df   Chisq Pr(>Chisq)
group1 0.64971  1 16.2692  0.0001649 ***
group2 0.54633  1  1.5204  0.4351216
group3 0.49384  1  0.0260  0.8719660
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

"group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.
```

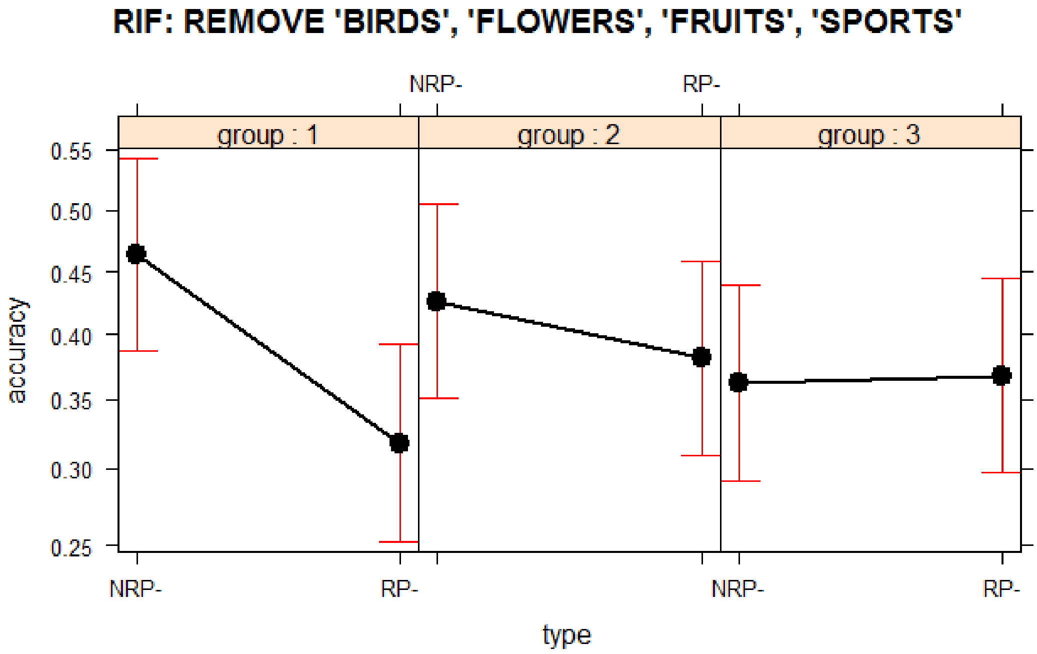

Figure 5.7 Interaction plot for each stimulation group separately, after removal of "BIRDS", "FLOWERS", "FRUITS", and "SPORTS" categories from Experiment 2 data. "group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.

It is worth noting that the procedure employed in this additional category-wise influence analysis allowed looking into the contribution of each category to the effect of interest (i.e., RIF) in the control group, and subsequently to the item type x stimulation group interaction, while keeping the random effect of item into account. Because of the valuable information provided by these additional analyses, we decided to reanalyse RPP data from the first experiment as well, in order to ascertain whether specific semantic categories had a similar impact on the results, and more specifically whether the same categories behaved similarly across the two experiments

5.3.4.2 Re-Analysis of Experiment 1

We carried out category-wise analyses to assess the contribution of each category to RIF in the control group. These new analyses revealed that different categories impacted differently on RIF in the control group. More specifically, four out of the eight semantic categories employed in the first experiment exhibited none to reversed RIF, with "BIRDS", "FRUITS", "JOBS", and

"WEAPONS", being the categories showing the least amount of forgetting for RP- items compared to the NRP-. Interestingly, two of them overlapped with the null-RIF categories detected in the previous re-ANALYSIS of Experiment 2 (i.e., "BIRDS" and "FRUITS"), although it should be noted that there were also some differences in the exemplars contributing to the same category in the two experiments. We then proceeded to compare the interaction model with the main effects model by excluding an increasing number of null-RIF categories. This procedure yielded a pattern similar to that observed in the second experiment. Indeed, when we removed the two categories that showed the least amount of RIF in the control group (i.e., "BIRDS" and "WEAPONS"), the available evidence favoured the interaction model, although to a very limited extent ($AICw_{(type*group)} = 0.517$, $AICw_{(type+group)} = 0.483$; Figure 5.8):

```
Chisq Test:
P-value adjustment method: holm
         Value Df  Chisq Pr(>Chisq)
group1 0.59476  1 5.3019    0.06391 .
group2 0.51142  1 0.0720    1.00000
group3 0.47564  1 0.2951    1.00000
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

"group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.
```

Further excision of the remaining null-RIF categories (i.e., "FRUITS" and "JOBS") resulted in much larger evidence in favour of the interaction model ($AICw_{(type*group)} = 0.629$, $AICw_{(type+group)} = 0.371$; Figure 5.9):

```
Chisq Test:
P-value adjustment method: holm
         Value Df  Chisq Pr(>Chisq)
group1 0.61588  1 6.5915    0.03074 *
group2 0.49313  1 0.0216    1.00000
group3 0.48566  1 0.0852    1.00000
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

"group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.
```

Once again, the interaction was mainly dependent on the increased RIF observed in the control group, whereas removing the "negative" categories did not affect RIF in the stimulated group as much as in the sham group.

Figure 5.8 Interaction plot for each stimulation group separately, after removal of "BIRDS" and "WEAPONS" categories from Experiment 1 data. "group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.

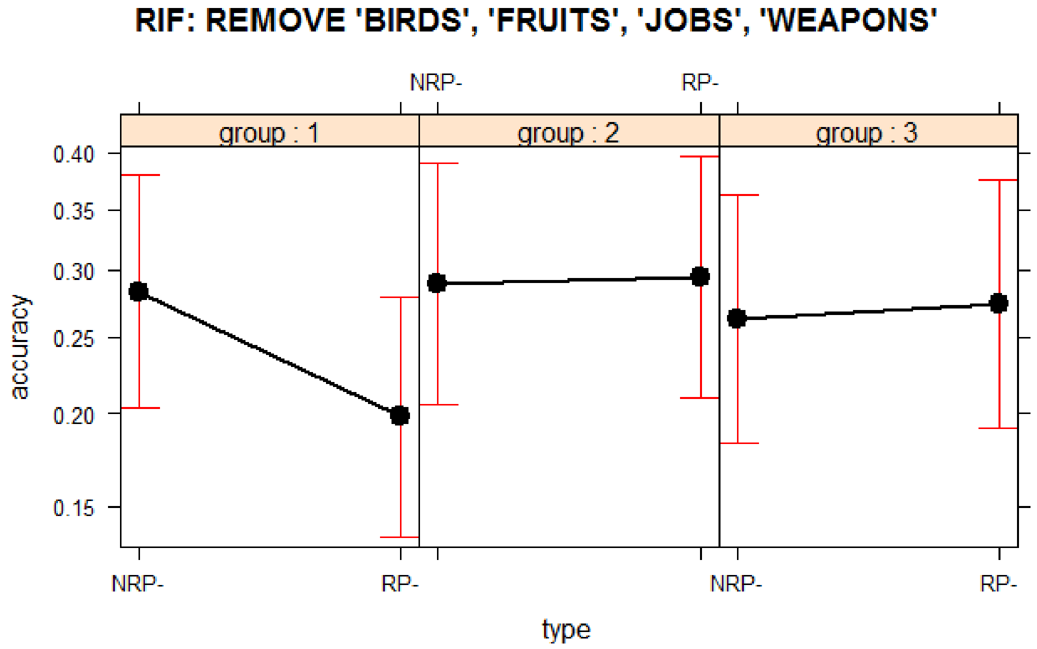

Figure 5.9 Interaction plot for each stimulation group separately, after removal of "BIRDS", "FRUITS", "JOBS", and "WEAPONS" categories from Experiment 1 data. "group1"=Sham tDCS; "group2"=Anodal tDCS; "group3"=Cathodal tDCS.

5.3.4.3 Stop-Signal Task (SST)

Data from one participant (Cathodal tDCS group) were discarded because of technical failure of the software. No differences were found between groups for either SSRTs, $F_{(2,68)} = 1.13$, $p > .250$ ($M_{SHAM\text{-}SSRT} = 286.025$, $SD_{SHAM\text{-}SSRT} = 38.906$; $M_{ANODAL\text{-}SSRT} = 287.186$, $SD_{ANODAL\text{-}SSRT} = 47.616$; $M_{CATHODAL\text{-}SSRT} = 269.370$, $SD_{CATHODAL\text{-}SSRT} = 48.851$), or NSRTs, $F_{(2,68)} = .03$, $p > .250$ ($M_{SHAM\text{-}NSRT} = 564.688$, $SD_{SHAM\text{-}NSRT} = 148.073$; $M_{ANODAL\text{-}NSRT} = 566.913$, $SD_{ANODAL\text{-}NSRT} = 131.117$; $M_{CATHODAL\text{-}NSRT} = 567.861$, $SD_{CATHODAL\text{-}NSRT} = 132.007$). The correlation between SSRTs and RIF was also not significant ($r = .069$).

5.3.5 Discussion

Results from the second experiment closely resembled the pattern observed by Penolazzi and Colleagues (2014). In particular, limiting the analysis to the subset of the experimental material that better expressed RIF in the control group reproduced results that were highly similar to Penolazzi and Colleagues' findings (2014), even though the detrimental effect of tDCS on the cathodal group was not as strong as in that study. There are several reasons that support the rationale for looking at category-specific patterns in our data. In particular, memory performance on the semantic categories employed here might have very well been influenced by the amount of pre-existing knowledge in our experimental groups, as well as possible different baseline levels of relevant psycholinguistic variables such as memorability and imageability, possibly leading to various degree of uncontrolled semantic integration (Goodmon & Anderson, 2011) whose effects would not just be ruled out by counterbalancing the categories across participants and groups, and which may have partially jeopardized our attempt to separate high- from low-interfering exemplars. These features may have the potential to specifically affect the amount of forgetting due to competition resolution (i.e., RIF), while not affecting the magnitude of the benefit from additional study (i.e., FAC) at all. Critical to our argument, across the new analyses the control group steadily constituted the main drive behind the interaction, showing a gradual increase in the detected RIF effect as we removed more "negative" categories, whose magnitude was not mirrored in the stimulation groups. Interestingly enough, there was some overlapping between the categories that negatively affected RIF (in the control group considered in isolation) in the first and in the second experiment. For example, “BIRDS” consistently showed a reversed RIF pattern, with higher recall for RP- than NRP- items. Unfortunately, indexes pertaining the specific features of the semantic categories that we hypothesized may have had a negative impact on RIF in the control group were not readily available to us, therefore we cannot directly quantify the potential contributions of these factors toward the observed pattern of results.

Turning to the results concerning the motor stopping task, Experiment 2 failed to show any difference (5.3.4.3), as opposed to what has been reported by previous studies (e.g., Cunillera et al, 2014; Dityie et al., 2012; Jacobson et al., 2011; Stramaccia et al., 2015). Moreover, we did not find a correlation between the individual ability to suppress competing memories as indexed by RIF, and the individual efficiency of the motor stopping process as indexed by SSRTs. We will address these null findings in the following section.

5.4 General discussion

The present study moved from the observation that, so far, only a handful of studies examined the potential of tDCS to modulate behavioural performance in tasks addressing cognitive control over covert mental processes such as the ability to overcome interference from competing memory traces (e.g., Anderson, J., et al., 2015; Penolazzi et al., 2014; Silas & Brandt, 2016; also see Oldrati et al., 2016, for relevant results in a different but related domain). In particular, the emerging pattern from this relatively scarce literature points to consistent, detrimental effects of prefrontal cathodal tDCS on suppression of competing memories and related abilities, across a range of slightly different stimulation parameters. This notion may prove important to design and implement therapeutic strategies intending to employ tES to alleviate cognitive control and impulsivity-related deficits, and constitutes a starting point for further investigation into the specific cognitive processes and neural underpinnings at the interface between non-invasive brain stimulation and its behavioural outcomes. In this view, our study presents a set of findings that support this prefrontal cathodal tDCS impairing effect, with a varying degree of generalizability of our results across the two experiments. Specifically, we delivered anodal, cathodal, or sham (control) tDCS to healthy volunteers in order to modulate memory control as indexed by RIF, which reflects the negative effects of selective memory retrieval in the face of competition on subsequent recall of competing memory traces. The tDCS procedure targeted the rIFG, a key area in the brain network deputed to inhibitory control (e.g., Aron et al., 2014), whose activity during the inhibitory effort in the RPP has been associated with the amount of RIF in previous neuroimaging studies (Wimber et al., 2008, 2009, 2015). Across two experiments that followed a similar rationale, results indicated that cathodal tDCS had the highest, detrimental impact on memory control. One the one hand, our work provided causal evidence for the involvement of the rIFG in this ability, and confirmed the feasibility of tDCS modulation of RIF. On the other hand, future research efforts should aim at identifying stimulation parameters that improve cognitive control over interference, which would yield a relevant applied potential.

5.4.1 No evidence for a relation between RIF and motor stopping

The inclusion of a measure of motor stopping ability was a remarkable feature of Experiment 2, because to our knowledge no other study so far attempted to manipulate cognitive control in both action and memory. Along with the two experiments reported here, past work hinted at the possibility to modulate control over interfering memories (Anderson, Davis, Fitzgerald, & Hoy, 2015; Penolazzi et al., 2014), as well as motor stopping (e.g., Jacobson et al., 2011; Stramaccia et a., 2015), by delivering tDCS to the PFC. Importantly, the two abilities may constitute different but interrelated instances of inhibitory control (Levy & Anderson, 2002; Schilling et al., 2014). In this view, combined investigations of memory control and motor stopping measures have the potential to be highly informative with respect to this theoretical stance. This was the main reason behind the inclusion of the SST in Experiment 2, whose aims were twofold: i) We sought to test the association between RIF and SSRTs, because of the mixed results provided so far by the literature concerning the positive relationship between memory control and motor stopping (Schilling et al., 2014; Storm & Bui, 2016); ii) We expected to replicate the anodal rIFG-tDCS modulation on motor stopping, specifically showing a reduction in SSRTs that would have indicated a speeding-up of the underlying stopping process, as first shown by Jacobson and Colleagues (2011) and replicated in subsequent studies (e.g., Stramaccia et al., 2015; Cunillera et al., 2014).

Concerning the former objective, we did not find any significant correlation between RIF and SSRTs. Interestingly, Schilling and colleagues (2014) who first detected a positive correlation between RIF and SSRTs employed a RPP that was extremely similar to the RPP used here (Experiment 2), in particular as concerns the format of the testing phase Importantly, in their study, participants that were administered a testing phase contaminated by output interference within an otherwise similar RPP showed a reverse correlation between RIF and SSRTs, compared to participants that received a RPP whose design matched the one in Experiment 2 from the present study. Failures to find a positive association between different measures of cognitive inhibition is not new in the literature (e.g., Noreen & MacLeod, 2015; Storm & Bui, 2016), and calls for further studies employing behavioural paradigms that are maximally informative with respect to the theoretical debate between the inhibitory account of phenomena such as RIF and other explanatory proposals based on different mechanisms (e.g., by competition at test; see Raaijmakers & Jakab, 2013). To better illustrate this point, it is worth noting that recent work suggested that when recall performance in the final test of the RPP is probed by category-plus-one-letter-stem cued recall tests, interference may still contribute the amount of observed RIF (e.g., Rupprecht & Bäuml, 2016), whereas recognition tests may be better suited at detecting the amount of forgetting that could be genuinely ascribed to inhibitory mechanisms.

Regarding the latter objective of Experiment 2, no differences in SSRTs emerged as a function of group (5.3.4.3). While being at odds with the aforementioned studies, this result is not entirely surprising, nor necessarily unexpected. For example, Cunillera and Colleagues (2015), observed prefrontal tDCS effects on electroencephalographic correlates of motor stopping, but failed to induce a behavioural modulation as concerns SSRTs. Because we did not employed central measures of neural activity on our study, we cannot rule out that our manipulation induced differences that were not detected behaviourally. Similarly, a recent study from a different research group failed to observe any significant of tDCS over a different but nonetheless widely used measure of behavioural inhibition, i.e., the go/no-go task, as a function of anodal stimulation of the inferior frontal cortex (Dambacher, Schuhmann, Lobbestael, Arntz, Brugman, & Sack, 2015). It is worth noting that both studies (Cunillera et al., 2015; Dambacher et al., 2015) employed a bilateral tDCS montage, as opposed to a fronto-polar montage such as the one used in Jacobson and Colleagues' study (2011) to first modulate SST performance with tDCS, indicating that future attempts at modulating motor inhibition should turn to fronto-polar montages, which produced more consistent results (with the exception of Experiment 2 presented here). In light of this conflicting evidence, additional research integrating both neuroimaging and neuromodulatory techniques is warranted to assess which one of the many tES protocols applied to modulation of motor stopping so far yields the highest consistency between behavioural and neural measures of the relevant outcomes, and also importantly why protocols targeting a similar area (i.e., rIFG) but employing different stimulation parameters (polarity, duration, intensity, etc.) produce different results (e.g., Sarkis et al., 2014).

5.4.2 Conclusions

The current study presented two experiments that overall provided evidence for a role of the rIFG in cognitive control over interfering memory traces as indexed by RIF. In particular, RIF was maximally reduced in the cathodal stimulation groups across the two experiments. However, the investigation of the relationship between RIF and cognitive control over prepotent motor responses, as well as the opportunity to jointly modulate the two abilities with tDCS, yielded inconclusive results. In this light, the main merits of the study are consolidating our previous finding concerning the effects of cathodal tDCS on RIF (Penolazzi et al., 2014), and extending it to the right IFG. This, in turn, strengthens the notion that tDCS can be effectively used to modulate cognitive control, and poses new research questions worthy of future research efforts, especially concerning the development of stimulation protocols that may induce enhancement, rather than disruption, of memory control abilities, which could in turn inform novel therapeutic approaches to cognitive control impairments based on electrical stimulation.

6 RIF IS IMPAIRED IN SUBSTANCE-RELATED AND ADDICTIVE DISORDERS

This chapter is currently in press as **Stramaccia, D. F.**, Penolazzi, B., Monego, A. L., Manzan, A., Castelli, L., & Galfano, G. Suppression of Competing Memories in Substance-Related and Addictive Disorders: A Retrieval-Induced Forgetting Study. *Clinical Psychological Science*.

Substance-related and addictive disorders have been strongly linked to inhibitory control impairment. However, so far, inhibitory deficits in this class of psychiatric disorders have been tested almost exclusively with measures of inhibition of motor, overt behaviour. Here, instead, we investigated inhibitory deficits in these disorders by assessing the integrity of inhibitory control over internal, covert responses. Two groups of patients with alcohol and drug addiction and a control group of healthy individuals were administered a retrieval- practice paradigm assessing inhibition of competing memories. All groups showed comparable beneficial effects of retrieval practice. In contrast, only the control group achieved successful suppression of competing memories. This indicates that the deficit in clinical groups can be ascribed to impairment in inhibitory control over memory retrieval, rather than to general memory impairment. In conclusion, inhibitory deficits in addiction are more widespread than previously shown, as they encompass memory control mechanisms.

6.1 Introduction

To maintain an adaptive and flexible behaviour, we need to be able to override habitual or inappropriate responses when circumstances require a change in the course of action. This ability, often termed “inhibitory control”, is a core cognitive process that is essential to goal-directed behaviour. Given the importance of this process, it is not surprising that it has been found to be impaired in a broad range of psychiatric conditions. In particular, inhibitory deficits represent a consistent feature characterizing substance-related and addictive disorders. Until now, however, research in this domain focused almost exclusively on inhibitory control of overt actions (e.g., Smith, Mattick, Jamadar, & Iredale, 2014).

Here, we investigated the relationship between substance-related and addictive disorders and inhibitory control, with a focus on alcohol and heroin addiction. Poor inhibitory control is indeed a key feature of this class of disorders, acting as both a development and maintenance factor, and potentially emerging as a consequence of it (Smith et al., 2014). For example, it has been hypothesized that individuals with lower levels of inhibitory control may have higher chances of developing substance use disorders. Related to this point, substance abuse often sets off during adolescence. According to some authors (e.g., López-Caneda, Rodríguez Holduín, Cadaveira, Corral, & Doallo, 2014), inhibitory mechanisms and their neural underpinnings are still immature during adolescence, and this may increase the propensity to engage in substance abuse compared to adults. Substance abuse, in turn, could produce marked alterations in the brain and either prevent or disrupt the complete development of inhibitory control mechanisms during adolescence (Petit, Maurage, Kornreich, Verbanck, & Campanella, 2013). Moreover, substance abuse may impair control over impulsive behaviour, thus further increasing the chances of relapse in chronic users (e.g., Perry & Carroll, 2008). For these reasons, research on the failures of inhibitory control is chiefly important to design effective anti-drug strategies.

Importantly, inhibitory control does not solely concern overt behaviour, but exerts its covert influence on the content of our thoughts, the unfolding of emotions, and the process of memory retrieval (Anderson & Weaver, 2009). The present work aims to broaden our understanding of inhibitory deficits in substance-related and addictive disorders by focusing on a different, internally directed aspect of inhibitory control, which is the suppression of episodic memories. The abilities to suppress competing or unwanted memories are thought to be specific sub-processes of a broader inhibitory control mechanism (e.g., Storm & Levy, 2012), and to be mediated by lateral Pre-Frontal Cortex (PFC) activity, as shown by both neuroimaging (e.g., Wimber et al., 2008) and non-invasive brain stimulation (Penolazzi et al., 2014) studies. These forgetting abilities have been associated to beneficial outcomes and may be important to achieve adaptive functions such as memory updating, overcoming of interference, creative problem solving, and emotion regulation (e.g., Storm, 2011). Suppression of competing or unwanted memories has been mainly investigated with the Retrieval-Practice Paradigm (RPP; Anderson et al., 1994), which probes incidental memory suppression, and the Think/No-Think paradigm (e.g., Anderson & Hanslmayr, 2014), which requires a voluntary memory suppression effort.

In the present study, we investigated inhibition of competing episodic memories in two clinical populations diagnosed with substance-related and addictive disorders for alcohol and heroin, respectively. Inhibitory deficits in overt behaviour have been documented in both alcohol (e.g., Kamarajan, Porjesz, Jones, Choi, Chorlian, Padmanabhapillai, et al., 2005) and drug (Fu, Bi, Zou, Wang, Ye, Ma, et al., 2008) abuse. Importantly, both addictive disorders are often associated to impairments in episodic memory (e.g., Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Pitel, Beaunieux, Witkowski, Vabret, Guillery-Girard, Quinette,,et al., 2007). However, little is known about deficits of incidental episodic memory *suppression* in relationship to these substances. To address this issue, we recruited a group of patients with a prevalent primary diagnosis of drug (mostly heroin) addiction and one group with primary diagnosis of alcohol addiction, and we compared them on performance in the RPP with a matched control group of healthy individuals. In the RPP, participants first study a list of category-exemplar word pairs. On a subsequent phase, they repeatedly practice half the exemplars from half the categories. In a final test phase, participants' memory for the entire study list is tested with a category-cued test. Typical results show memory enhancement for practiced over non-practiced exemplars (facilitation effect, FAC), and memory impairment for non-practiced exemplars from practiced categories, compared to non-practiced exemplars from non-practiced categories. The latter result shows that, under some circumstances, the very act of retrieving information from memory can elicit subsequent forgetting of related information, an effect that has been called Retrieval-Induced Forgetting (RIF, Anderson et al., 1994; see also Murayama et al., 2014).

We predicted a stronger RIF effect in the control group, compared to the clinical groups, in which we expected a reduced or abolished effect. Because of the documented episodic memory deficits in both alcoholism and heroin abuse (e.g., Fernández-Serrano et al., 2011; Pitel et al., 2007), we did not necessarily expect performance in the FAC effect to be comparable across groups. However, unlike RIF, we expected the FAC effect to be reliable within each group and uncorrelated to RIF. Indeed, according to the inhibitory account of memory suppression (Anderson et al., 1994), FAC and RIF would reflect independent processes.

6.2 Methods

6.2.1 Participants

84 participants entered the study: 56 patients with a primary diagnosis of addiction, and 28 healthy individuals (see Table 6.1). We recruited the patients in a clinic located in Northern Italy, where they were undergoing treatment for their disorder. Diagnoses were made by a board-certified attending research team of psychiatrists using the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM 5*, American Psychiatric Association, 2013). 28 patients were included in the alcohol addiction (AA) group, and the other 28 were included in the drug addiction (DA) group, mainly composed of polyabusers (with a strong prevalence of opioid consumption). Most patients in the AA group were in treatment with disulfiram. Most patients in the DA group were in substitution

therapy with methadone or buprenorphine. Patients were tested at least three hours after receiving their daily treatment.

All participants were native Italian speakers with no history of neurological disease or learning disability. The ethical committee for psychological research of the University of Padua approved the study. All participants signed an informed consent form prior to their participation.

Table 6.1 Demographics and BIS-11 mean scores. Standard deviations are given in parentheses. * $p < .05$.

Characteristic	AA	DA	Control group	Group comparison
	(n=28)	(n=28)	(n=28)	(*F*, *t*, or χ^2)
Age (years)	49.3 (8.2)	35.4 (10.2)	42.9 (15.5)	$F = 9.92$*
Gender	23 males	24 males	22 males	$\chi^2 = 0.49$
Education (years)	9.8 (2.8)	10.3 (2.1)	11.3 (1.9)	$F = 3.89$*
Employed	20	21	25	$\chi^2 = 2.97$
Duration of addiction (days)	3525.4 (3181.0)	3830 (3110.1)		t =-0.36
Duration of abstinence (days)	449.8 (625.7)	210.7 (439.4)		$t = 1.66$
BIS-11 (mean score)	61.4 (8.4)	69.5 (11.6)	58.6 (8.5)	$F = 9.85$*
Attentional	16.9 (3.9)	18.6 (4.7)	15.3 (2.9)	$F = 5.09$*
Motor	19.7 (3.2)	23.4 (3.7)	19.3 (3.1)	$F = 12.88$*
Nonplanning	24.8 (3.8)	27.5(5.1)	23.9 (4.5)	$F = 4.90$*

6.2.2 Retrieval Practice Paradigm

Participants sat approximately 57 cm from a 15-in. laptop monitor (1024 × 768 pixels, 60 Hz) on which stimuli were presented, using E-prime 1.1, in black against a grey background.

All material was selected from the categorical production norms for the Italian language (Boccardi & Cappa, 1997). 84 category-exemplar word pairs belonging to 12 semantic categories were included, with 7 exemplars for each category. Stimuli were selected according to the following criteria: (i) within each category, 4 exemplars had high taxonomic strength (strong exemplars) and 3 had low taxonomic strength (weak exemplars); (ii) words within the same category always had a different initial letter; (iii) semantic associations between and within categories were minimized; (iv) all words were between 5 and 10 letters long.

In the study phase, participants studied all the 84 category-exemplar word pairs (e.g. “fruit-prune”). They were instructed to memorize each exemplar by relating it to its category. Trials started with a 500-ms fixation cross, followed by a 500-ms blank screen; after that, the category-exemplar word pair appeared and remained visible for 3500 ms, followed by a final 500-ms blank screen. To discourage integration strategies, which can impair RIF (Murayama et al., 2014), stimuli were presented in a randomized blocked order, with the constraint that 2 items from the same category could not be shown one after another. Blocks consisted of 12 items, with each item randomly drawn from one of the 12 semantic categories.

In the practice phase, participants practiced 4 times only the weak exemplars of half the semantic categories (72 trials in total). This was done to increase RIF, as the remaining strong exemplars are more likely to exert competition (Anderson et al., 1994). In this phase, on each trial, participants were shown only the category and the first two letters of each exemplar (e.g. “fruit-pr___”). Each pair was visible for 8000 ms. Participants were instructed to type the full name of the associated exemplar. Since about half the patients had poor familiarity with computers, they received a modified version of the task, where they answered by speaking loudly to the experimenter, who then typed the answer. An identical number of participants in the control group performed the practice phase in the same fashion.

To allow for subsequent analysis of RIF and FAC effects, the weak exemplars practiced during this phase were labelled as RP+ items, while non-practiced strong items belonging to practiced categories were labelled RP-. Weak items belonging to non-practiced categories were labelled NRP+, whereas strong items belonging to non-practiced categories were labelled NRP-. Categories shown in this phase were counterbalanced across participants and groups, so that every category contributed equally to all four types of items, and to the suppression and facilitation effects at a group level. To this end, we used four counterbalanced lists.

Between the practice phase and the final test phase of the RPP, participants filled several questionnaires as a distractor task. The semantic content of the items in the questionnaires was unrelated to the category-exemplar pairs used in the RPP. The questionnaires also included the *Barratt Impulsiveness Scale-11* (*BIS-11*; Patton, Stanford, & Barratt, 1995) consisting of 30 items rated on a 4-point Likert scale, encompassing Motor Impulsiveness, Nonplanning Impulsiveness, and Attentional Impulsiveness.

In the test phase, participants were shown all stimuli (84 trials) again. Presentation format and response modality for the stimuli was the same as in the practice phase, with the exception that on each trial participants were now shown the category plus the first letter of an exemplar (e.g. “fruit-p____”). Participants were instructed to type the full name of the associated exemplar. Presentation order was similar to the previous phases, with the additional constraint that all RP- and NRP- items were shown before all the RP+ and NRP+ items, thus allowing to control for test-based output interference effects on the RIF measure (e.g., Storm & Levy, 2012). Moreover, it has been shown that RIF measured with this specific final test format, as opposed to test formats that allow for greater contribution of interference, is positively correlated with the efficiency of motor inhibition in healthy individuals (Schilling et al., 2014).

6.2.3 Sustained Attention to Response Task (SART)

After the participants had completed the RPP, they performed the SART (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), included as a control measure for a general attentional or reactivity impairment. The participants were instructed to respond to each item of a rapid sequence of digits, interleaved with masks, except for the digit "3" for which they were asked to withhold response. 225 single digits from "1" to "9" were centrally presented for 250 ms, 25 times each, interleaved with a mask ("#") lasting 900 ms. To discourage perceptual strategies, digits were presented at varying font size (48, 72, 94, 100, or 120 point, Symbol font). Participants were instructed to respond as quickly and accurately as possible by pressing the spacebar. The SART is intended to elicit and probe slips of attention, as the task is very fast and repetitive but also includes highly infrequent trials (4%) associated to a different instruction.

6.2.4 Analysis

6.2.4.1 Retrieval Practice Paradigm (RPP)

For the RPP, only the test phase data were analysed. For each participant, the proportion of correct recall for each item type (i.e. RP+, NRP+, RP-, NRP-) was computed. Subsequently, we computed individual FAC (RP+ minus NRP+) and RIF (NRP- minus RP-) effects. Higher values of FAC indicate the beneficial effects of practice, whereas higher values of RIF indicate more efficient memory suppression. Next, we performed a mixed-design ANOVA for FAC, with group (i.e. AA, DA, Control) as a between-participant and item type (i.e. RP+, NRP+) as a within-participant factor. Similarly, we conducted a mixed-design ANOVA for RIF, with group as a between-participant and item type (i.e. NRP-, RP-) as a within-participant factor. Because groups were different in terms of age and education (see Table 6.1), in the presence of significant effects involving group as factor, we also reported the outcomes of ANCOVA, in which the impact of these variables was controlled for.

6.2.4.2 Sustained Attention to Response Task (SART)

A similar approach was adopted to analyse SART data, with Group as factor, and RTs for correct responses, percentage of total errors, and percentage of commission errors as dependent measures. To address group differences in self-reported impulsivity, a measure that might potentially be related to memory suppression, we computed BIS-11 total scores and submitted them to an ANOVA with group as factor. Because group was significant (see Table 6.1), we performed an ANCOVA on RIF scores with BIS-11 total score as covariate to ascertain whether group differences in memory suppression could be affected by different self-reported impulsivity. Finally, Pearson's correlations were performed to address possible associations between cognitive processes underlying RPP, SART, and self-reported impulsivity.

6.3 Results

6.3.1 Retrieval Practice Paradigm (RPP)

As for the FAC effect, the ANOVA revealed a significant main effect of Item Type, $F(1,81) = 146.88$, $p < .001$, $\eta^2_p = .64$, reflecting a better recall of RP+ (M = 34.19, 95%CI = 30.30/38.09) items than NRP+ items (M = 14.88, 95%CI = 12.59/17.17). Neither the main effect of Group, $F(2,81) = 2.79$, $p = .068$, $\eta^2_p = .06$, nor the Group x Item Type interaction, $F(2,81) = 1.10$, $p > .250$, $\eta^2_p = .03$, were significant. Hence, all groups were able to learn from practice to a similar extent (see Figure 6.1, Panel A).

As for the RIF effect, the ANOVA revealed a significant main effect of Group, $F(2,81) = 3.47$, $p = .036$, $\eta^2_p = .08$. Critical for the purpose of the study, the Group x Item Type interaction approached statistical significance, $F(2,81) = 3.05$, $p = .053$, $\eta^2_p = .07$. As anticipated above, to rule out the possibility that differences in RIF among the three groups reflected differences in age/education (see Table 6.1) rather than cognitive alterations in memory suppression mechanisms related to substance abuse, an ANCOVA was conducted using the two variables as covariates. Neither the Age x Item Type interaction, $F(1,79) = 1.30$, $p > .250$, $\eta^2_p = .02$, nor the Education x Item Type interaction, $F(1,79) = 1.05$, $p > .250$, $\eta^2_p = .01$, were significant. The main effect of Group disappeared when controlling for age and education, $F(2,79) = 1.41$, $p > .250$, $\eta^2_p = .03$. Most important, the Group x Item Type interaction yielded the predicted significant effect, $F(2,79) = 3.68$, $p = .030$, $\eta^2_p = .08$ (Figure 6.1, Panel

B), whereas the main effect of Item Type was not significant, $F(1,79) = 2.47$, $p = .120$, $\eta^2_p = .03$. Two-tailed Bonferroni-corrected t-tests indicated that RIF was significant in the control group, $t(27) = 2.78$, $p = .010$, but not in the DA, $t(27) = -.17$, $p > .250$, and AA, $t(27) = -.06$, $p > .250$, groups. The Bayesian information criterion (BIC) was computed to disentangle which model (null vs. alternative hypothesis) was more strongly supported by the data regarding the presence of RIF in each group. The posterior probability favoring the alternative hypothesis (NRP- items recalled better than RP- items) in the control group was $p_{\mathrm{BIC}}(H_1|D) = 0.866$ which, according to the conventional categorization of degrees of evidence (Masson, 2011), constitutes a positive evidence for the presence of RIF in this group. In sharp contrast, the posterior probability supporting the alternative hypothesis was $p_{\mathrm{BIC}}(H_1|D) = 0.161$, for the DA group and $p_{\mathrm{BIC}}(H_1|D) = 0.159$ for the AA group, clearly indicating that no RIF was present in these patients.

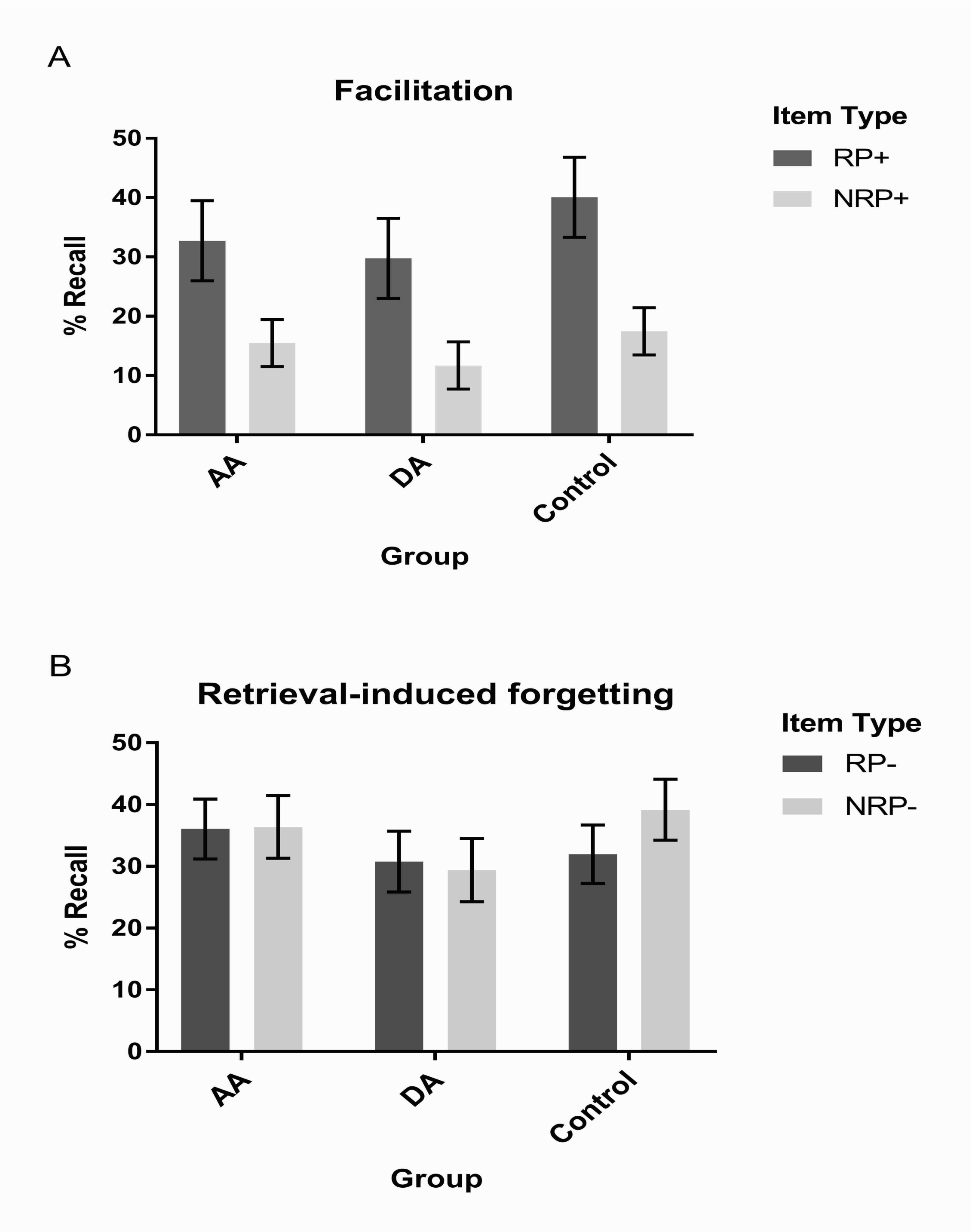

Figure 6.1 Recall data from the final test phase in the three groups. Panel A shows that FAC (better recall of RP+ items than NRP+ items) was significant and comparable in the three groups. Panel B shows that RIF (better recall of NRP- items than RP- items) was significant only for the control group. Bars represent 95% CIs.

Given that the DA group was not entirely homogeneous in terms of diagnosis, we re-run all the analyses by restricting this group to the 24 patients with a primary diagnosis of heroin addiction. The overall results were virtually unchanged.

6.3.2 Sustained Attention to Response Task (SART)

Turning to SART, the Group factor did not yield a significant effect in the ANOVAs conducted on RTs for correct responses, $F(2,81) = .79$, $p > .250$, $\eta^2_p = .02$, percentage of total errors, $F(2,81) = 1.79$, $p = .174$, $\eta^2_p = .04$, and percentage of commission errors, $F(2,81) = .23$, $p > .250$, $\eta^2_p = .01$. Thus, the three groups did not exhibit any reliable differences in their sustained attention abilities.

The ANOVA on BIS-11 total scores revealed a significant main effect of Group, $F(2,81) = 9.85$, $p < .001$, $\eta^2 = .20$. Bonferroni-corrected post-hoc analyses revealed that participants in the DA group reported to be significantly more impulsive (M = 69.54, 95%CI = 65.05/74.02) than both participants in the AA (M = 61.39, 95%CI = 58.12/64.66) and the control group (M = 58.57, 95%CI = 55.29/61.85), which were not significantly different from each other (see Table 6.1). An ANCOVA on the proportion of correct recall for RP- and NRP- items (RIF effect) with total BIS-11 score as covariate confirmed the presence of a significant Group x Item Type interaction, $F(2,80) = 3.25$, $p = .044$, $\eta^2_p = .08$, in the absence of a significant BIS-total x Item Type interaction, $F(1,80) = .48$, $p > .250$, $\eta^2_p = .01$. This pattern clearly shows that the differences in RIF among the three groups were not driven by differences in self-reported impulsivity.

Finally, Pearson's correlation analyses conducted between RPP measures, SART measures, and BIS-11 scores revealed that RIF and FAC were not associated with each other ($p > .250$), and that neither RIF nor FAC exhibited significant correlations with the different SART measures and BIS-11 total and subscale scores. A similar lack of association was also observed when correlating SART and BIS-11 measures.

6.4 Discussion

Deficits in inhibition and cognitive control are a key feature of substance-related and addictive disorders, as they may contribute to the onset, maintenance, and relapse of addiction (e.g., Smith et al., 2014). The majority of research so far has focused on motor inhibition and impulsivity. However, inhibitory mechanisms have been hypothesized also in the context of episodic memory. Failures of inhibitory control in this domain may be as important for our understanding of this class of disorders as those observed in overt action, but remain largely unexplored. The present study opens a new window in this regard, by investigating the suppression of competing memories in two distinct clinical populations, namely individuals affected by alcohol- and heroin- use disorders. Indeed, previous research has documented impairment of intentional memory suppression in these patients (e.g., Noël, Billieux, Van der Linden, Dan, Hanak, de Bournonville, et al., 2009; Zou, Zhang, Huang, & Weng, 2011), although the paradigms used so far do not allow establishing the involvement of a pure inhibitory mechanism (e.g., Sahakyan & Delaney, 2005). Importantly, here we focused on incidental suppression mechanisms, which have been found to be impaired in other clinical populations characterised by dysregulation of executive control, such as patients suffering from ADHD (Storm & White, 2010), or schizophrenia (Racsmány, Conway, Garab, Cimmer, Janka, Kurimay , et al., 2008).

Our hypothesis was primarily driven by two sets of evidence: The known inhibitory deficits regarding motor action, extensively investigated in substance abuse, and the prefrontal loci of brain damage due to extensive substance abuse. As discussed above, substance-related and addictive disorders can have a dramatic impact on cognitive and neurological integrity. With respect to the clinical populations examined here, both alcoholism and opioid abuse have been associated to widespread deficits in executive control and to structural changes comprising the fronto-temporal cortices and the hippocampus (e.g., Stavro, Pelletier, & Potvin, 2013; Wang, Li, Zhou, Liao, Tang, Liu, et al., 2012). Given that PFC has been proposed as one of the key nodes in the neural network supporting memory suppression (e.g., Anderson & Hanslmayr, 2014; Penolazzi et al., 2014), we hypothesized that substance abuse might be associated to impairments in the ability to suppress competing memories.

Our results from the RPP confirmed the hypothesis, with both clinical groups showing impaired RIF (i.e., memory suppression) compared to the control group. Importantly, the present clinical samples exhibited an intact FAC effect. This opposed pattern of impaired RIF and intact facilitation points to a specific deficit in suppressing competing memories, rather than an overarching impairment of the episodic memory system. Moreover, we provided two additional and mutually independent pieces of evidence in favour of a selective deficit interpretation of our results: i) overall recall performance in the test phase did not significantly differ across groups, when controlling for demographic variables that were not evenly matched between groups; ii) similarly, performance in the SART was comparable across groups, indicating that our participants in the clinical samples did not display a deficit in sustained attention compared to the control group.

6.4.1 Relevance

These findings have important implications for the understanding of substance-related and addictive disorders and for their relevance in testing extant accounts of RIF. An interesting future development of this study will be testing the same clinical populations with material specifically tailored to the disorders under examination. This approach has recently proved very effective in the investigation of selective forgetting deficits in anxiety disorders as a function of the semantic relatedness of the material with respect to the disorder (Kircanski, Johnson, Mateen, Bjork, & Gotlib, 2016; Law, Groome, Thorn, Potts, & Buchanan, 2012). This latter approach might further clarify the source and extent of the inhibitory deficits characterizing substance-related and addictive disorders. For example, it could be hypothesized that category-exemplar word pairs that directly relate to substance abuse may undergo even poorer memory suppression in these patients, due to increased familiarity with such material or, alternatively, the presence of a memory bias that forces toward additional processing of disorder-relevant material (e.g., Saunders, 2012). Turning to extant accounts of RIF, the present study provides strong evidence of inhibitory deficits in episodic memory suppression within substance-related and addictive disorders. Importantly, although deficits in episodic memory have been reported in addictive disorders (e.g., Fernández-Serrano et al., 2011; Pitel et al., 2007), in the present study, this deficit was specific for the detrimental (i.e. RIF), but not for the beneficial effects (i.e. FAC) of retrieval practice. This pattern, together with the observation of a null correlation between the two phenomena, is in line with predictions stemming from inhibitory accounts of RIF (see Storm & Levy, 2012), which posit RIF and facilitation to reflect independent cognitive mechanisms, and less consistent with alternative accounts based on either interference or inappropriate contextual cuing (e.g., Raaijmakers & Jakab, 2013). Extending inhibitory impairment to the memory domain in addictive disorders may lend support to a more domain-general account based on the proposal of a unitary inhibitory mechanism over action and memory (Anderson & Weaver, 2009).

6.4.2 Limitations

Due to the present experimental design, it is difficult to establish whether the deficit in memory suppression is either caused by, or rather responsible for, the onset of the disorders examined here, and inhibitory deficits could entail either or both these relationships with substance addiction. Longitudinal studies, along with research addressing the recovery of cognitive performance in abstinent patients, will contribute to disentangle the role of inhibitory deficits within substance abuse, and their relationship with possible altered working memory functioning.

6.4.3 Conclusions

In conclusion, the present findings highlight that alterations in inhibitory abilities in substance-related and addictive disorders are more widespread than previously shown, as they involve not only overt behaviour but also internally-directed aspects of inhibitory control related to memory and the content of our thoughts. This result suggests that neuropsychological assessment of addicted patients should also test memory suppression abilities. Future clinical research will have the important task of addressing whether other types of addictive disorders (e.g., pathological gambling) exhibit a similar cognitive profile with respect to internal inhibitory mechanisms. This, in turn, might have important implications for a better understanding of addictions and for planning more comprehensive clinical interventions taking into account all of the different facets of inhibitory control impairments.

7 RIF IN ANOREXIA AND BULIMIA NERVOSA

This chapter has been submitted for publication as **Stramaccia, D. F.**, Penolazzi, B., Libardi, A., Genovese, A., Castelli, L., Palomba, D., & Galfano, G. Control over Interfering Memories in Eating Disorders.

Recent studies have suggested that patients suffering from either anorexia nervosa (AN) or bulimia nervosa (BN) exhibit abnormal performance in the ability to control cognitive interference in response selection. Here, we assessed the status of cognitive control in episodic memory, by addressing the ability to inhibit interfering memories. To this end, we used the retrieval-practice paradigm, which allows for measuring both the beneficial and the detrimental effects of memory practice. The latter phenomenon, known as retrieval-induced forgetting (RIF), is thought to reflect an adaptive inhibitory mechanism aimed at reducing competition in memory retrieval. Twenty-seven healthy controls and 27 patients suffering from eating disorders (either AN or BN) performed a retrieval-practice paradigm and a control task addressing general reactivity, and filled a self-report questionnaire on impulsivity. No differences between patients and healthy controls were observed for the beneficial effects of practice. The same pattern also emerged for RIF. However, when patients with AN and BN were analyzed separately, a clear dissociation emerged: Patients with AN displayed no hint of RIF, whereas patients with BN showed an intact memory suppression performance that was even better than that of the control group. No group differences emerged in the control task. Limitations The limited sample size does not allow to draw inferences about subtypes of AN. Our findings suggest a specific impairment in the ability to suppress interfering memories in patients with AN, thus extending current evidence of cognitive control deficits in AN to episodic memory.

7.1 Introduction

Research aimed at investigating the nature and the aetiology of eating disorders (ED) has been the target of an increasing number of studies in recent years (e.g., Treasure, Claudino, & Zucker, 2010). Indeed, there is a great bulk of knowledge concerning behavioural manifestations involved in the psychopathology of anorexia nervosa (AN) and bulimia nervosa (BN), with some studies suggesting a link between AN and compulsive traits on the one hand (e.g., Serpell, Livingstone, Neiderman, & Lask, 2002) and BN and impulsive personality on the other hand (e.g., Fischer, Smith, & Cyders, 2008). Yet, much more effort needs to be directed towards characterising the cognitive profile of patients with ED, as the cognitive reflections of these mental disorders are not fully understood (Zakzanis, Campbell, & Polsinelli, 2010). For instance, evidence is accumulating suggesting that AN patients exhibit an alteration in the ability to control shifts of spatial attention (Dalmaso, Castelli, Franchetti, Carli, Todisco, Palomba, & Galfano, 2015; Dalmaso, Castelli, Scatturin, Carli, Todisco, Palomba, & Galfano, 2016; Watson, Werling, Zucker, & Platt, 2010). However, a less consistent picture emerges from studies addressing executive functions and cognitive control, which yielded mixed results. For example, in their systematic review of reactive inhibitory control in EDs, Bartholdy, Dalton, O'Daly, Campbell, and Schmidt (2016) showed that many studies failed to observe impairment of reactive inhibition, as indexed by Stop-Signal Reaction Times (SSRTs), which are thought to reflect the individual covert latency of the cognitive process that reactively inhibits motor behaviour (Logan, Schachar, & Tannock, 1997). They further argued that other inhibitory control components could have a stronger relationship with EDs and their symptoms. In contrast, a meta-analysis on inhibitory control in bulimic-type EDs (Wu, Hartmann, Skunde, Herzog, & Friederich, 2013), which tried to address the variability in the results observed so far on this issue, found a general impairment of inhibitory control in both reactive inhibition tasks (e.g., stop-signal task) and cognitive interference control tasks (e.g., Stroop task). A similar deficit has recently been documented by Yano, Kawano, Tanaka, Kohmura, Katayama, Nishoka et al. (2016), who found dysfunctional cognitive control in ED patients (mainly diagnosed with AN) as measured by a modified Simon task, despite preserved sustained attention.

Neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) have also been used, in order to provide additional evidence regarding the status of inhibitory control in EDs, as well as its neural underpinnings. For example, Skunde, Walther, Simon, Wu, Bendszus, Herzog, et al. (in press) found evidence of altered activation in the fronto-striatal circuit during inhibitory performance in BN, and suggested that it could moderate the severity of the disease symptoms. Moreover, a few studies found altered prefrontal activity in AN, related to cognitive control tasks (e.g., Lock, Garrett, Beenhakker, & Reiss, 2011; Zastrow, Kaiser, Stippich, Walther, Herzog, Tchanturia et al., 2009). For instance, Collantoni, Michelon, Tenconi, Degortes, Titton, Manara, and Colleagues (2016) reported impaired response inhibition in a stop-signal task accompanied by aberrant functional connectivity in the right inferior frontal gyrus, which is a critical brain region in inhibitory control (e.g., Stramaccia et al., 2015).

An important aspect of the studies reviewed so far is that they highlighted how executive functions and inhibitory processing are important not only in the control of action, but also in the control of covert behaviour, potentially involved in the pathogenesis of ED symptoms (e.g., compulsive eating or uncontrolled food restriction). However, a limited variety of tasks (e.g., Simon task, Go/No-Go task) has been used to address the issue in EDs. Here, we aimed to further this line of research by investigating control of interference over episodic memory, which may also be important regarding the cognitive profile of patients suffering from EDs. In particular, recent works with healthy participants have pointed out the beneficial role that suppression over interfering or unwanted memories can play in achieving goal-oriented behaviour, emotion regulation, and wellbeing (e.g., Nørby, 2015; Storm, 2011; Storm & Angello, 2010).

Because of that, the aim of the present study was to investigate whether the specific ability to recruit executive control mechanisms deputed to suppress interfering memories is altered in patients with a primary diagnosis of ED. To this end, we measured for the first time the amount of retrieval-induced forgetting (RIF) in a sample of ED patients, and compared it to a healthy control group. The RIF effect describes the counterintuitive situation where retrieving items from episodic memory impairs subsequent recall of related items. RIF represents the detrimental effect of practice and is generally interpreted as the by-product of inhibitory mechanisms that are recruited to reduce interference from associated, task-irrelevant items, in order to promote retrieval of the task-relevant items (Anderson, 2003). Moreover, RIF seems to be a ubiquitous effect in episodic memory, as it has been measured with a broad variety of stimuli (e.g., Galfano et al., 2011), and it has been found to be impaired in a variety of psychiatric and neuropsychological conditions other than EDs (e.g., Storm & Levy, 2012). In the present study RIF was investigated by using the retrieval-practice paradigm (RPP; Anderson, 1994), which is the procedure most commonly used to probe RIF in a laboratory setting. In the RPP, participants study a list of numerous word pairs composed of a semantic category and an exemplar belonging to that category. Subsequently, they perform repeated practice on half the exemplars from half the categories. Lastly, participants' memory for the entire study list is tested, most frequently by means of a category-plus-letter cued recall test. This procedure bears two typical findings: on the one hand, memory at test is enhanced for practiced over non-practiced exemplars, an effect often called “facilitation” (FAC); on the other, and more surprisingly, memory is impaired for non-practiced exemplars that belong to practiced categories, compared to non-practiced exemplars that belong to non-practiced categories, which is what is usually referred to as RIF effect.

Clinical populations characterized by symptoms associated with either impulsivity or compulsivity (e.g., Attention Deficit Hyperactivity Disorder; Obsessive-Compulsive Disorder, OCD) often show reduced levels of RIF which has been interpreted as evidence for a deficit in the mobilization of inhibitory mechanisms in the context of episodic memory (e.g., Demeter et al., 2014;

Racsmány et al., 2008; Storm & White, 2010). Similar findings have been reported with other experimental tasks that probe memory control, such as the think/no-think paradigm (Depue et al., 2010; Sala, Caverzasi, Marraffini, De Vidovich, Lazzaretti, d'Allio, et al., 2009). Because patients with ED are characterized by impulsive and compulsive symptoms, with the former apparently being more prominent in BN (e.g., Fischer et al., 2008) and the latter in AN (e.g., Serpell et al., 2002), patients with ED could exhibit alterations in exerting control over interfering memories. According to an influential class of models available in the literature (Anderson, 2003; Bäuml, Pastötter, & Hanslmayr, 2010), RIF and FAC would be independent phenomena, as only RIF would rely on executive processing and suppression mechanisms. This view is supported by evidence suggesting that the two phenomena rely on dissociable neural underpinnings (e.g., Penolazzi et al., 2014; Wimber et al., 2009). In this regard, it is worth noting that the brain regions that seem to be chiefly involved in RIF (mainly located in the prefrontal cortex, see Wimber et al., 2009) are partially overlapping with those showing a reduced activity in patients with ED performing cognitive control tasks (e.g., Lock et al., 2011; Zastrow et al., 2009). Based on this reasoning, and in consideration of the possible link between ED and dysfunctional executive processing (Wu et al., 2013), we expected to observe a weaker RIF effect in the ED group, compared to the control group, signifying impairment in memory control ability. In contrast, we expected to observe similar levels of FAC across the two groups, reflecting an intact ability to strengthen items in episodic memory through repeated retrieval practice.

7.2 Methods

7.2.1 Participants

54 participants took part in the study: 27 malnourished outpatients with a primary diagnosis of eating disorders (ED group) in treatment at the *Azienda Provinciale per i Servizi Sanitari*, Trento, Italy, and 27 healthy volunteers recruited from the local community and university (Control group). All patients were diagnosed by a board-certified attending research team of psychiatrists

according to the DSM-5 criteria for ED (American Psychiatric Association, 2013). The ED group was composed of 2 males and 25 females, and included 15 AN patients (mean age = 29.53, *SD* = 10.97; mean years of education = 14.33, *SD* = 1.76; mean BMI = 17.3, *SD* = 2.06) and 12 BN patients (mean age = 27.42, *SD* = 8.72; mean years of education = 14.25, *SD* =1.76; mean BMI = 22.51, *SD* = 3.94). Five of the AN patients were classified as Binge Purge subtype, and 10 as Restrictive subtype. Two AN patients were reported to display OCD and borderline personality disorder symptoms, respectively. Four BN patients were reported to display depressive symptoms. Sixteen patients were medicated (10 patients with AN, 6 patients with BN). Most common medications consisted of benzodiazepines and/or SSRI antidepressants. Medical treatment also included vitamins and dietary supplements. The Control group consisted of 8 males and 19 females (mean age = 27.22, *SD* = 7.63; mean years of education = 15.67, *SD* = 2.97; mean BMI = 21.88, *SD* = 2.52). There was no significant difference in either age, *t*(52) = -.57, *p* = .57, or years of education, *t*(52) = 1.90, *p* = .07, between the ED group and the healthy control group. All participants were native Italian speakers with no history of neurological disease or learning disability. The Ethics Committee for Psychological Research of the University of Padua approved the study. All participants signed an informed consent form prior to their participation, and another one at the end of the whole procedure.

7.2.2 Retrieval Practice Paradigm (RPP)

Participants sat in front of a 15-in. laptop monitor (1366 × 768 pixels, 60 Hz), where stimuli were presented in black against a grey background (Courier New bold font, 30pt). All tasks were delivered using E-prime 2.0.

We used an adapted version of the Retrieval-Practice Paradigm (Anderson et al., 1994). All stimuli were selected and adapted from the categorical production norms for the Italian language (Boccardi & Cappa, 1997). Ninety-six category-exemplar word pairs belonging to 12 semantic categories were included, with 2 parallel subsets of 4 exemplars for each category. Stimuli were selected according to the following criteria: (i) semantic associations within and between categories were minimized; ii) exemplars had medium to high taxonomic strength; (iii); on average, exemplars had a very low lexical frequency, according to the online database itWac (Baroni, Bernardini, Ferraresi, & Zanchetta, 2009); (iv) categories and subsets were roughly balanced in term of taxonomic strength and lexical frequency of their respective exemplars v) exemplars within the same category never begun with the same initial letter; (vi) all words were no longer than 11 and no shorter than 5 letters.

The participants proceeded to study all the 96 category-exemplar word pairs (e.g. “birds-sparrow”), with the instruction to memorize each exemplar by thinking of how it could be related to its category (see Figure 7.1). Study trials started with a 500-ms fixation cross, followed by a category-exemplar word pair that stayed on screen for 4000 ms, followed by a 500-ms blank screen. Stimuli were presented in a randomized blocked order, with the constraint that 2 items belonging to the same category were never shown one after another. Each block consisted of 12 items, and each item was randomly drawn from one of the 12 semantic categories. These precautions were used to discourage strategies known to promote integration, which in turn can reduce RIF (Anderson & McCulloch, 1999).

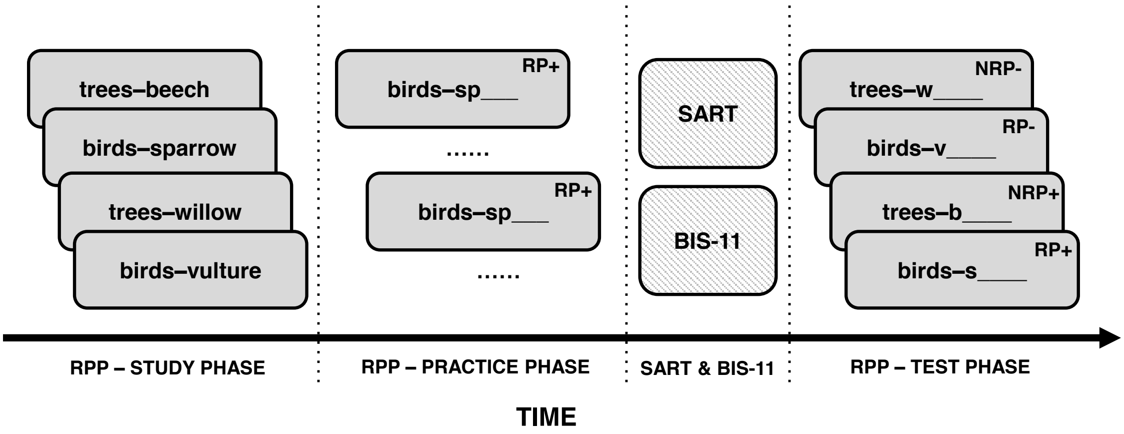

Figure 7.1 Schematic illustration of the experimental procedure, with tasks ordered chronologically from left to right. Participants studied all the experimental material from the RPP first, and after that they immediately engaged in repeated practice on a subset of the material (see section 2.2.1.2.). Subsequently, participants performed the SART and filled the BIS-11 questionnaire. Finally, participants performed the test phase of the RPP, where they were tested on all the stimuli from the study phase.

In the following practice phase, the participants actively practiced one subset (four exemplars) of half categories for three times, with 72 trials in total. Presentation order was similar to the previous phase. On each trial, participants were first shown a fixation cross for 500 ms, followed by the presentation of a semantic category alone (e.g. “birds”) for 1500 ms to promote activation of interfering exemplars (see Bajo, Gómez-Ariza, Fernandez, & Marful, 2006) and subsequent need for memory control, followed by the same category and the first two letters of an exemplar (e.g. “birds-sp___”) for 8000 ms. During that time, participants were instructed to type in full the name of the associated exemplar that they had previously studied that matched both the category and the stem provided. Exemplars that received practice during this phase were labelled as RP+ items, while non-practiced exemplars belonging to practiced categories were labelled RP-. Exemplars from one of the subsets of each non-practiced categories were labelled NRP+, whereas exemplars from the remaining subsets of non-practiced categories were labelled NRP-. The designation of practiced and control categories and exemplars that contributed to the measurement of both RIF (NRP- minus RP-) and FAC (RP+ minus NRP+) effects was roughly counterbalanced across all participants by using predetermined lists (24 lists in total).

After the practice phase and the Sustained Attention to Response Task (SART, Robertson et al., 1997; see 7.2.3 below), participants took part in the test phase of the RPP (see Figure 7.1), and they were tested on all the stimuli presented in the study phase (96 trials). Each trial started with a 500-ms fixation cross, followed by the stimulus for 8000 ms, with a similar presentation format and response modality as in the practice phase, with the exception that participants were shown the category along with the first letter only (e.g. “birds-s____”). Participants were instructed to type the corresponding exemplar in full. Presentation order was handled as in the previous phases, with the additional constraint that all RP- and NRP- items were shown before all the RP+ and NRP+ items, to avoid output interference effects that could inflate the RIF measure (Anderson, 2003).

7.2.3 Sustained Attention to Response Task (SART)

Between the practice phase and the final test phase of the RPP, participants performed the SART (Robertson et al., 1997), which was included as a control measure to address a more general impairment of attentional or reactivity abilities, as opposed to a specific deficit in the ability to exert cognitive control over interference. Participants were instructed to respond to each item of a rapid sequence of digits, interleaved with masks, except for the digit "3" for which they were asked to withhold response. Two-hundred and twenty-five single digits from "1" to "9" were presented for 250 ms, 25 times each, interleaved with a mask ("#") lasting 900 ms. Digits were presented at a varying font size (48, 72, 94, 100, or 120 point, Symbol font), in order to discourage participants from using perceptual strategies. Stimuli were presented centrally, in black against a grey background. Participants were instructed to respond as quickly and accurately as possible with a key press of the spacebar, and to withhold response upon presentation of the digit "3". As the main purpose of the SART is to elicit slips of attention, the task works at a very quick and repetitive pace, but also incorporates highly infrequent trials (4%) that require a different response. After completing the SART, participants also filled the Italian version of the Barratt Impulsiveness Scale-11 (BIS-11; Fossati, Di Ceglie, Acquarini, & Barratt, 2001), whose semantic content is unrelated to the material used in the RPP. The questionnaire consists of 30 items rated on a 4-point Likert scale, pertaining to three dimensions: Motor Impulsiveness (tendency to act on impulse without forethought), Nonplanning Impulsiveness (lack of future planning), and Attentional Impulsiveness (difficulty in maintaining attention).

7.2.4 Analysis

7.2.4.1 Retrieval Practice Paradigm (RPP)

For the RPP, we analysed the data collected during the test phase to obtain an individual measure of FAC and RIF effects. For each participant, we computed the proportion of correct recall for each Item Type (i.e., RP+, NRP+, RP-, NRP-). We then focused on the beneficial and the detrimental effects of practice, by computing FAC (RP+ minus NRP+) and RIF (NRP- minus RP-)

effects, respectively. We first performed two mixed-design ANOVAs on FAC and RIF effects, with Group (ED, Control) as a between-participant factor and Item Type (i.e., RP+, NRP+ for FAC, NRP-, RP- for RIF) as a within-participant factor. Subsequently, we explored whether patients diagnosed with AN and those diagnosed with BN displayed similar patterns of cognitive response. Because visual inspection of the data suggested different patterns in the two types of patients, we performed the same analyses on FAC and RIF effects, with the Group factor now consisting of three levels (i.e., AN, BN, Control). Because the latter analyses yielded the most informative results, all the subsequent analyses were performed with Group as a three-levels factor.

7.2.4.2 Sustained Attention to Response Task (SART)

For the SART, we conducted three one-way ANOVAs with Group as factor, each dealing with a different dependent measure (mean RTs for correct responses only, percentage of total errors, and percentage of commission errors). A similar approach was used to analyse data from the BIS-11 measures of self-reported impulsivity (total score, and Motor Impulsiveness, Nonplanning Impulsiveness, and Attentional Impulsiveness subscales). Finally, we computed Pearson's correlations to detect potential associations between the measure of cognitive control over interference (RIF), the measure of the beneficial effect of practice (FAC), sustained attention (SART), and self-reported impulsivity (total BIS-11 score, Motor Impulsiveness, Nonplanning Impulsiveness, and Attentional Impulsiveness scores).

7.3 Results

7.3.1 Retrieval Practice Paradigm (RPP)

For the FAC effect, the mixed ANOVA revealed a significant main effect of Item Type, $F(1,52) = 274.53$, $p < .01$, $\eta^2_p = .84$, reflecting a better recall of RP+ items ($M = 67.75$, *95%CI* = 64.48/71.01) than NRP+ items ($M = 38.04$, *95%CI* = 34.44/41.64), in line with a FAC effect. The main effect of Group, $F(1,52) = 13.49$, $p < .01$, $\eta^2_p = .21$, was also significant, with patients ($M = 58.26$, *95%CI* = 54.11/62.4) displaying an overall better performance than controls ($M = 47.53$, *95%CI* = 43.39/51.67), in line with recent evidence of elevated performance-based perfectionism in patients with EDs (Lloyd, Yiend, Schmidt, & Tchanturia, 2014). The Group × Item Type interaction was not significant, $F(2,52) = .82$, $p = .37$. Therefore, all groups benefited from retrieval practice to a similar extent.

Concerning the RIF effect, a mixed ANOVA revealed a significant main effect of Item Type, $F(1,52) = 14.76$, $p < .01$, $\eta^2_p = .22$, indicating better recall of NRP-items ($M = 48.26$, *95%CI* = 44.64/51.81) than RP- items ($M = 40.51$, *95%CI* = 36.79/44.22), consistent with a standard RIF effect (Murayama et al., 2014). Again, Group yielded a significant main effect, $F(1,52) = 6.72$, $p = .02$, $\eta^2_p = .11$), suggesting an overall better memory performance in the patient group ($M = 48.30$, *95%CI* = 44.00/52.61) compared to healthy controls ($M = 40.43$, *95%CI* = 36.13/44.74). Most importantly for the purpose of the study, the Group × Item Type interaction was not significant, $F(1,52) = .02$, $p = .88$, suggesting an intact ability to suppress interfering memories in the ED group, and was at odds with our predictions, as well as with previous evidence hinting at an altered ability to control interference in EDs (e.g., Wu et al., 2013b).

Next, we aimed to ascertain whether the two categories of patients included in the ED group displayed the same pattern for both RIF and FAC. Performing the same analysis on the three groups (Control, BN, AN) yielded quite different results.

The scenario observed for the FAC effect was consistent with that emerged in the previous analysis, as a mixed ANOVA showed a main effect of Item Type, $F(1,51) = 252.21$, $p < .01$, $\eta^2_p = .83$, a significant main effect of Group, $F(2,51) = 6.69$, $p < .01$, $\eta^2_p = .21$ (Control, $M = 47.53$, *95%CI* = 43.35/51.71; BN, $M = 57.47$, *95%CI* = 51.19/63.74; AN, $M = 58.89$, *95%CI* = 53.28/64.50), and no Group × Item Type interaction, $F(2,51) = .57$, $p = .57$ (see Figure 7.2), confirming that the three groups displayed a robust and very similar FAC effect.

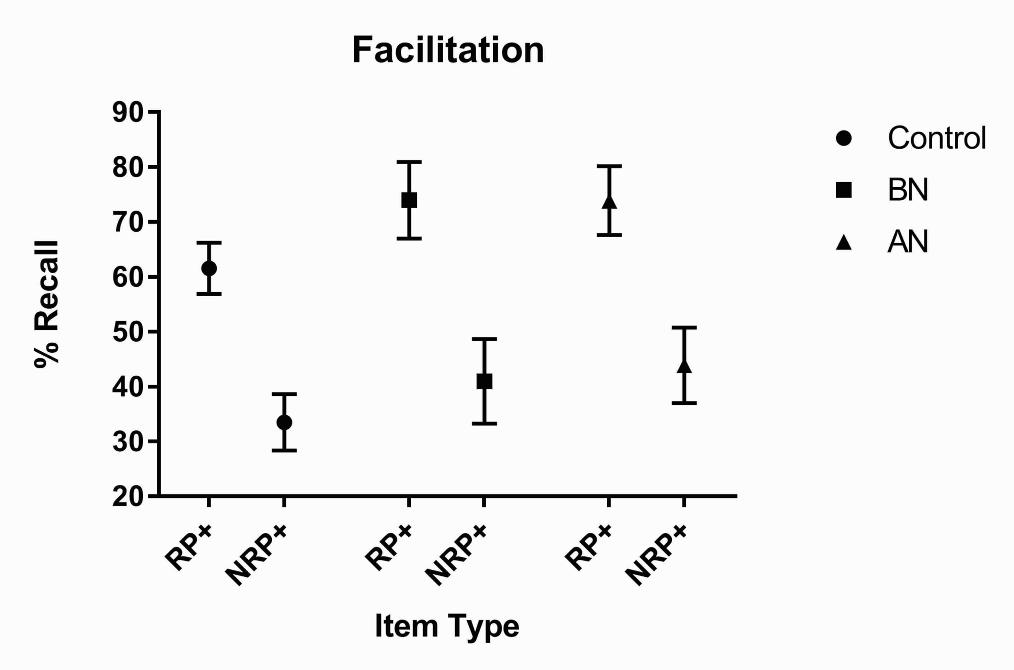

Figure 7.2 Recall performance from the final test phase for items relevant to the Facilitation (FAC) effect (RP+ minus NRP+ items) in the three groups. The FAC effect was significant in all groups. Bars represent 95% CIs.

In sharp contrast, a mixed ANOVA for the RIF effect not only confirmed a significant effect of Item Type, $F(1,51) = 20.70$, $p < .001$, $\eta^2_p = .29$, as well as a significant main effect of group, $F(2,51) = 7.40$, $p < .01$, $\eta^2_p = .23$ (Control, M = 40.43, *95%CI* = 36.36/44.50; BN, M = 42.19, *95%CI* = 36.08/48.29; AN, M = 53.19, *95%CI* = 47.73/58.66), but, crucially, also a significant Group × Item Type interaction, $F(2,51) = 7.80$, $p < .01$, $\eta^2_p = .23$ (see Figure 7.3). Two-tailed t-tests comparing memory performance on NRP- and RP- items showed that RIF was present in healthy controls, $t(26) = 2.85$, $p < .01$, in BN patients, $t(11) = 4.64$, $p < .01$, but not in AN patients, $t(14) = -.29$, $p = .77$. In addition, RIF was significantly more pronounced in BN patients compared to healthy controls, $t(37) = 2.46$, $p = .02$. These analyses suggest that AN patients have an impaired ability to overcome interference in memory, in the absence of a generalized memory problem, as testified by a reliable FAC effect with the same magnitude as that displayed by healthy controls (see Figure 7.3).

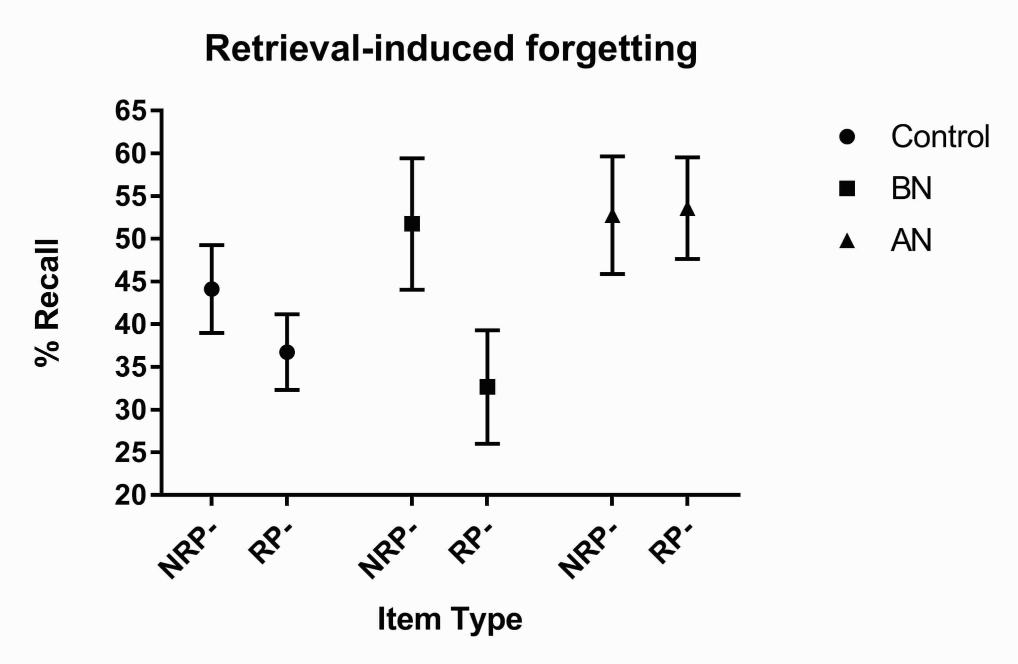

Figure 7.3 Recall performance from the final test phase for items relevant to the Retrieval-Induced Forgetting (RIF) effect (NRP- minus RP- items) in the three groups. RIF was significant in the Control and BN groups only. Bars represent 95% CIs.

7.3.2 Sustained Attention to Response Task (SART)

The series of one-way ANOVAs performed on SART measures with Group as factor did not reveal any significant effect (mean RTs for correct responses: *F*(2,51) = 1.29, *p* =.28; percentage of total errors: *F*(2,51) = .13, *p* = .88; percentage of commission errors: *F*(2,51) = 1.53, *p* = .23). Therefore, the three groups exhibited a similar ability to maintain attention.

7.3.3 Barratt Impulsiveness Scale (BIS-11)

The series of one-way ANOVAs performed on the BIS-11 questionnaire measures with Group as factor failed to show significant effects (total BIS-11 score: *F*(2,51) =.23, *p* = .80; Motor Impulsiveness score: *F*(2,51) =.12, *p* =.88; Nonplanning Impulsiveness score: *F*(2,51) =.66, *p* =.52; Attentional Impulsiveness score: *F*(2,51) = 1.61, *p* = .21). This suggests that the three groups were not different in terms of impulsiveness.

7.3.4 Correlations

Pearson's correlation analyses conducted between RPP measures, SART measures, and BIS-11 scores showed a clear lack of association between RIF and FAC (*r* = .02). In addition, neither RIF nor FAC displayed significant correlations with the different SART measures and BIS-11 scores. A similar pattern was also observed when correlating SART and BIS-11 measures.

7.4 Discussion

The present study was aimed at enriching the knowledge concerning the cognitive profile of ED patients. Specifically, our goal was addressing cognitive control in a group of patients with either AN or BN, by focusing on the previously unexplored domain of episodic memory. To this end, we used the RPP, a task that is known to elicit two phenomena thought to reflect both the beneficial and the detrimental effects of memory retrieval practice on the subsequent recall (Anderson et al., 1994). The former phenomenon, known as FAC effect, reflects the well-established advantage of trained over untrained material due to active practice. The latter phenomenon, known as RIF, is thought to probe an adaptive aspect of forgetting which, according to a prominent class of models, is achieved through the implicit recruitment of inhibitory processing aimed at decreasing interference between competing memories (Anderson, 2003; Bäuml et al., 2010). This choice of paradigm was motivated by the fact that, despite evidence of impaired cognitive control over interference has been reported in EDs, this pattern has been observed almost exclusively by means of tasks addressing selective attention (e.g., Yano et al., 2016; see Wu et al., 2013b for a review). Therefore, the present research represents the first attempt to investigate the cognitive profile of ED patients in the specific domain of resistance to interference in episodic memory.

The procedure also included the SART as a control task to rule out general reactivity deficits (Robertson et al., 1997), and the BIS-11 questionnaire (Fossati et al., 2001) to explore potential correlations between self-reported dimensions of impulsivity and cognitive control in memory.

We expected ED patients to exhibit a weaker RIF compared to a group of healthy controls based on two lines of evidence: (i) hampered cognitive control in EDs (Wu et al., 2013b; Yano et al., 2016), (ii) similar prefrontal brain regions associated with abnormal activity in ED patients performing cognitive control tasks (e.g., Collantoni et al., 2016) and RIF in healthy participants (e.g., Wimber et al., 2009). In addition, we hypothesized no group difference in either the beneficial effects of memory practice (i.e., FAC effect; see Demeter et al., 2014 for a similar dissociation in patients with Obsessive-Compulsive Disorder) or general reactivity (i.e., SART measures; e.g., Yano et al., 2016).

The results were partially in line with our predictions. Indeed, both FAC and SART measures were preserved in ED patients, as expected. However, a similar pattern emerged also for RIF. Subsequently, based on an explorative inspection of the data that suggested a different performance in the RPP depending on the specific ED type, we re-analysed the data with Group as a three-level factor (i.e., AN, BN, Control). These analyses confirmed that the groups had comparable levels of performance in both SART and FAC measures. In sharp contrast, critical for the purpose of the study, the new analyses revealed a striking difference in memory control, as indexed by RIF, as a function of Group. Specifically, patients with AN did not display any evidence of RIF, whereas patients with BN exhibited a significant RIF effect whose magnitude was larger than that of healthy controls.

7.4.1 Memory control differences between AN and BN

The results observed in patients with AN are in line with our predictions, and extend our knowledge about the status of cognitive control to the domain of episodic memory in this clinical population, which was previously unexplored, pointing to a very specific deficit. Indeed, cognitive control over interference appeared to be selectively impaired in patients affected by AN, which otherwise perform as well as healthy individuals in both control measures of attention and reactivity, and in the ability to benefit from memory practice. The specificity of this impairment in inhibition is in line with recent findings of dissociable cognitive control and sustained attention (Yano et al., 2016), and is further supported by the version of the RPP used here, which was designed to control for the main confounds that may affect RIF (e.g. Anderson, 2003; Storm & Levy, 2012). Interestingly, Demeter and Colleagues (2014) found a similar pattern of results (impaired RIF in the face of intact FAC) in patients suffering from OCD, which are thought to share many important similarities to patients diagnosed with AN (Altman & Shankman, 2009; Pollack & Forbush, 2013; Serpell et al., 2002). Because the psychopathological features shared by AN, OCD, and obsessive-compulsive personality disorder are not fully understood (Altman & Shankman, 2009; Boisseau, Thompson-Brenner, Pratt, Farchione & Barlow, 2013), our results suggest that the RPP may be used as a benchmark to further investigate differences and similarities between these psychiatric disorders, which could, in turn, provide useful information to orient both their diagnosis and treatment.

Turning to BN patients, the results were unexpected, in that we hypothesized a decreased RIF effect irrespective of the specific type of ED diagnosis. The obtained pattern of findings suggests that the ability to suppress interfering memories was fully preserved in patients with BN. Indeed, RIF in the BN group persisted even when participants showing a RIF that exceeded 2 SD from sample average were removed from the analyses. A possible interpretation to account for the observed findings is related to the observation that patients with BN were not significantly more impulsive than the control group according to the BIS-11 questionnaire. To the extent that an altered control ability in BN can be, at least partially, ascribed to an impulsive disposition, as some studies seem to suggest (e.g., Kemps, & Wilsdon, 2010), it might be speculated that the presence of an intact RIF effect could simply result from the low level of self-reported impulsiveness in our sample of patients with BN. Clearly, this pattern of results calls for further studies in order to possibly confirm these findings and shed light on this issue.

7.4.2 Limitations

Although we made every effort to control for major confounds in this study, a few important limitations remain that need to be addressed. First, due to the small sample size, we were not able to distinguish performance as a function of whether patients affected by AN were diagnosed with the restrictive subtype or the binge-purge subtype. Because past work has provided mixed evidence concerning different behavioural performance between the two subtypes in several cognitive tasks (see, Dalmaso et al., 2016; Rosval, Steiger, Bruce, Israël, Richardson, & Aubut, 2006; Yano et al., 2016), we have no specific reason to hypothesize that a dissociation should emerge in the RPP. However, this is an open empirical question that needs to be addressed in future studies.

Another relevant limitation is the presence of medicated patients in the clinical sample, within both the AN and BN groups, which could have influenced the results. While we cannot entirely exclude medication effects on our measures of interest, additional control analyses, summarised below, comparing medicated vs. non medicated patients in RIF magnitude, FAC magnitude, and the three SART measures in the groups of patients with AN and BN indicate that this is not the case. Indeed, a series of independent samples, two-tailed t-tests failed to show any differences due to medication in both AN and BN patients (lowest $p = .11$). In addition to medication, depression could also have influenced the results, specifically by reducing the magnitude of RIF (e.g., Groome & Sterkaj, 2010), due to the presence of comorbidity in four of the BN patients tested here. However, because the BN subgroup displayed an intact RIF, we can safely assume that the presence of depressive symptoms played only a limited role – if any – in shaping the results.

7.4.3 Conclusions

In conclusion, the present study found a selective impairment of the ability to inhibit interference from competing information in episodic memory, which was specific for patients suffering from AN, compared to a healthy control group, whereas this ability was preserved in patients with BN. No general deficit in sustained attention or motor reactivity, nor substantial differences in self-reported dimensions of impulsive behaviour were found that could provide alternative accounts for our findings. These results significantly extend our knowledge about the status of executive functioning in EDs, and open the way for future research on the features of a previously unexplored instance of cognitive control in this clinical population. In this view, a valuable trajectory for future work would be using experimental stimuli relevant to the disorders (e.g., Kircanski et al. ,2016; Tekcan, Taş, Topçuoğlu, & Yücel, 2008) such as food-related categories/words (or pictures), which would provide a deeper understanding of the nature and generalizability of this cognitive control impairment in EDs.

8 GENERAL DISCUSSION

In the following chapter, I provide a concise summary of the main findings of each experiment presented over the course of this dissertation, and discuss whether or not a coherent narrative can be inferred from the bulk of evidence provided by the present work in the subsequent paragraphs. In particular, I focus on the contribution of our experiments to the notion that right lateralized brain regions in the PFC serve an important role in memory control, and on the observation that RIF is impaired in clinical populations suffering from psychiatric disorders that are characterized by impulsivity, cognitive control problems, and altered PFC functioning. The importance of appropriate statistical analyses that can also take into account features of the experimental material employed in the RPP, and the fuzzy status of the evidence in respect to the putative relationship between memory control and motor stopping are also discussed. Finally, I suggest few research trajectories that stem from the main findings of the present dissertation, and discuss their theoretical and applied relevance.

8.1 Brief summary of experiments

8.1.1 tDCS over the rDLPFC abolishes RIF

In this first experiment, we first provided causal evidence for a role of the rDLPFC in overcoming interference from competing memory traces, as indexed by RIF. To do so, we delivered anodal, cathodal, or sham tDCS to healthy volunteers while performing the retrieval practice phase of the RPP. Compared to the sham group, participants that received real stimulation displayed weaker RIF. In particular, RIF was abolished in the group that received cathodal stimulation. Moreover, FAC was unaffected by the stimulation, suggesting a specific role of the rDLPFC in the detrimental, but not in the beneficial, effects of selective memory retrieval, as well as a differentiation between the cognitive mechanisms underlying the two facets of selective memory retrieval, as posited by the inhibitory account of RIF.

8.1.2 A comparison of tDCS montages for motor inhibition

In this experiment, we turned to another instance of cognitive control that is overriding a prepotent motor response. Here we examined the effects of four different tDCS montages, compared to sham tDCS, over this ability, as indexed by SSRT. Specifically, we administered 20 min of tDCS on five different groups of healthy volunteers, each receiving a different tDCS montage, prior to a SST that was administered with a delay of about 15 minutes in respect to the offset of stimulation. In line with previous work, we found that only anodal tDCS to the rIFG modulated behavioural performance in the SST. Specifically, anodal tDCS to the rIFG enhanced motor stopping (i.e., shorter SSRTs), whereas RTs in go trials were unaffected, suggesting that this particular tDCS montage may be able to selectively affect SSRTs up to 15 min after stimulation ends.

8.1.3 tDCS modulation of memory control and motor stopping

In this experiment, we adopted an identical procedure to our previous investigation of tDCS effects on RIF. However now we delivered tDCS to the rIFG, as opposed to our previous work on the rDLPFC, while keeping all the other stimulation parameters and behavioural procedures fixed. The aims of the experiment were twofold: i) Ascertain whether the rIFG is involved in RIF; ii) Pave the way to concurrent investigation of memory control and motor stopping. We expected rIFG stimulation to have at least some impact on RIF, but not necessarily as much as rDLPFC stimulation (as seen in our previous experiment). To our surprise, we could not provide a clear interpretation of results: In fact, even though visual inspection of the data suggested reduced RIF in volunteers receiving real stimulation, particularly in the cathodal stimulation condition, we did not find any interaction between stimulation group and item type. This was mainly due to an extremely weak effect in the control group. Therefore, we could not infer either favourable or problematic results in respect to our initial hypothesis and objectives.

Because the previous experiment failed to provide straightforward results, we designed an experiment with a similar rationale but also improved on the behavioural procedure in order to have a more efficient test of memory control. Therefore, in this experiment we employed similar tDCS parameters and a revised RPP. However, we also added a SST immediately after the retrieval practice phase of the RPP, in order to stimulate participants during both memory suppression and motor stopping, thereby allowing investigating tDCS effects on both abilities, and potential relationships between the two as well. Analyses on the different stimulation groups revealed significant RIF in the sham tDCS group only. However, group differences were not statistically significant. Again, visual inspection of the data suggested that a weak effect in the control group might have been primarily responsible for the lack of interaction. Moreover, interestingly, visual inspection also revealed peculiar differences in the observed pattern of results that appeared to depend on the experimental material. To ascertain whether this was the case, we carried out additional analyses that looked into the contribution of the stimuli into the main effect in the control group. These analyses revealed that some of the semantic categories employed in the experiment displayed a large reversed difference between recall from the critical item types for RIF. Obviously, reanalysing the whole dataset excluding these specific categories improved RIF in the control group. More surprisingly, this increase in RIF was not mirrored in the real stimulation groups, so that even though larger effects were observed in these groups, the interaction between stimulation group and item type was now significant. Therefore, we concluded that tDCS to the rIFG is able to impair memory control, but this effect appears to be highly susceptible to features of the stimuli. In addition to that, re-analysing the previous experiment targeting the rIFG with tDCS to modulate RIF revealed a similar, although weaker, pattern of results. Finally, we did not find any evidence in favour of a relationship between RIF and SSRTs and, in partial contrast with results from the second experiment of this dissertation, anodal tDCS to the rIFG did not affect motor stopping.

8.1.4 RIF is impaired in substance-related and addictive disorders

In this experiment we first investigated RIF in two groups of patients suffering from alcohol and drug (mainly opioids) addiction respectively, and compared their behavioural performance with that of a group of matched healthy volunteers. The RPP used here was similar to those of previous RIF experiments discussed in the context of this dissertation. In agreement with our initial hypothesis, the results showed that both groups displayed impairments in memory control compared to the control group. Moreover, no group differences were observed with respect to FAC, suggesting that general memory deficits were not responsible for their reduced memory control ability, and to an attention and reactivity task. Altogether, the results pointed toward a specific inhibitory impairment in the patients.

8.1.5 RIF in Anorexia and Bulimia Nervosa

This experiment first investigated the status of inhibitory control over interfering memory traces in patients suffering from eating disorders, compared to a group o matched healthy volunteers. We used the RPP to obtain a measure of the participants' memory control ability as indexed by RIF. However, visual inspection of the data suggested different patterns of behavioural performance depending on the specific diagnosis assigned to the patients. Therefore, we carried out additional analysis splitting the patients group in two distinct AN and BN groups. Unfortunately, sample size was not sufficient to further differentiate the patients in the various sub-types of AN and BN. Nonetheless, results revealed quite a different pattern compared to the previous analysis. In fact, RIF was abolished in patients affected by AN , whereas patients affected by BN displayed intact RIF.

8.2 Causal evidence for the role of right PFC in RIF

Recent studies presented a new aspect of forgetting: From accidental occurrence or side effect of our memory systems' limitation, to an adaptive process that actively shapes our mental life (e.g., Anderson & Hanslmayr, 2014; Nörby, 2015; Storm, 2011), thereby contributing to our every day well-being and the efficient functioning of memory systems. In this dissertation, I focused on an instance of adaptive forgetting, i.e., RIF, that putatively manifests itself as a consequence of inhibitory mechanisms that suppress interference during selective memory retrieval in the face of completion from memory traces that are associated to the target memory, but irrelevant to the task at hand (Anderson, 2003; Storm & Levy, 2012). In particular, several experiments presented here attempted at identifying brain regions causally involved in RIF by altering their activity with non-invasive brain stimulation.

Numerous findings from past studies that investigated RIF with neuroimaging techniques revealed a strong association between activity in the PFC and the ability to overcome interference from competing memory traces (e.g., Wimber et al., 2008, 2009, 2011), as indexed by RIF through the RPP (1.4.4). In particular, the right DLPFC and IFG appear to be candidate brain regions for a primary role in supporting the cognitive mechanisms underlying RIF. This notion is also supported by neuroimaging (see Anderson & Hanslmayr, 2014, for a review) and non-invasive brain stimulation (e.g, Hanslmayr, et al., 2012; Oldrati et al., 2016; Silas & Brandt, 2016) studies that investigated putatively similar cognitive processes. However, so far, causal evidence for PFC involvement in RIF was lacking in the literature. Across three experiments (see chapters 3 and 5) presented here we first demonstrated that perturbing the activity of the rDLPFC and the rIFG is sufficient to weaken or even abolish memory control over competing memories. Specifically, in these experiments we delivered anodal, cathodal, or sham tDCS to healthy volunteers in a between-subjects design, while they engaged in repeated selective retrieval in the retrieval practice phase of the RPP. Overall, this manipulation selectively impaired RIF, whereas FAC was unaffected by tDCS. In particular, cathodal stimulation had the highest detrimental effects on memory control performance. Importantly, the dissociation between tDCS effects on RIF and FAC, along with the absence of correlation between the two measures, suggest differential underlying cognitive mechanisms, thereby appearing mostly consistent with the inhibitory account of RIF (see 1.2.4), whereas according to alternative theoretical models based on associative interference (e.g., Mensink & Raaijmakers, 1988) the two phenomena should be directly proportional.

The importance of PFC for adaptive memory control, and most importantly, the specific neural effects and after-effects of its involvement in suppression of competing memory traces, was recently object of an elegant neuroimaging study published by Wimber and Colleagues (2015). In their study, the Authors were first able to track down the suppression of distributed activation patterns in the neocortex corresponding to competing memory traces during the retrieval practice phase of the RPP, and subsequently showed their weaker reactivation compared to baseline items during the test phase of the behavioural procedure. The study revealed that during retrieval practice the cortical patterns corresponding to the competing memories were reactivated in the visual cortex and hippocampus, and then gradually weakened on each repetition of the items, to the point that their cortical traces displayed below-baseline activity, as posited by the inhibitory account of RIF, whereas associative interference accounts of the phenomenon would just predict baseline levels for competing memory traces at best. Moreover, the characteristics of the observed neural pattern suppression suggests that the inhibitory mechanisms targeted those features of competing memory traces that distinguished them from other members of their categories, as well as from the target, as one would predict on the basis of the inhibitory account of RIF (Anderson et al., 2000a). Most relevant to our work, PFC regions were found to be maximally responsible for weakening of interfering memory traces, highlighting the goal-directed, task-relevant nature of the instance of memory suppression observed in this study, as argued by the Authors, as opposed to past computational modelling work (Norman et al., 2007) which excluded PFC contribution to RIF. In particular, activity in the ventrolateral PFC (VLPFC) positively predicted the suppression of irrelevant memory traces at the level of sensory patterns of activation in the ventral visual cortex. Interestingly, the hippocampus showed much weaker evidence for pattern suppression, suggesting that memory traces stored at neocortical level may be more prone to interference). In summary, Wimber and Colleagues (2015) provided an effective method to pinpoint the brain mechanism underlying suppression of competing memory traces, and track the dynamic changes in individual memories' activity over the course of the RPP, providing an unparalleled window into the neural underpinning of RIF. In my opinion, the impressive results obtained by Wimber and Colleagues (2015) pave the way to a wide range of future studies that may very well benefit from the opportunity to modulate RIF with non-invasive brain stimulation that we thoroughly explored in our own experiments.

8.3 Relevance of RIF in studies of clinical populations

Across the chapters of this dissertation I tried to convey the notion that RIF results from mechanisms that are highly adaptive and essential to an optimal cognitive functioning. In keeping with this stance on forgetting, it becomes important to assess whether this ability is intact in clinical populations characterized by impairments of cognitive control, as previously indexed by more traditional measures (e.g., in substance-related and addictive disorders, Smith et al., 2014; in bulimic-type EDs, Wu et al., 2013b).

Several studies already found impaired RIF in few psychiatric disorders (e.g., in OCD, Demeter et al., 2014; in ADHD, Storm & White, 2010; in schizophrenia, Racsmány et al., 2008), as well as evidence of impaired suppression-induced forgetting as measured through the think/no-think paradigm (e.g., Depue et al., 2010; Sala et al., 2009). Dysfunctional memory control abilities in these patients may originate from compromised brain regions or networks including the PFC, from structural or functional alterations in the connectivity between the PFC and other sites in the brain that are targeted by its top-down inhibitory modulation, but also from changes in the amount of neurotransmitter that have been linked to inhibitory control in memory (e.g., prefrontal dopamine, Wimber et al., 2011).

In respect to some of the psychiatric disorders that have been associated with impulsivity (e.g., substance-related and addictive disorders; EDs), most research so far focused on motor inhibition and self-report measures of impulsivity. While highly informative, these measures do not cover the entire range of abilities and behaviours that are putatively associated with cognitive control. In particular its more covert aspects, like the memory control ability captured by RIF, remain under-investigated, even though a more comprehensive assessment of the many facets of cognitive control could provide valuable information to orient diagnosis and clinical interventions, since inhibitory impairments are likely to contribute to the onset, maintenance, and relapse of psychiatric disorders characterized by impulsivity.

Across two experiments presented in this dissertation (chapters 6 and 7), we contributed at filling this gap in the literature, by assessing the status of memory control as indexed by RIF in groups of patients affected by substance-related and addictive disorders (chapters 6) and EDs (chapter 7). Specifically, the former experiment employed a RPP to probe RIF in two patients groups affected by alcohol addiction and drug (mostly opioids) addiction respectively, compared to a matched healthy control group, while the latter experiment adopted a similar approach to investigate differences in memory control in a group of patients affected by EDs, which were subsequently differentiated in patients suffering from AN and patients suffering from BN, and compared them to a matched group of healthy volunteers. In these experiments, we also implemented an additional control measure for attention motor reactivity (SART; Roberston et al., 1997), and a self-report questionnaire about multiple aspects of impulsivity (BIS-11; Fossati et al., 2001) to evaluate the presence of potential relations between these dimensions of impulsivity and memory control. Critically, in both experiments, we predicted to find evidence of significant RIF only in healthy volunteers as opposed to patients.

The choice of clinical populations was dictated by three main reasons: i) The absence of previous studies addressing suppression of competing memory traces in patients suffering from these specific psychiatric disorders; ii) Evidence of structural or functional alterations at the level of brain regions that have been involved in RIF (e.g., for substance-related and addictive disorders, Stavro et al., 2013; Wang et al., 2012; for EDs, Collantoni et al. 2016; Lock et al., 2011;

Skunde et al., in press; Zastrow et al., 2009); iii) Previous evidence of impaired inhibitory performance in tasks probing cognitive control or motor stopping (e.g., for substance-related and addictive disorders, Fu et al., 2008; Kamarajan et al., 2005; Noël et al., 2009; Zou et al., 2011; for EDs, Yano et al., 2016).

The results from these experiments partially confirmed our initial hypothesis: In fact, we did not find evidence of RIF in three out of the four patients group (EDs group is considered as split in two groups of patients suffering from AN and BN, respectively). The only exception was the group of patients affected by BN, which displayed a RIF effect that was not only intact, but also even larger than that of the control group. While we already provided tentative explanations for this pattern of results in the discussion section of the relevant chapter (7.4.1), we could further speculate that observing intact RIF in the BN may relate to the clinical observation that patients affected by bulimia often display exaggerated control over their attitudes and behaviour (which would explain normal RIF), but lose this constant grip when confronted with stimuli that are relevant for their condition, i.e., food. This notion warrants additional research efforts, which should employ stimuli that are relevant for the specific clinical condition under investigation, in order to uncover potential attention and/or memory biases that could further inform our understanding of the disorders, as well as clinical practice. Related to this point, few studies have already employed disorder-relevant material in studies of cognitive control in psychiatric disorders (e.g., Kircanski et al., 2016; Tekcan et al., 2008). This strategy could help clarifying the origin and pervasiveness of inhibitory deficits in the different clinical populations, such as those explored in our studies, which could either show even poorer memory suppression for material salient in respect to their pathological condition. Moreover, it could be an important point for the characterization of the cognitive profile of these disorders, more so since RIF has been proposed as the behavioural phenotype of cognitive control mechanisms that promote memory efficiency and wellbeing (e.g., Nørby, 2015; Storm, 2011).

8.4 RIF is highly variable across different semantic categories

In chapter 5, I presented an approach to data analysis of RPP data that is rather different from the rationale typically employed in the literature (and in our other RIF experiments as well). Specifically, after separating FAC- and RIF-relevant items, we fitted generalized linear (logistic) mixed models using the glmer procedure in the lme4 package (Bates et al., 2015), with recall accuracy as our main dependent binary valuable, whereas accuracy in the RIF literature is typically analysed as percentage of correct answers proportion. This particular approach is better suited at analysing accuracy data (and nowadays computationally feasible) in respect to repeated measures ANOVA (e.g., Jaeger, 2008), and allows to account for both subject- and item-related variability, the latter being particularly relevant when employing linguistic stimuli (e.g., Clark, 1973). We then used AIC weights (Wagenmakers & Farrell, 2004) to select the most informative models throughout the analysis. An additional advantage of this analytical approach was the opportunity to explore and quantify the contribution of each individual semantic category to RIF in the control group, which we took advantage of when visual inspection of the data hinted at the possibility of category-specific patterns in RIF. As a matter of fact, we discovered a large variability in the amount of RIF associated to each semantic category in Experiment 1 (5.2), where about half categories did not show any RIF at all, and a smaller but relevant variability in Experiment 2 (5.3), with fewer categories displaying null or negative RIF in the control group. Because our experimental hypothesis concerned the presence of an interaction between stimulation with tDCS and item type, we gradually excluded categories from the analysis on the basis of their contribution to RIF in the control group, as looking at the impact on the interaction would have been recursive (i.e., we would have just discarded data that did not fit with our hypothesis). Crucially, removing these categories also improved the interaction, as the increase in RIF in the control group was not mirrored by an increase of similar magnitude in the stimulated groups. In particular, the cathodal tDCS group consistently displayed the smaller amount of RIF. In addition to that, we carried out a re-analysis of the data from our very first experiment as well (not reported here) as a diagnostic check on the consistency of results and to further validate the analytical approach employed in the subsequent experiments. The analysis with the glmer procedure essentially mirrored the pattern observed with conventional analyses reported here (0), while also providing an efficient way to quantify the amount of evidence in favour of RIF within each group. Moreover, looking into each category's contribution to RIF in the control group, we found that a similar pattern as compared to the subsequent experiments, where removing categories that had a negative impact on RIF also improved the interaction.

A number of considerations support the rationale of formulating hypotheses about category-specific effects in RPP data. For instance, it is possible that different categories display large variability in a number of psycholinguistic dimensions, such as concreteness, imageability, and memorability, and similarity (see Bäuml & Hartinger, 2002), of their constituting exemplars, that could interact with RIF. This in turn, could also lead to varying degrees of semantic integration (Goodmon & Anderson, 2011), which is generally detrimental to RIF. Because at the time when our experiments were designed we did not have access to means to control for all of these characteristics of the stimuli, all of these linguistic dimensions may have entered the experimental material and contributed in shaping the results. Moreover, it is also extremely difficult to quantify these variables post-hoc, especially due to the scarcity of standardized norms for the Italian language. Nevertheless, future studies should take advantage of the category-wise analytical procedure presented here in order to better clarify how specific groupings of stimuli along defined features may moderate suppression of competing memories. Importantly, this approach could also benefit related studies aimed at uncovering memory biases for specific stimuli, i.e., stimuli relevant to a particular psychiatric disorder (e.g., Kircanski et al., 2016).

It is worth noting that the semantic categories that showed the least amount of RIF in the first experiment were not fully overlapping with the problematic categories detected in the subsequent experiments, although one category in particular (i.e., "BIRDS") seemed to detrimentally affect RIF in the control group across the three experiments. This finding may implicate that along with the categories' linguistic features, certain characteristics pertaining to participants may also interact with the different semantic categories, and they should also be explored as possible moderators of RIF (e.g., pre-existing knowledge about a certain category, which may promote integration; see 1.3.2).

8.5 Memory control and motor stopping

Over the course of our work on neuromodulation of memory control, we also took the opportunity to investigate the putative relationship between RIF and the ability to override an initiated course of action. This detour from our main research goal, i.e., the investigation of memory control in the context of non-invasive brain stimulation and clinical populations, was mainly motivated by few Authors' theoretical stance that the two abilities may share at least partially overlapping neural substrates and related cognitive processes (e.g., Levy & Anderson, 2002). In fact, neuroimaging and neuromodulation studies provided converging evidence for an involvement of similar brain areas in memory control and motor stopping, with regions within the PFC such as the DLPFC and the IFG emerging as the leading actors in the inhibitory scenario (e.g., for studies on memory control, Hanslmayr et al., 2012; Wimber et al. 2008, 2009, 2011; for motor stopping, Aron et al. 2007, Chevrier et al, 2007, Ditye et al., 2012, Jacobson et al., 2011, Li et al. 2006; see also Aron et al., 2014, for a review on evidence suggesting a primary role of the IFG in cognitive control over different cognitive domains). Moreover, past evidence for an impairment of motor stopping was among the main reasons that prompted our studies on clinical populations. In fact, previous work showed that SSRTs, and therefore the modulation of their underlying mechanisms, may entail clinical relevance, because poor SSRTs have been associated with clinical conditions such as attention-deficit hyperactivity disorder (e.g., Depue et al., 2010), eating disorders (e.g., Bartholdy et al., 2016), obsessive–compulsive disorder (Boisseau et al., 2012; Morein-Zamir, Voon, Dodds, Sule, van Niekerk, Sahakian, et al., 2015), schizophrenia (Hughes, Fulham, Johnston, & Michie, 2012), and substance abuse and addiction (Fillmore & Rush 2002; Smith et al., 2014).

The three memory control neuromodulation experiments reported in the present work (chapters 3 and 5), along with few other that employed a similar approach (Anderson, J., et al., 2015) or investigated cognitive control in different but related task (Silas, & Brandt, 2016), showed that tDCS to the right PFC was able to modulate control over interfering memories. Similar tDCS protocols also resulted in the modulation of motor stopping performance (e.g., Jacobson et al., 2011). These relatively segregated lines of research support the notion that the two abilities may share similar neural underpinnings and cognitive mechanisms (e.g., Levy & Anderson, 2002), and that tDCS may be particularly effective at modulating behavioural performance associated to them. The latter point also suggest that tDCS may hold the potential to become a therapeutic tool in clinical populations affected by disorders of cognitive control (e.g., Bikson, Paneri, & Giordano, 2016; Kuo, Paulus, & Nitsche, 2014).

Because of the above reasons, we deemed potentially informative to employ tDCS to attempt at concurrently modulating cognitive control over interference from competing memory traces, as reflected in RIF, and prepotent motor responses, as indexed by SSRTs. The first step of our investigation was identifying the most suitable tDCS montage to selectively modulate SSRTs in the SST, which resulted in selecting the rIFG (4.4.1) as the target area for a subsequent experiment (5.3), where we inserted few SST blocks within the RPP, i.e., in place of the buffer tasks typically employed between the retrieval practice and test phases of the RPP, in order to deliver tDCS during the motor stopping task immediately after the inhibitory window of the RPP. However, in sharp contrast with our previous experiment (chapter 3) whose results we relied on to inform the combined modulation of RIF and SSRTs (5.3), we did not find any evidence in favour of modulation of motor stopping by administering tDCS to the rIFG, in the face of stimulation effects on RIF. Moreover, we failed to observe a significant correlation between RIF and SSRTs, which we expected to detect in line with Schilling and Colleagues' previous work (2014), more so since we employed a RPP that was similar to that implemented by the Authors.

These results should be contextualized with the mixed findings of both RIF and tDCS literature. In respect to the latter results (i.e., absence of correlation), other studies failed to provide evidence in favour of an association between different inhibitory measures (e.g., Noreen & MacLeod, 2015; Storm & Bui, 2016). Moreover, recent work suggests that RPPs employing recognition memory tests are least influenced by interference (e.g., Rupprecht & Bäuml, 2016), thus implying that experiments aimed at detecting correlations with other inhibitory measures should implement this particular testing format. Importantly, Schilling and Colleagues (2014) already showed that RIF detected by a test phase maximally contaminated by output interference was negatively associated to SSRTs, whereas a reversed correlational pattern was observed between motor stopping and RIF measured by a more controlled test format.

Concerning the former results (i.e., absence of modulation), it is worth noting that in our experiment (5.3) tDCS was delivered online in respect to the SST, whereas previous work that successfully modulated motor stopping performance stimulated before the SST (e.g., Jacobson et al., 2011; Dityie et al., 2012; Stramaccia et al., 2015). This is not a trivial point when electrical stimulation is employed to modulate behavioural measures, as the optimal timing of the stimulation (i.e., when to stimulate) is object of on-going debate, and most probably different depending on the target function and the desired outcome of the stimulation protocol.

In addition to that, other studies failed to find evidence for prefrontal modulation of behavioural performance in motor stopping tasks (e.g., in the SST, Cunillera et al., 2015; in the go/no-go task, Dambacher et al., 2015). In particular, there is evidence of tDCS-induced modulation of EEG correlates of motor stopping in the absence of behavioural changes (Cunillera et al., 2015). Therefore, multimodal studies combining non-invasive brain stimulation and neuroimaging techniques may be essential to shed light on the mixed results reported in the literature.

8.6 Conclusions

A total of six experiments presented here examined various aspects of cognitive control in selective memory retrieval: The brain regions underlying such ability, the opportunity to modulate its behavioural manifestations with tDCS, its relationship with motor stopping, and its integrity in several clinical populations. The bulk of evidence provided by these experiments highlights few major achievements of this line of research: First, it provided causal evidence for involvement of right PFC in supporting the cognitive processes underlying memory control, because altering the activity of this region was sufficient to disrupt the RIF effect. Secondly, it demonstrated the effectiveness and viability of tDCS as a tool to modulate this peculiar effect. Thirdly, it provided compelling evidence for the advantages of analysing RPP data with a statistical approach that is more consistent with the nature of the data, as well as informative in respect of the different dimensions of the data that contribute to results. Last, but not least, it contributed to the characterization of the cognitive profile of patients affected by substance-related and addictive disorders and EDs, paving the way to future research that could further investigate the extents and specificity of the previously unexplored memory control deficits that we unveiled in these patients.

8.7 Future research trajectories

In this dissertation, I presented several experiments that may constitute the starting point toward a range of more finely tuned investigations of memory control, in both healthy volunteers and patients, taking advantage of different techniques and behavioural approaches. In the following paragraphs I provide a brief outline of the main implications and suggestions for future research that stem from our results.

8.7.1 Testing the inhibitory account of RIF with tDCS

Non-invasive brain stimulation techniques may offer the opportunity to test specific predictions of the inhibitory account of RIF (Anderson, 2003) other than the fundamental role of PFC in the genesis of the effect (which is, in itself, a rather specific prediction of the inhibitory account; e.g., Wimber et al., 2015). Moreover, designing tDCS experiments on RIF needs to account for the on-going theoretical debate on the determinants of the phenomenon, in order to validate the specificity of tDCS effects on inhibitory mechanisms rather than alternative processes, which may be important for future application in clinical settings.

In keeping with this reasoning, our results already provided a partial test of the strength independence tenet of RIF (1.2.4), because the two facets of selective memory retrieval, i.e., FAC and RIF, were always found to be unrelated to each other, (this point applies to our studies on patients as well), or even trending toward a negative association in our very first tDCS experiment (see also Weller et al., 2013). In addition to that, output interference (1.2.1) was always accounted for in our experiments, thus ruling out otherwise potentially relevant inflations of our measures of forgetting due to interference dynamics in the final test phases of the RPPs employed here. However, future studies should employ test formats that are even more impervious to the contribution of interference to RIF, such as recognition memory tests (e.g., Rupprecht & Bäuml, 2016), implicit tests, or measures of the integrity of the memory traces that rely on neuroimaging techniques (e.g., Wimber et al., 2015).

The retrieval specificity tenet of RIF (1.2.3) may also be tested with tDCS, by stimulating at different stages of the behavioural procedure. In particular, stimulation may be delivered during either the retrieval practice phase or the test phase of the RPP. If retrieval specificity holds true, only stimulation during the retrieval practice phase should selectively affect RIF, whereas potential effects of stimulation at test, if any, should have a more generalized impact on the overall memory performance, across all item types. Note, however, that in keeping with this reasoning a test format impervious to interference should be used at all costs: For instance, if tDCS at test is somehow able to reduce interference by ways other than altering the putative inhibitory mechanisms responsible for RIF, stimulation on either the retrieval practice or test phases of the RPP may end up having similar effects on memory performance, even though by different underlying neural dynamics. This would be especially true if the test format employed to measure RIF in the RPP is contaminated by interference. Moreover, it is not necessarily the case that stimulation would equally affect general memory performance across all items, given that presentation order at test is rarely fully randomized, thus allowing for interaction between stimulation and serial position effects. Finally, it is also problematic to assume at all costs that to-be-forgotten items (i.e., RP-) may benefit less or suffer more from stimulation than the relevant control items (i.e., NRP-), as RP- would be putatively far below the activation threshold for recall or recognition as compared to NRP-.

8.7.2 Testing the context account of RIF with tDCS

Even though the three experiments presented in chapter 3 and 5 were not designed to directly test competing theoretical accounts of RIF, nonetheless they do not fit well with a recent model of the phenomenon based on context shift rather than inhibitory mechanisms (Jonker, Seli, & MacLeod, 2015). According to Jonker and Colleagues (2015), forgetting for RP- items at test compared to NRP- items is mediated by a context shift that would happen between the study and retrieval practice phases of the RPP, due to different task features associated with the two distinct phases. In the subsequent test phase, participants would erroneously search for RP- items within the retrieval practice phase context, because their associated category cues were last shown at that point in the procedure. However, RP- items were never produced during the retrieval practice phase, thus rendering this search effort ineffective. On the contrary, categories associated with the NRP- items were last seen during the study phase, alongside the relevant exemplars, so that upon presentation of the relevant category cues participants spontaneously search within the appropriate retrieval context that matches the actual presentation of the target items in memory, subsequently enhancing the probability of correct recall. Therefore, a “RIF-like” forgetting should emerge when confronting items searched for in an inappropriate context (i.e., the retrieval practice phase for the RP-) with the relevant control items recovered from an appropriate context (i.e., the study phase for the NRP- items). Although we did not test specific predictions regarding this theoretical proposal, some features of our experiments should have produced rather different scenarios. In fact, across our three tDCS experiments on RIF (chapters 3 and 5), RIF was neither reduced nor abolished in the real stimulation groups even though we employed a manipulation (i.e., tDCS) that should have made the transition between the study and retrieval practice phases even more pronounced than that of a typical RPP, because of the sensations associated to the stimulation, as well as the initial nervousness experienced by many participants that were naïve to the technique. This line of reasoning should be especially valid for both Experiment 1 (in chapter 5) and our very first tDCS investigation (in chapter 3), where the presentation order of the experimental material in the study phase (i.e., blocked-by-category randomization) was even more different to that of the subsequent retrieval practice phase, compared to experiment 2 (i.e., blocked randomization). According to the context account of RIF, this should have induced an even stronger context shift between the study and retrieval practice phases of the RPP in experiment 2, because of the increased difference between the two phases. Finally, we argue that the suboptimal test format used in Experiment 1 (in chapter 5) and chapter 3 should have favoured RIF within the theoretical framework provided by the context account of the phenomenon, because RP-items were systematically presented before all the remaining items, thus providing the participants with no opportunities at all to reactivate the study context that could have promoted their retrieval, until all RP- items were presented. Yet, all the stimulation groups in both Experiment 1 and Penolazzi and Colleagues' work (2014), as well as those in Experiment 2, consistently showed reduced to abolished RIF.

One possibility, however, is that the neuromodulatory manipulations employed in our studies could have impaired context formation during the retrieval practice phase, or else, interfered with context search in the subsequent test phase, if delayed effects of stimulation are hypothesized (as observed before, e.g., Stramaccia et al., 2015), to the point that "RIF-like" forgetting would have been reduced or abolished. At the same time, it should be noted that several studies have directly addressed the hypothesis that context alone may be sufficient to explain RIF, and provided convincing evidence against a context-exclusive account of RIF (Buchli, Storm, & Björk, 2016; Rupprecht & Bäuml, 2016; Soares et al., 2016). Therefore, while the above reasoning could challenge the specificity of our manipulation as far as the role of inhibitory mechanisms in RIF is concerned, and is therefore deserving of further investigation (for example, to characterize context effects due to tDCS, whose relevance could extend well beyond the phenomenon investigated here), the current status of the literature speaks in favour of the inhibitory account of RIF.

8.7.3 A potential test for the net zero-sum model of tDCS effects

Establishing cathodal right prefrontal tDCS as a reliable neuromodulatory approach toward cognitive control over memory also opens the possibility to test new intriguing research hypotheses. For example, a recent study by Gómez-Ariza and Colleagues (*in press*) found that participants struggled to produce RP-items as solutions to an ad-hoc *Remote Associate Test* (a test of creative problem solving; Mednick, 1962) delivered in place of the typical test phase of a RPP, and was therefore preceded by a retrieval practice phase where these items were supposedly weakened by inhibition. In light of this finding, and in keeping with research arguing that the application of tES techniques should be framed within a net zero-sum model, i.e., that we should expect performance gains due to neuromodulation to be always accompanied by performance losses, and vice-versa (see Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014), it would be interesting to test whether applying cathodal tDCS, which we assume to detrimentally modulate cognitive inhibition, within a similar RPP-RAT combined procedure, would allow participants to exhibit better creative problem solving performance, at the cost of diminished memory control capabilities.

8.7.4 Neuromodulation of memory control: what’s next?

According to Anderson and Hanslmayr (2014), efficient memory control mechanisms are essential towards a range of adaptive behaviours such as negative affect regulation, forgiveness, attachment, deceptiveness, and the preservation of one’s self-image, beliefs, and attitudes. Therefore, not surprisingly, many scientists are devoting increasing efforts to clarify the neural substrates that support memory control mechanisms, which in turn may help the development of more effective strategies aimed at modulating their functioning. Related to this point, throughout the present PhD thesis, I tried to make the point that non-invasive brain stimulation techniques such as tDCS may constitute a viable method, or at least a promising starting point, toward developing stimulation protocols that can accomplish this goal.

So far, one fundamental missing piece in studies of neuromodulatory strategies of memory control is constituted by within-participants, repeated measures experiments where participants undergo several sessions of stimulation and RPP, thereby exploring the parameter space of tDCS (i.e., polarity, target, intensity, to name a few) or manipulations of the paradigm like the retrieval practice or the test phase format. For example, in our neuromodulation experiments on memory control, one may have expected a smaller RIF effect as a result of better recall of RP- items for the active stimulation groups, compared to sham control groups. Instead, in the former groups, we observed different recall performance for both RP- and NRP- items. Because we always employed between-participant designs, and because we did not have a tDCS-free baseline for RIF in active stimulation groups, we cannot rule out the possibility that the active stimulation groups were different in their baseline compared to the sham groups. Therefore, we only relied on comparisons involving differential (i.e., relative) rather than absolute scores, focusing on relative variations in the performance on the two item types relevant for RIF and FAC within each group, and compared such effects. The combined use of brain stimulation and retrieval-practice paradigm in a within-participant design may help addressing this issue in a more straightforward manner.

To our knowledge, so far, only one study has attempted at modulating RIF within a repeated measures design (Anderson, J., et al., 2015). Interestingly, the study showed that cathodal tDCS to the PFC was beneficial to participants that displayed the least amount of RIF in the sham condition, but detrimental those participants with the highest amount of RIF at baseline. However, this study suffered from a series of methodological shortcomings (i.e., minimal sample size, delivery of tDCS before the study phase of the RPP, sub-optimal test format in respect to interference dynamics, to name the most relevant). Therefore, although these findings provided compelling evidence for individual differences in participants' response to the tDCS, and for the possibility to enhance memory control as indexed by RIF extreme caution is warranted in their interpretation, as future studies are needed to clarify whether this pattern of results is replicable and, therefore, can be improved upon.

Finally, in my view combining tDCS with other neuroscientific investigation methods may be a necessary step forward to accurately describe the effects of tDCS on memory control. For instance, the neuroimaging-based method to track item-specific inhibitory dynamics at the neural level described by Wimber and Colleagues (2015; see 8.2) could be combined to non-invasive brain stimulation techniques such as tDCS, which appears to be a reliable strategy to modulate activity in the PFC. This approach would not only strengthen the evidence in favour of the causal role of PFC in memory control, but also clarify whether the effects of tDCS on memory control are mediated by modulation of the same inhibitory mechanisms revealed by Wimber and Colleagues (2015), or else rely on different neural dynamics.

APPENDICES

RETRIEVAL PRACTICE PARADIGM: STIMULI

Stimuli used for the RPP employed in chapter 3 and chapter 5 (Experiment 1). Ninety-six category-exemplars word pairs were adapted from the category production norms for Italian language compiled by Boccardi and Cappa (1997). Twelve exemplars were selected for each of the 8 semantic categories, among which 7 were high-ranked, frequently reported exemplars, and 5 were low-ranked, infrequently reported selected exemplars according to the norms. Rank and production frequency for each exemplar and summary statistics for each category are reported below. The categories were assigned to 4 different counterbalance lists, with each category equally contributing to target and control items.

ABBIGLIAMENTO			ARMI			BEVANDE			FRUTTA		
high freq	rank	pfreq	high freq	rank	pfreq	high freq	rank	pfreq	high freq	rank	pfreq
PANTALONI	2	156	PISTOLA	1	188	GRAPPA	3	139	BANANA	3	176
GONNA	4	122	FUCILE	2	179	VODKA	4	119	ARANCIA	4	157
CRAVATTA	14	65	CANNONE	3	113	AMARO	7	61	FRAGOLA	10	88
SCIARPA	15	49	BOMBA	5	99	COGNAC	8	57	CILIEGIA	11	81
REGGISENO	17	34	SPADA	6	71	BRANDY	9	55	MANGO	13	66
IMPERMEABILE	22	19	ARCO	13	39	TEQUILA	11	36	PAPAIA	17	53
BOXER	24	17	LANCIA	14	28	SAMBUCA	14	19	LIMONE	18	50
mean	14,00	66,00	mean	6,29	102,43	mean	8,00	69,43	mean	10,86	95,86
low freq	rank	pfreq	low freq	rank	pfreq	low freq	rank	pfreq	low freq	rank	pfreq
ACCAPPATOIO	34	6	GRANATA	22	15	LAMBRUSCO	27	1	RIBES	27	27
MANTELLA	34	6	RAZZO	31	5	MALVASIA	27	1	DATTERO	28	22
TANGA	36	4	ESPLOSIVO	33	3	NOCINO	27	1	NESPOLA	32	14
VESTAGLIA	37	3	MAZZA	33	3	PINOT	27	1	SUSINA	33	13
FRAC	38	2	DARDO	34	2	ROSOLIO	27	1	GIUGGIOLA	39	4
mean	35,80	4,20	mean	30,60	5,60	mean	27,00	1,00	mean	31,80	16,00

INSETTI			PROFESSIONI			SPORT			UCCELLI		
high freq	rank	pfreq	high freq	rank	pfreq	high freq	rank	pfreq	high freq	rank	pfreq
MOSCA	1	172	INSEGNANTE	5	68	TENNIS	3	146	AQUILA	1	136
ZANZARA	2	148	MURATORE	9	44	GOLF	11	54	CANARINO	5	87
FORMICA	4	111	COMMERCIALISTA	11	41	CICLISMO	14	39	RONDINE	6	77
VESPA	6	76	DENTISTA	12	38	BASEBALL	15	35	MERLO	8	73
RAGNO	7	73	ARCHITETTO	14	33	PATTINAGGIO	18	28	PAPPAGALLO	9	65
COCCINELLA	13	43	ELETTRICISTA	15	32	VELA	19	26	GUFO	13	47
GRILLO	16	29	GIORNALISTA	22	20	SCHERMA	21	22	USIGNOLO	19	28
mean	7,00	93,14	mean	12,57	39,43	mean	14,43	50,00	mean	8,71	73,29
low freq	rank	pfreq	low freq	rank	pfreq	low freq	rank	pfreq	low freq	rank	pfreq
BRUCO	26	10	TAXISTA	32	10	ALPINISMO	32	10	NIBBIO	30	7
TARMA	28	8	FABBRO	34	8	MARATONA	33	9	FENICOTTERO	32	5
PIDOCCHIO	29	7	BARBIERE	37	5	LOTTA	37	5	TUCANO	32	5
ACARO	30	5	OCULISTA	38	4	DELTAPLANO	42	1	BECCACCIA	34	3
LOCUSTA	32	3	REGISTA	40	2	RAFTING	42	1	SPARVIERO	34	3
mean	29,00	6,60	mean	36,20	5,80	mean	37,20	5,20	mean	32,40	4,60

Stimuli used for the RPP employed in chapter 5 (Experiment 2) and chapter 6. Eighty-four category-exemplars word pairs were adapted from the category production norms for Italian language compiled by Boccardi and Cappa (1997). Seven exemplars were selected for each of the twelve semantic categories, among which 4 were high-ranked, frequently reported exemplars, and 3 were low-ranked, infrequently reported selected exemplars according to the norms. Rank and production frequency for each exemplar and summary statistics for each category are reported below. The twelve categories were assigned to 4 different counterbalance lists, with that each category equally contributing to target and control items.

FRUTTA	rank	totrec	METALLI	rank	totrec	STRUMENTI	rank	totrec
albicocca	9	103	alluminio	6	85	basso	11	79
ciliegia	11	81	nichel	10	39	clarinetto	9	96
mango	13	66	platino	8	65	flauto	7	115
papaia	17	53	zinco	5	98	tamburo	13	70
mean - high	12,50	75,75	mean - high	7,25	71,75	mean - high	10,00	90,00
giuggiola	39	4	berillio	32	7	liuto	39	6
nespola	32	14	cobalto	21	9	ocarina	43	2
susina	33	13	titanio	24	5	sonaglio	44	1
mean - low	34,67	10,33	mean - low	25,67	7,00	mean - low	42,00	3,00
mean - total	23,58	43,04	mean - total	16,46	39,38	mean - total	26,00	46,50

SPORT	rank	totrec	INSETTI	rank	totrec	UCCELLI	rank	totrec
baseball	15	35	cimice	10	64	corvo	7	76
ciclismo	14	39	formica	4	111	merlo	8	73
nuoto	4	137	libellula	14	39	piccione	11	55
rugby	12	53	vespa	6	76	rondine	6	77
mean - high	11,25	66,00	mean - high	8,50	72,50	mean - high	8,00	70,25
deltaplano	42	1	acaro	30	5	allocco	35	2
pugilato	29	13	pidocchio	47	1	sparviero	34	3
snowboard	41	2	tarlo	34	1	folaga	36	1
mean - low	37,33	5,33	mean - low	37,00	2,33	mean - low	35,00	2,00
mean - total	24,29	35,67	mean - total	22,75	37,42	mean - total	21,50	36,13

VERDURE	rank	totrec	FIORI	rank	totrec	PESCI	rank	totrec
lattuga	18	45	ciclamino	11	44	anguilla	7	58
melanzana	9	77	giglio	6	59	carpa	13	43
sedano	7	82	orchidea	4	75	orata	17	32
verza	12	61	papavero	12	42	sogliola	8	57
mean - high	11,50	66,25	mean - high	8,25	55,00	mean - high	11,25	47,50
bietola	36	5	azalea	22	16	lampreda	40	1
cicoria	29	17	dalia	24	13	murena	32	9
porro	30	13	begonia	24	13	persico	32	9
mean - low	31,67	11,67	mean - low	23,33	14,00	mean - low	34,67	6,33
mean - total	21,58	38,96	mean - total	15,79	34,50	mean - total	22,96	26,92
DESSERT	rank	totrec	ARMI	rank	totrec	ALCOLICI	rank	totrec
budino	4	91	cannone	3	113	brandy	9	55
crostata	5	64	sciabola	15	26	cognac	8	57
meringa	22	15	pugnale	11	47	spumante	10	39
sorbetto	12	32	balestra	17	23	vodka	4	119
mean - high	10,75	50,50	mean - high	11,50	52,25	mean - high	7,75	67,50
granita	30	1	dinamite	32	4	lambrusco	27	1
torrone	29	7	forca	35	1	malvasia	27	1
zabaione	33	3	mannaia	35	1	rosolio	27	1
mean - low	30,67	3,67	mean - low	34,00	2,00	mean - low	27,00	1,00
mean - total	20,71	27,08	mean - total	22,75	27,13	mean - total	17,38	34,25

Stimuli used for the RPP employed in chapter 5 (Experiment 2) and chapter 6. Ninety-six category-exemplars word pairs were adapted from the category production norms for Italian language compiled by Boccardi and Cappa (1997). Eight exemplars were selected for each of the twelve semantic categories, among which 4 were assigned to a subset (A), and 4 to a different subset (B), which were similar for lexical frequency (Baroni et al., 2009) and taxonomic strength (Boccardi & Cappa, 1997). Rank and production frequency for each exemplar and summary statistics for each subset are reported below. The twelve categories were assigned to 24 different counterbalance lists, with each category equally contributing to target and control items.

CATEGORY	SET	EXEMPLAR	LFREQ	TSTR	CATEGORY	SET	EXEMPLAR	LFREQ	TSTR
ALBERI	A	quercia	7,7	2	ALCOLICI	A	grappa	4,7	3
		faggio	1,6	8			marsala	3,5	17
		pioppo	1,3	7			spumante	2,3	10
		larice	0,6	13			brandy	1	9
		mean	2,8	7,5			mean	2,875	9,75
	B	cipresso	1,4	11		B	cognac	0,9	8
		salice	1,6	11			amaretto	0,3	23
		abete	3	3			tequila	0,5	11
		betulla	0,9	6			vodka	1,4	4
		mean	1,725	7,75			mean	0,775	11,5

CATEGORY	SET	EXEMPLAR	LFREQ	TSTR	CATEGORY	SET	EXEMPLAR	LFREQ	TSTR
AUTOMOBILE	A	cofano	1,5	8	DESSERT	A	tartufo	4,6	24
		motore	72,6	3			panettone	1,6	20
		freno	10,8	7			sorbetto	0,6	12
		lunotto	0,4	24			gelato	8,4	1
		mean	21,325	10,5			mean	3,8	14,25
	B	batteria	19,4	21		B	meringa	0,2	22
		pistone	3,2	15			crostata	0,8	5
		sedile	5,7	2			budino	0,7	4
		ruota	27,8	3			frittella	0,9	31
		mean	14,025	10,25			mean	0,65	15,5

CATEGORY	SET	EXEMPLAR	LFREQ	TSTR	CATEGORY	SET	EXEMPLAR	LFREQ	TSTR
FIORI	A	giglio	4,7	6	FRUTTA	A	mango	1,2	13
		tulipano	1,1	3			pesca	50,3	7
		azalea	0,3	22			banana	5,5	3
		narciso	1,5	20			dattero	1,2	28
		mean	1,9	12,75			mean	14,55	12,75
	B	orchidea	1,5	4		B	arancia	6	4
		papavero	0,6	12			limone	10,1	18
		ciclamino	0,4	11			fragola	3,8	10
		mimosa	0,8	23			ciliegia	3,1	11
		mean	0,825	12,5			mean	5,75	10,75

CATEGORY	SET	EXEMPLAR	LFREQ	TSTR	CATEGORY	SET	EXEMPLAR	LFREQ	TSTR
INSETTI	A	pulce	2,2	18	METALLI	A	magnesio	1,6	15
		mosca	19,2	1			piombo	12,5	7
		termite	0,3	19			zinco	1,7	5
		vespa	6,1	6			cromo	1,1	19
		mean	6,95	11			mean	4,225	11,5
	B	pulce	2,2	18		B	alluminio	7,6	6
		mosca	19,2	1			litio	0,9	19
		termite	0,3	19			stagno	5,9	12
		vespa	6,1	6			nichel	0,8	10
		mean	6,95	11			mean	3,8	11,75

CATEGORY	SET	EXEMPLAR	LFREQ	TSTR	CATEGORY	SET	EXEMPLAR	LFREQ	TSTR
PESCI	A	branzino	1	19	SPORT	A	atletica	25,1	8
		sogliola	0,6	8			pattinaggio	1,8	18
		trota	2,5	1			rugby	2,5	12
		orata	0,6	17			tennis	8,3	3
		mean	1,175	11,25			mean	9,425	10,25
	B	carpa	1,4	13		B	ippica	0,6	17
		luccio	1	14			ciclismo	11	14
		merluzzo	0,9	10			nuoto	7,5	4
		anguilla	1,7	7			basket	8,4	6
		mean	1,25	11			mean	6,875	10,25

CATEGORY	SET	EXEMPLAR	LFREQ	TSTR	CATEGORY	SET	EXEMPLAR	LFREQ	TSTR
UCCELLI	A	merlo	3	8	VERDURE	A	lattuga	1	18
		rondine	2,2	6			finocchio	2	5
		struzzo	1,6	22			carota	4,8	2
		passero	1	3			melanzana	2,8	9
		mean	1,95	9,75			mean	2,65	8,5
	B	merlo	3	8		B	lattuga	1	18
		rondine	2,2	6			finocchio	2	5
		struzzo	1,6	22			carota	4,8	2
		passero	1	3			melanzana	2,8	9
		mean	1,95	9,75			mean	2,65	8,5

Mean lexical frequency (Baroni et al., 2009) and mean taxonomic strength (Boccardi & Cappa, 1997) for all item types in each of the twenty-four lists employed in chapter 5 (Experiment 2) and chapter 6 are reported below.

LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
1	RP-	2,188	11,500	2	RP-	5,479	11,333	3	RP-	2,188	11,500
	NRP-	5,363	10,583		NRP-	6,792	10,292		NRP-	6,792	10,292
	RP+	6,792	11,333		RP+	5,363	11,500		RP+	5,363	11,333
	NRP+	5,479	10,292		NRP+	2,188	10,583		NRP+	5,479	10,583
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927
LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
4	RP-	5,479	11,333	5	RP-	3,654	11,000	6	RP-	4,013	11,833
	NRP-	5,363	10,583		NRP-	7,088	10,458		NRP-	5,067	10,417
	RP+	6,792	11,500		RP+	5,067	11,833		RP+	7,088	11,000
	NRP+	2,188	10,292		NRP+	4,013	10,417		NRP+	3,654	10,458
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927
LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
7	RP-	5,363	10,583	8	RP-	6,792	10,292	9	RP-	5,363	10,583
	NRP-	2,188	11,500		NRP-	5,479	11,333		NRP-	5,479	11,333
	RP+	5,479	10,292		RP+	2,188	10,583		RP+	2,188	10,292
	NRP+	6,792	11,333		NRP+	5,363	11,500		NRP+	6,792	11,500
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927
LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
10	RP-	6,792	10,292	11	RP-	5,067	10,417	12	RP-	7,088	10,458
	NRP-	2,188	11,500		NRP-	4,013	11,833		NRP-	3,654	11,000
	RP+	5,479	10,583		RP+	3,654	10,458		RP+	4,013	10,417
	NRP+	5,363	11,333		NRP+	7,088	11,000		NRP+	5,067	11,833
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927
LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
13	RP-	5,225	10,167	14	RP-	8,775	10,375	15	RP-	5,225	10,167
	NRP-	2,325	11,917		NRP-	3,496	11,250		NRP-	3,496	11,250
	RP+	3,496	10,375		RP+	2,325	10,167		RP+	2,325	10,375
	NRP+	8,775	11,250		NRP+	5,225	11,917		NRP+	8,775	11,917
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927

LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
16	RP-	8,775	10,375	17	RP-	7,200	10,333	18	RP-	6,800	10,208
	NRP-	2,325	11,917		NRP-	3,254	11,667		NRP-	2,567	11,500
	RP+	3,496	10,167		RP+	2,567	10,208		RP+	3,254	10,333
	NRP+	5,225	11,250		NRP+	6,800	11,500		NRP+	7,200	11,667
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927
LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
19	RP-	2,325	11,917	20	RP-	3,496	11,250	21	RP-	2,325	11,917
	NRP-	5,225	10,167		NRP-	8,775	10,375		NRP-	8,775	10,375
	RP+	8,775	11,250		RP+	5,225	11,917		RP+	5,225	11,250
	NRP+	3,496	10,375		NRP+	2,325	10,167		NRP+	3,496	10,167
	mean	4,955	10,927		mean	4,955	10,927		mean	4,955	10,927
LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR	LIST	ITEM	LFREQ	TSTR
22	RP-	3,496	11,250	23	RP-	2,567	11,500	24	RP-	3,254	11,667
	NRP-	5,225	10,167		NRP-	6,800	10,208		NRP-	7,200	10,333
	RP+	8,775	11,917		RP+	7,200	11,500		RP+	6,800	11,500
	NRP+	2,325	10,375		NRP+	3,254	10,333		NRP+	2,567	10,208
	mean	4,955	10,927		mean	4,955	10,885		mean	4,955	10,927

QUESTIONNAIRES

Italian version of the BIS-11 questionnaire (Fossati et al., 2001; Patton et al., 1995) employed in chapter 6 and chapter 7. The scoring grid is reported in the following page.

BIS-11[1]

Gentile Signore/a, nel seguente questionario vengono elencate una serie di situazioni nelle quali le persone usualmente vengono a trovarsi nel corso della propria vita. Ad ogni frase può rispondere scegliendo la modalità che si presta meglio a descriverLa. Il questionario va compilato nella sua totalità secondo quanto Lei pensa e senza l'aiuto di altre persone. Ovviamente, non esistono risposte giuste o sbagliate; è importante solo descrivere i propri sentimenti personali.

	Mai/ Raramente	**Talvolta**	**Spesso**	**Quasi sempre/ Sempre**
1. Pianifico le attività attentamente				
2. Faccio le cose senza pensarci				
3. Decido velocemente				
4. Mi affido alla sorte				
5. Non “focalizzo l’attenzione”				
6. I miei pensieri “vanno a gran velocità”				
7. Pianifico i viaggi con molto anticipo				
8. Ho autocontrollo				
9. Mi concentro facilmente				
10. Risparmio con regolarità				
11. Non riesco a star fermo durante gli spettacoli o le lezioni				
12. Sono un attento pensatore				
13. Faccio progetti per una sicurezza lavorativa				
14. Dico cose senza pensare				
15. Mi piace pensare a problemi complessi				
16. Cambio lavoro				
17. Agisco “d’impulso”				
18. Mi annoio facilmente quando devo risolvere dei problemi concettuali				
19. Agisco sull’impulso del momento				
20. Sono un pensatore assiduo				
21. Cambio residenza				
22. Compro le cose d’impulso				
23. Riesco a pensare ad un solo problema per volta				
24. Cambio hobby				
25. Spendo più di quello che guadagno				
26. Quando penso ho spesso pensieri estranei				
27. Mi interesso più al presente che al futuro				
28. Sono irrequieto a teatro o durante le lezioni				
29. Mi piacciono i rompicapo				
30. Sono orientato verso il futuro				

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[1] Traduzione italiana curata da Andrea Fossati, Michela Donini, Deborah Donati.

BIS-11 – GRIGLIA DI CORREZIONE

Mai/Raramente = 1 – Talvolta = 2 – Spesso = 3 – Quasi Sempre/Sempre = 4.
Se (r): Mai/Raramente = 4 – Talvolta = 3 – Spesso = 2 – Quasi Sempre/Sempre = 1.

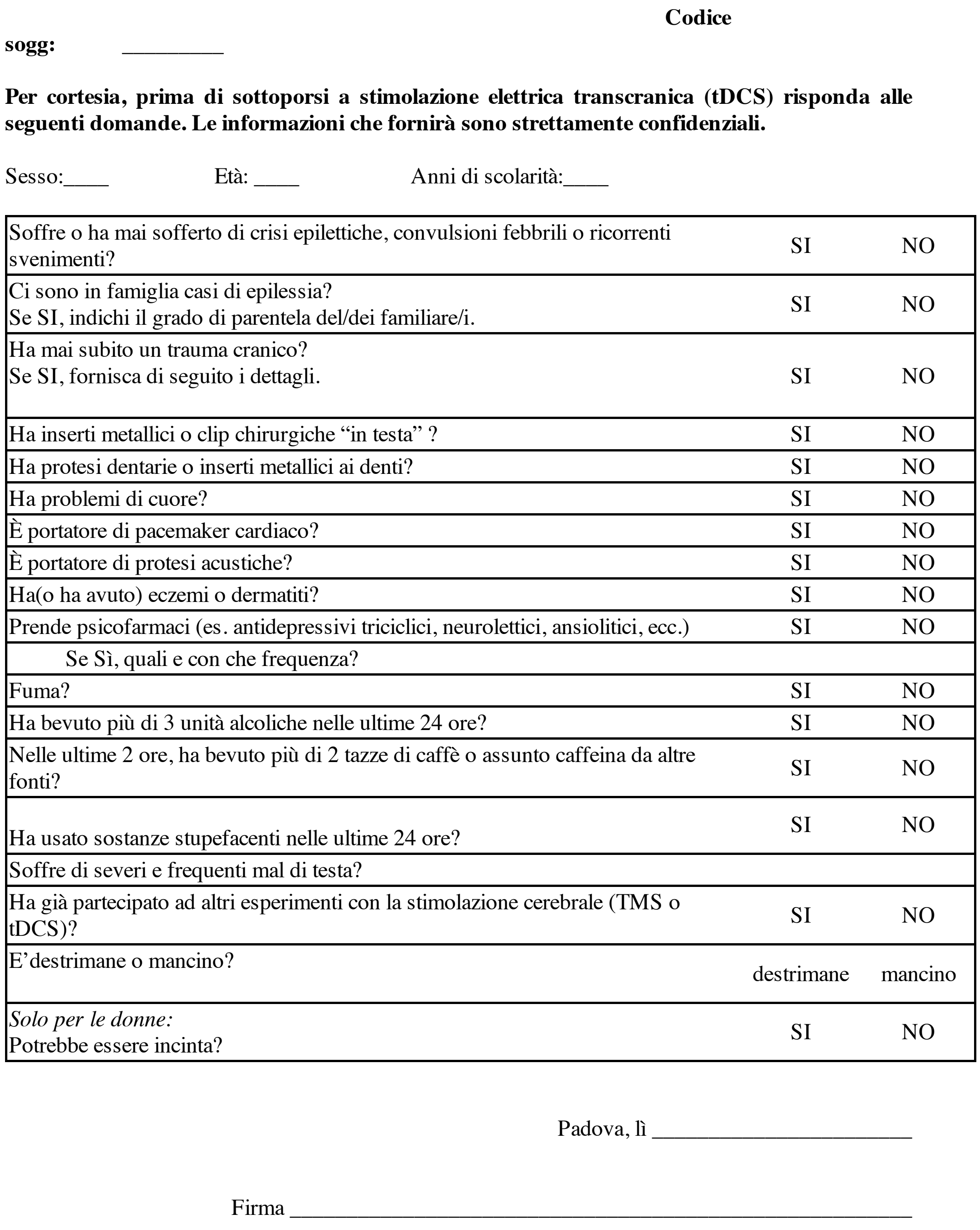
A	Im	Ac	Cc	P	Ic
5.	2.	1.(r)	10.(r)	16.	6.
9.(r)	3.	8.(r)	15.(r)	21.	24.
11.	4.	7.(r)	18.	23.	26.
20.(r)	17.	12.(r)	27	30.(r)	Totale:
28.	19.	13.(r)	29.(r)	Totale:	
Totale:	22.	14.	Totale:		
	25.	Totale:			
	Totale:				

Impulsività Attentiva	Impulsività Motoria	Impulsività da Non Pianificazione
Totale A	Totale Im	Totale Ac
Totale Ic	Totale P	Totale Cc
Totale:	Totale:	Totale:

Totale BIS-11 (Impulsività Attentiva+Motoria+Non Pianificazione):	

A = Attenzione – Im = Impulsività Motoria – Ac = Autocontrollo – Cc = Complessità Cognitiva – P = Perseveranza – Ic = Instabilità Cognitiva.

Screening form employed prior to every tDCS experiment reported in the present PhD dissertation (Chapters 3-5).



Codice
sogg: _________

Per cortesia, prima di sottoporsi a stimolazione elettrica transcranica (tDCS) risponda alle seguenti domande. Le informazioni che fornirà sono strettamente confidenziali.

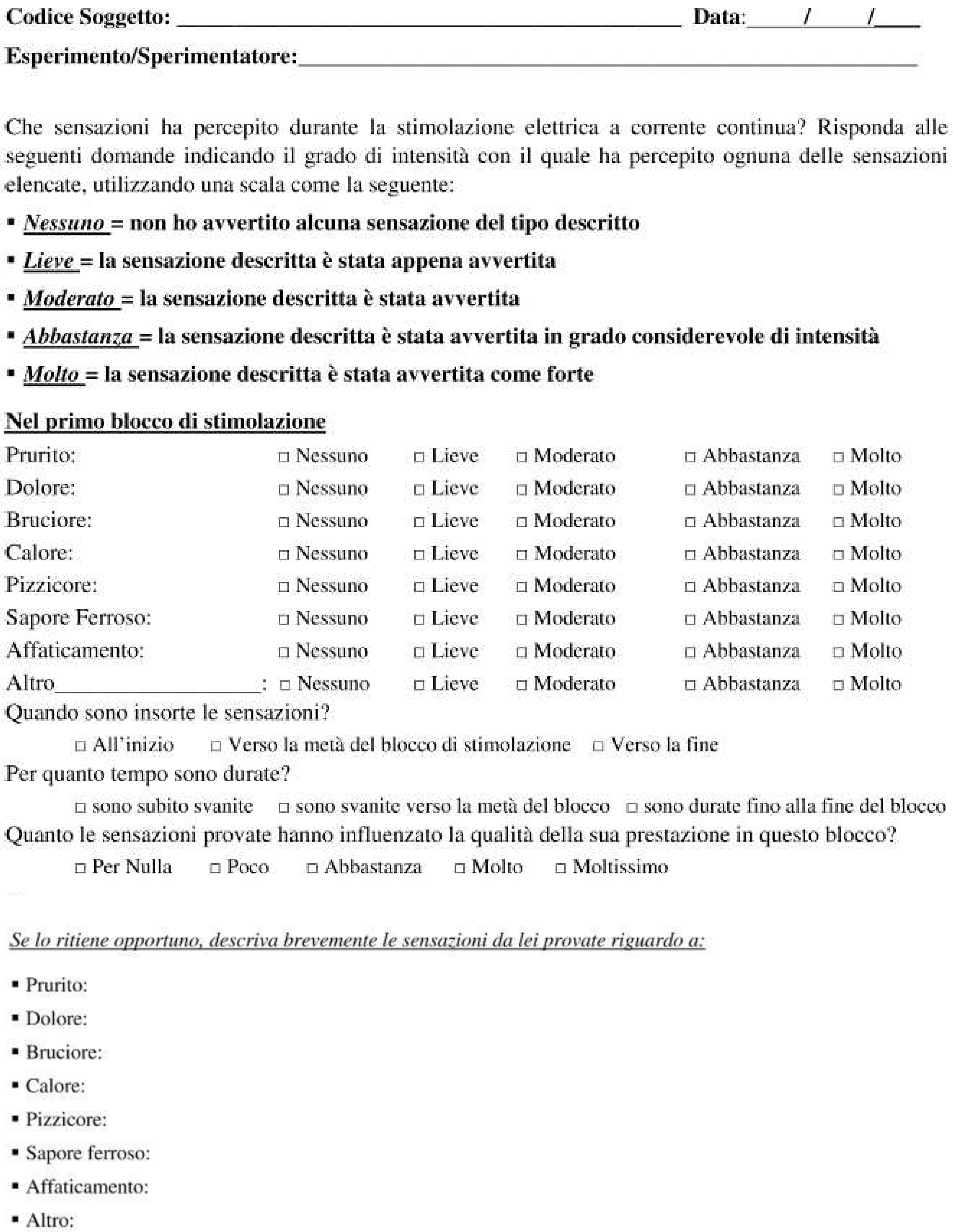
Sesso:____ Età: ____ Anni di scolarità:____

Soffre o ha mai sofferto di crisi epilettiche, convulsioni febbrili o ricorrenti svenimenti?	SI	NO
Ci sono in famiglia casi di epilessia? Se SI, indichi il grado di parentela del/dei familiare/i.	SI	NO
Ha mai subito un trauma cranico? Se SI, fornisca di seguito i dettagli.	SI	NO
Ha inserti metallici o clip chirurgiche "in testa" ?	SI	NO
Ha protesi dentarie o inserti metallici ai denti?	SI	NO
Ha problemi di cuore?	SI	NO
È portatore di pacemaker cardiaco?	SI	NO
È portatore di protesi acustiche?	SI	NO
Ha(o ha avuto) eczemi o dermatiti?	SI	NO
Prende psicofarmaci (es. antidepressivi triciclici, neurolettici, ansiolitici, ecc.)	SI	NO
Se Sì, quali e con che frequenza?		
Fuma?	SI	NO
Ha bevuto più di 3 unità alcoliche nelle ultime 24 ore?	SI	NO
Nelle ultime 2 ore, ha bevuto più di 2 tazze di caffè o assunto caffeina da altre fonti?	SI	NO
Ha usato sostanze stupefacenti nelle ultime 24 ore?	SI	NO
Soffre di severi e frequenti mal di testa?		
Ha già partecipato ad altri esperimenti con la stimolazione cerebrale (TMS o tDCS)?	SI	NO
E'destrimane o mancino?	destrimane	mancino
Solo per le donne: Potrebbe essere incinta?	SI	NO

Padova, lì ______________________

Firma ____

Discomfort questionnaire (Fertonani et al., 2010) delivered at the end of every tDCS experiment reported in the present PhD dissertation (Chapters 3-5).



Codice Soggetto: ________________________________ **Data**:____/____/____

Esperimento/Sperimentatore:________________________________

Che sensazioni ha percepito durante la stimolazione elettrica a corrente continua? Risponda alle seguenti domande indicando il grado di intensità con il quale ha percepito ognuna delle sensazioni elencate, utilizzando una scala come la seguente:

- ***Nessuno*** **= non ho avvertito alcuna sensazione del tipo descritto**
- ***Lieve*** **= la sensazione descritta è stata appena avvertita**
- ***Moderato*** **= la sensazione descritta è stata avvertita**
- ***Abbastanza*** **= la sensazione descritta è stata avvertita in grado considerevole di intensità**
- ***Molto*** **= la sensazione descritta è stata avvertita come forte**

Nel primo blocco di stimolazione

Prurito:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Dolore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Bruciore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Calore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Pizzicore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Sapore Ferroso:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Affaticamento:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Altro__________________:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto

Quando sono insorte le sensazioni?

□ All'inizio □ Verso la metà del blocco di stimolazione □ Verso la fine

Per quanto tempo sono durate?

□ sono subito svanite □ sono svanite verso la metà del blocco □ sono durate fino alla fine del blocco

Quanto le sensazioni provate hanno influenzato la qualità della sua prestazione in questo blocco?

□ Per Nulla □ Poco □ Abbastanza □ Molto □ Moltissimo

Se lo ritiene opportuno, descriva brevemente le sensazioni da lei provate riguardo a:

- Prurito:
- Dolore:
- Bruciore:
- Calore:
- Pizzicore:
- Sapore ferroso:
- Affaticamento:
- Altro:

Come accade in ogni protocollo sperimentale i partecipanti sono casualmente assegnati o alla condizione di reale stimolazione o alla condizione di controllo in cui la stimolazione non è reale, ma solo simulata. Se dovesse scommettere su che tipo di trattamento le è stato somministrato oggi, pensa di far parte del gruppo che ha ricevuto la stimolazione con corrente continua o del gruppo che non l'ha ricevuta (= condizione di simulazione o placebo)?

☐ reale stimolazione con corrente continua

☐ simulazione di stimolazione

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