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CICLO XXXI

BEHAVIORAL AND NEUROPHYSIOLOGICAL MODULATION OF ERROR-RELATED PROCESSES

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Contents

List of acronyms

ACC	Anterior cingulate cortex
ADHD	Attention-deficit/hyperactivity disorder
AIC	Anterior inferior insula
BDNF	Brain-derived growth factor
BESA	Brain electromagnetic source analysis
CA	Cornu Ammonis
cTBS	Continuous TBS
DLPFC	Dorsolateral prefrontal cortex
EAT	Error awareness task
EEG	Electroencephalography
EMG	Electromyography
EPSP	Excitatory postsynaptic potential
ERN	Error-related negativity
ERP	Event-related potential
FDA	Food and drug administration
fMRI	Functional magnetic resonance imaging
FST	Forced swim test
ISI	Interstimulus interval
iTBS	Intermittent TBS
LTD	Long-term depression
LTP	Long-term potentiation
MEP	Motor-evoked potential
MRI	Magnetic resonance imaging
MT	Motor threshold
NGF	Nerve growth factor
NIBS	Noninvasive brain stimulation
NMDA	N-methyl-D-aspartate
NT-3	Neurotrophin-3
NT-4/5	Neurotrophin-4/5
NT-6	Neurotrophin-6
NT-7	Neurotrophin-7
PAS	Paired associative stimulation
Pe	Error positivity
PERI	Post-error reduction of interference
PES	Post-error slowing
PET	Positron emission tomography
PFC	Prefrontal cortex
PIA	Post-error improvement in accuracy
pMFC	Posterior medial frontal cortex
ppTMS	Paired-pulse TMS
PT	Phosphene threshold
RSI	Stimulus-response interval
rTMS	Repetitive TMS
spTMS	Single-pulse TMS
tACS	Transcranial alternating current stimulation
TBS	Theta burst stimulation
tDCS	Transcranial-direct current stimulation
TEP	TMS-evoked potential
tES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
tRNS	Transcranial random noise stimulation

Abstract

The term brain modulation refers to a wide range of interventions that allow modifying the central nervous system. The general purpose of this dissertation will regard the investigation and modulation of error-related processes through the use of behavioral interventions and noninvasive brain stimulation (NIBS). In order to accomplish this aim, three studies were conducted.

Study 1 investigated the motivation-cognition interaction. In particular, this study aimed to increase error awareness by using rewards in a group of healthy older adults, compared to younger adults. Results showed a reduction of error awareness when participants were rewarded, both older and younger adults. This detrimental effect of rewards suggests more attention in planning motivational interventions with the aim to modulate error awareness.

Study 2 aimed to investigate the neural bases of error awareness and modulate error awareness by using on-line transcranial magnetic stimulation (TMS). Results revealed an implication of the dorsolateral prefrontal cortex (DLPFC) in error awareness. However, this modulation was specifically induced by a single-pulse TMS paradigm, compared to a paired-pulse TMS paradigm that did not produce a modulation of the process. These results highlight how subtle variations of the TMS paradigm can differently affect error awareness.

Study 3 investigated the behavioral and neurophysiological modulation of error-related processes induced by a low-frequency repetitive TMS paradigm. Results showed a reduction of the error positivity (Pe), an electrophysiological component associated with error awareness, only when the left DLPFC was stimulated, compared to the homologous right DLPFC and the Vertex. This result contributes to provide new knowledge about error-related processes, in particular about the neural bases of the Pe.

Finally, a critical review of these studies will provide general insights for the design of future modulatory interventions.

Introduction

The term brain modulation refers to a wide range of methods that allow modifying brain functioning, namely to modulate or change the central and peripheral nervous systems. The magnitude of these modifications can act at a micro-level, such as the alteration of the membrane potential of a single neuron, up to extended modifications able to affect behavior. In terms of duration, brain modulation produces effects that can last from few milliseconds to long-lasting effects that cover all life of an individual.

The humanity's history is rich in evidence that shows how our species has always been interested in researching ways to change the state of mind, enhance cognitive performance or alter the level of consciousness. The spectrum of means to reach this form of modulation can range from the use of popular psychotropic substances, such as alcohol and caffeine, to metacognitive strategies to improve memory, such as the famous "Method of Loci". Together with these simple and ordinary methods, which have a long past, other more systematic and recent methods have been applied in extraordinary situations. A typical example is noninvasive brain stimulation (NIBS). This family of methods includes different kinds of techniques highly used with patients in which a neurological or psychiatric pathology has altered brain functioning and has produced cognitive deficits (Kuo, Paulus, & Nitsche, 2014; Obeso, Oliviero, & Jahanshahi, 2016; Schulz, Gerloff, & Hummel, 2013).

In clinical settings, many treatments rely on the possibility of modifying our brain and it is not surprising that modulation of the nervous system is among the fastest-growing areas of medicine (Krames, Hunter Peckham, Rezai, & Aboelsaad, 2009). In addition, brain modulation allows us understanding the normal functioning of the brain. In fact, it is extremely informative to investigate how the brain reacts to modulatory interventions, showing its impressive ability to change both functionally and structurally (Schaefer et al., 2017).

In a critical review published in Nature, Farah and colleagues (2004) compare the human ability to modulate its own brain function to the development of metallurgy in the Iron Age, mechanization in the Industrial Revolution or genetics in the second half of the twentieth century.

This analogy can be considered appropriate because the perspective of modulating our brain is extremely winsome, especially with the aim to enhance cognitive functioning in above mentioned clinical situations.

Apart from these cases, in which the use of brain modulation can be justified by the purpose of reducing the impact of a cognitive impairment, it is important to highlight that the topic of cognitive enhancement, especially in everyday life contexts, raises important ethical issues. For example, normal aging is associated with a decline in cognitive functions (Cabeza, Nyberg, & Park, 2009; Salthouse, 2010). In this case, can the use of brain modulation methods be ethically acceptable to restore cognitive functioning in elderly? Although these ethical aspects are relevant, they will not be under discussion in this dissertation. Nevertheless, for further information, we recommend some reviews (Bostrom & Sandberg, 2009; Farah et al., 2004).

This dissertation will critically debate brain modulation. In **Chapter 1**, we will introduce an important aspect linked to brain modulation, namely neural plasticity. This property of the brain is at the base of any form of behavioral and neural change. Afterward, in **Chapter 2**, drivers of brain modulation will be described. In particular, related to this dissertation, we will describe two kinds of interventions that can modulate behavior and brain functioning: modulation induced by reward and modulation induced by NIBS. After these premises, in **Chapter 3**, we will move our focus to the core of this dissertation, namely error-related processes. Given that the general purpose of this dissertation was to produce a modulation of error-related processes, the following chapters will describe three studies in which different interventions aimed to induce behavioral and neurophysiological changes. In particular, in **Chapter 4**, performance was supported by means of incentives, in order to increase error awareness in a group of elderly, whereas, in **Chapters 5** and **6**, brain modulation was induced by NIBS. Finally, in **Chapter 7**, we will conclude this dissertation by a critical review of our results and providing insights on a conscious application of modulatory interventions, especially we will summarize some significant points into a set of suggestions and strategies for designing modulatory interventions.

Chapter 1

Neural Plasticity

According to Bateson & Gluckman (2011), the phenotype of every organism is determined by a combination of two mutually interdependent properties: *robustness* and *plasticity*. *Robustness* refers to a property that is insensitive to environmental changes or genetic mutations and, therefore, contributes to maintaining stable the phenotype. On the contrary, *plasticity* is defined as a flexible property of each organism in expressing physiological, morphological, and behavioral differences in response to innate or acquired factors. *Robustness* and *plasticity* are not totally independent properties. In fact, *plasticity* can be regulated by robust mechanisms, and, *vice-versa*, *robustness* can be affected by mechanisms of *plasticity* (Bateson, 2017). For example, some innate traits typically regulated by robust mechanisms, like smiling in human babies, are rapidly modified after the social interaction, that is an example of plastic mechanism. Thus, the interaction between *robustness* and *plasticity* determines a unique phenotype.

Importantly, *plasticity* should not be confused with *elasticity,* another property involved in the generation of the phenotype. In fact, e*lasticity* is the ability of a body to return to its original size and shape after a distorting influence. In biology, for example, some types of *elasticity* relate to the ability of the skeletal tissue to repair itself after a damage or some homeostatic mechanisms of the human body, such as the re-acquisition of body weight after a period of fast.

If it is true that *robustness, plasticity*, and *elasticity* mutually contribute in the expression of a phenotype, it is likewise true that they act differently along the ontogenetic stages (childhood, adulthood, old age), and their impact is different depending on the characteristics of the tissue they interact with (e.g. skin, muscles, skeleton, brain).

As regards the brain, one of the most fascinating properties that characterized this organ is its ability to change the neural architecture in response to internal or external factors. The brain can be considered a structure in which plastic mechanisms act massively. This flexibility, known as **neural plasticity**, is the basic mechanism of memory formation (Fauth & Tetzlaff, 2016; Schaefer et al., 2017), allows facing new experiences in a variable environment (Mandolesi et al., 2017; Sale, Berardi, & Maffei, 2014), and, crucial from a clinical point of view, leads to compensate for

negative effects of brain damage (Kaas, 2015; Kou & Iraji, 2014). The final output of neural plasticity is an experience-modulated behavior that can react to environmental demands.

Neural plasticity is defined as any change in cortical or subcortical properties either structural or functional (Sala & Segal, 2014). Structural plasticity is defined as any morphological changes (Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013), such as the generation of new synapses and new neurons, whereas functional plasticity considers some forms of functional reorganization (Schaefer et al., 2017), such as when the strength of synapses changes, as in long-term potentiation (LTP) or long-term depression (LTD). Similarly, but with a focus on behavior, Berlucchi & Buchtel (2009) consider neural plasticity as several kinds of behavioral modifiability, including maturation and adaptation to a changing environment, specific and unspecific kinds of learning, and compensatory adjustments after functional losses from normal aging or brain lesion.

Up until the 1950s, a spread and shared conviction claimed that after the adolescence the brain was destined to a progressive decay, without any possibility to observe forms of neural plasticity. However, nowadays this static vision has been abandoned and a more plastic conception has been accepted from scientists. In fact, neural plasticity is not necessarily restricted to the first stages of life, since it is typically retained by the individual throughout the lifespan.

In line with this view, to date more and more evidence shows forms of neural plasticity in elderly as well (Burke & Barnes, 2006; Grady, 2012; Lazarov & Hollands, 2016). In an interesting study, Greenwood (2007) suggests that structural losses, typically observed in elderly, lead to a functional reorganization of the brain. In detail, Greenwood (2007) describes this sequence of events: (a) age-related atrophy (attributed to dendritic regression), synapse loss, and white matter degeneration lead to cognitive decline in elderly; (b) the cognitive decline lead to a changing in strategies used to process information; (c) these new processing strategies trigger different forms of functional reorganization of cortex, by modification in cortical innervation; (d) this functional reorganization is proofed by neuroimaging studies in which elderly show increased activity in regions adjacent and contralateral to those brain areas that typically present shrinkage in elderly.

As regards neurogenesis phenomena, animal models confirm a continuous proliferation of neurons in two brain regions of adult rodents: the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus (Ming & Song, 2005; Ming & Song, 2011; Seri, García-Verdugo, Collado-Morente, McEwen, & Alvarez-Buylla, 2004). Again, this evidence

suggests that neural plasticity is not only significant during the developmental period. Contrary, also the adult brain presents several forms of plasticity.

Even if nowadays neural plasticity is broadly accepted from the scientific culture, before the *Decade of the Brain* (1990-2000) the word "neural plasticity" was accompanied by skepticism and many articles were rejected from prestigious journals when they tempted to report evidence against the dogma of the inflexibility of the adult brain. However, some pioneering evidence in favor of neural plasticity has come long before 1990.

William James was among the first to bring attention to the hypothesis that the neural bases of learning depend on neural plasticity. In the volume *The principles of Psychology* (James, 1890), he postulated that the organic matter, especially the nervous tissue, seemed characterized by an extraordinary level of plasticity. When a stimulus is perceived, it leaves a sort of trace, a connection among several parts of the brain. If the sensory stimulation is repeated, this connection becomes stronger by reinforcement of the pre-existing connections or by generation of new connections.

In 1892, Santiago Ramòn y Cajal thought that the connections among neurons changed both in response to physiological processes associated with the development, and through learning processes. He hypothesized that the brain could adapt to the environment thanks to dynamic histological changes resulting from mental activity.

A huge step forward in the knowledge of neural plasticity was made by Sir Charles Sherrington, when in 1897 introduced the term "synapse" to explain how neurons exchange their chemical messages. Sherrington postulated that learning was strictly related to a sprouting of new synapses.

Several years later, in 1949, both the hypotheses of Cajal and Sherrington were re-considered by Donald Olding Hebb. In his work, *The organization of behavior* (Hebb, 1949), he introduced the famous theory of Hebbian learning. In this important work, Hebb claimed that learning was an experience-dependent process in which new neural networks were generated by several circumstances. For example, he said:

> *"When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."*

This dynamic interaction among neurons, according to Hebb, would contribute to create, maintain, and reinforce neural networks. Moreover, another important contribution from Hebbian learning is the distinction between short-term and long-term memory. In order to explain the differences between these processes, Hebb assumed that in short-term memory the information is briefly retained through temporary and functional modifications of neurons, whereas the long-term memory required structural modifications of neurons.

The synaptic changes during learning can happen only when cells synthesize some proteins involved in learning processes (Rosenberg et al., 2014). Thus, protein expression is the base of structural and functional modifications of neurons. These modifications range from changes of the pre-existing synapses to creation of new synapses (Holtmaat & Svoboda, 2009). For example, during some training sessions, when an individual is involved in learning new information, neurons may present some structural modifications, such as the genesis of new synapses and dendritic spines. Alternatively, or in conjunction with structural modifications, other phenomena may generate functional changes, such as a reduction/improvement of neurotransmitter release (Nabavi et al., 2014; Nicoll, 2017).

Since a strict distinction between structural and functional plasticity can be misleading, because both the processes are closely associated and coexist (Cramer, 2004; Swain et al., 2003), the next section will point out the main mechanisms underlying structural and functional plasticity, without to artificially categorize a mechanism within one or another form of plasticity.

Mechanisms of neural plasticity

This section aims to provide a synthetic overview of mechanisms underlying neural plasticity. In recent years, more and more empirical evidence allows understanding which different neural mechanisms lead to modifications of the adult brain. Several mechanisms are at the base of neural plasticity:

- dynamics of synaptic structures
- neurogenesis
- neurotrophins

- modifications of gray and white matter
- reorganization of cortical maps (remapping)
- LTP and LTD

Dynamics of synaptic structures - With the advent of new powerful cell imaging techniques, such as the confocal microscopy, it has been possible to identify the dynamic processes occurring within synaptic structures. Although all these studies mainly use animal models, they allow characterizing these neural plasticity processes in the adult mammalian brain. Sprouting of new synapses, together with the properties that dendrites show in contact with synapses, are the most important factors at the base of neural plasticity.

Long-term *in vivo* imaging studies can reveal the structural dynamics of neurons as Holtmaat & Svoboda (2009) argue in a review. Although the large-scale organization of synaptic structures is generally stable, authors show a subset of structures that display an experience-dependent structural plasticity. In particular, Holtmaat & Svoboda (2009) show a dynamic turnover of dendritic spines that grow and retract according to sensory experience. Besides sensory experience, the dynamic of this turnover is also affected by sensory deprivation and neural damage (Holtmaat & Svoboda, 2009).

In a study, also Brown and colleagues (2007) show a reorganization of dendritic spines following a stroke, in adult transgenic mice. Compared to the control mice, in which no significant modifications of dendritic spines was observed, after stroke, the survived areas undergo a long period of dendritic remodeling (up to 6 weeks after the stroke). These changes were mainly evident in the peri-infarct areas and appeared to be associated with a reorganization of the vasculature in the peri-infarct cortex.

In general, changing in dendritic spines represent probably the main factor to explaining structural brain changing throughout life (Chen, Lu, & Zuo, 2014; Schaefer et al., 2017).

Neurogenesis - Adult neurogenesis is a multiphase process that requires the production of cell progenitors, their migration, their differentiation, and maturation into fully integrated neurons. As previously reported, there are two brain areas in which neurogenesis processes are evident: the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricles. Most of the studies on neurogenesis, which reported the first results already in the mid-1960s (see for example Altman, 1962), observed neurogenesis mainly in animal models

(rodents, non-human primates, and other mammals). However, the most exciting discovery that neurogenesis is a phenomenon also presents in adult humans derives from more recent years.

One of the first evidence comes from the study of Eriksson and colleagues (1998), in which they demonstrated that new neurons were generated from dividing progenitor cells in the dentate gyrus of adult humans and, interestingly, indicating that the human hippocampus could generate neurons throughout life.

A second site of production of new neurons is the sub-ventricular zone lining the walls of the lateral ventricles. The stem cells of the subventricular zone generate new neurons that are grouped into cell aggregates. It is shown that in mice these newly-generated neurons migrate towards the olfactory bulb along a path of migration known as the rostral migratory stream (Lim & Alvarez-Buylla, 2016; Lois & Alvarez-Buylla, 1994).

Although the potential implications of neurogenesis are exiting, for example in the prospective to repair the central nervous system using endogenous and transplanted neural stem cells, the precise role played by the production of new neurons is still unclear. Especially in human beings, the question of the role of the new neurons is far from being clarified (Couillard-Després, 2012; Gheusi, Lepousez, & Lledo, 2012).

Neurotrophins - This group of proteins is considered a molecular mediator in neural plasticity. Since these proteins modulate the electrical properties and the structural organization of the synapses, neurotrophins could be considered biological markers of memory and learning processes (Gómez-Palacio-Schjetnan & Escobar, 2013). The main neurotrophins are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), neurotrophin-6 (NT-6), and neurotrophin-7 (NT-7).

NGF is one among the first proteins discovered and it seems implicated in several functions, mainly NGF elicits axonal growth, promotes neuronal survival, and acts to sensitize the response to specific nociceptive inputs (Bothwell, 2014; Petruska & Mendell, 2009). Moreover, NGF contributes to affect the architecture of neural circuits, for example stimulating the maturation of Purkinje cells. Cohen-Cory and colleagues (1991) show how in a cell culture the simultaneous exposure to glutamate and aspartate (excitatory neurotransmitters) and NGF enhanced the size of Purkinje cells and increased their survival (figure 1).

Several studies have focused the attention on BDNF as well. For example, this protein seems to modulate the synaptic activity by modulation of postsynaptic mechanisms. A brief exposure to BDNF in hippocampus produces a long-term increase in synaptic transmission, similar to the LTP (Gazzaniga, 2004; Lu, Nagappan, & Lu, 2015).

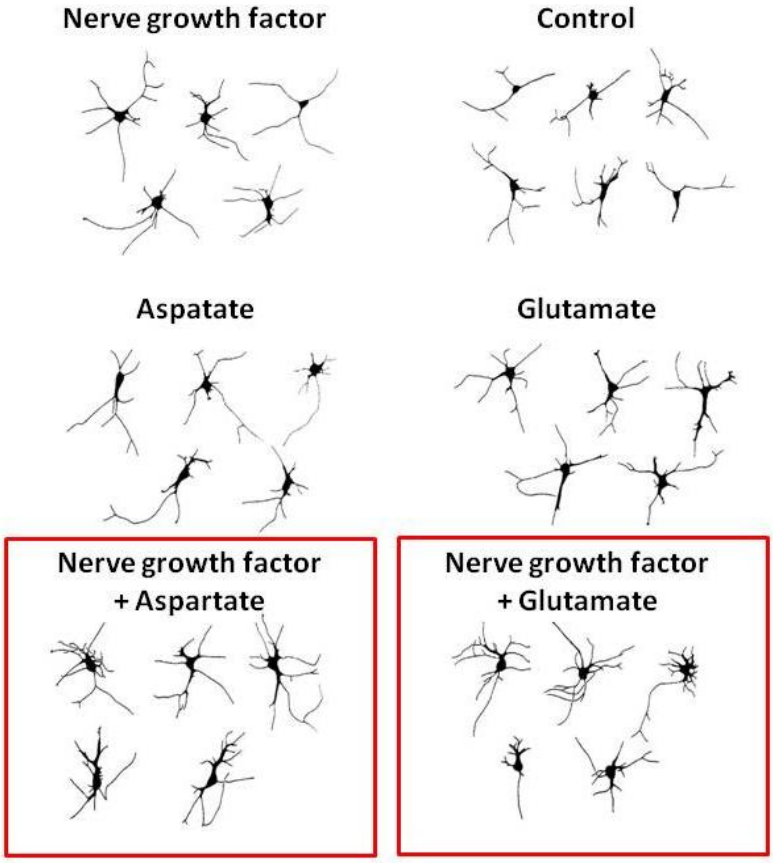

Figure 1 | Morphological structure of Purkinje cells after the expose to excitatory neurotransmitters, or nerve growth factor, or a combination between excitatory neurotransmitters and nerve growth factor (red squares). Modified by Cohen-Cory et al., 1991.

The study of these proteins opens new line of research and may provide new treatments in various diseases, such as cognitive deficits, brain damage and neurological disorders. For example, some studies report an association between antidepressant drugs and increased BDNF in the hippocampus (Banasr & Duman, 2008; Mattson, Maudsley, & Martin, 2004; Taupin, 2006) that could explain the effects of antidepressants in reducing some cognitive deficits typically present in depression. Furthermore, also NIBS seem to positively interact with these neurotrophins. For instance, Floel & Cohen (2010) show that transcranial-direct current stimulation (tDCS) produces its effects through BDNF activation. Similarly, but using transcranial magnetic stimulation (TMS),

Niimi and colleagues (2016) show that the synergic combination of rehabilitation and repetitive TMS (rTMS) improves motor function in patients after stroke, by activating BDNF processing. Finally, several studies convey that the use of BDNF could open new frontiers of intervention in neurological diseases (for a review, Longo & Massa, 2013).

Modifications of gray and white matter - Current non-invasive neuroimaging techniques, such as magnetic resonance imaging (MRI) or functional magnetic resonance imaging (fMRI) have allowed to investigate modifications in human brain *in vivo*. In particular, these techniques allow to observe structural modifications of gray and white matter.

In a study (probably one of the most emblematic study in neuropsychology), Maguire and colleagues (2000) demonstrate experience-dependent modifications of the hippocampus, a crucial structure implicated in the representation of environment through cognitive maps (O'Keefe & Nadel, 1978). In detail, in Maguire and colleagues' study, structural MRIs of London taxi drivers revealed larger posterior hippocampi of taxi drivers compared to the control group who did not drive taxis. Interestingly, hippocampal volume correlated with the number of hours spent on driving a taxi.

Another suggestive evidence in favor of experience-dependent modifications of gray matter comes from a study of Gaser & Schlaug (2003). Using the voxel-based morphometry, they found differences between professional musicians and two control groups (nonmusicians and amateur musicians) in motor, visuospatial, and auditory brain regions. These anatomical differences may represent the outcome of long-term skill learning and repeated practice in professional musicians.

White matter consists of axons connecting different brain regions and represents about half of the total human brain volume. The typical color of white matter depends on the chemical composition of myelin, a lipidic-rich substance that surrounds the axons of some neurons. White matter is essential to coordinate the timing of action potentials and its functions are particularly evident when it has damaged by white matter diseases, such as multiple sclerosis.

More and more evidence highlights continuous modifications of white matter along the lifespan. Although myelinogenesis is maximum in the first infancy, it continues during the adolescence and the adult life as well (Sampaio-Baptista & Johansen-Berg, 2017). In a study, the anterior part of corpus collosum was modified after an intensive cognitive training. Compared to control group, the group of younger and older trained participants showed experience-dependent plasticity of the white matter microstructure. In particular, several diffusion-tensor imaging

metrics revealed an increment in size of the anterior part of the corpus callosum (Lövdén et al., 2010). Thus, the study demonstrates that white matter plasticity extends into old age. Furthermore, within this theoretical framework of experience-dependent plasticity, Schlaug and colleagues (2009) show that a long instrumental music training (around 29 months) caused an increase of the anterior midbody of the corpus callosum.

Reorganization of cortical maps (remapping) - The above-mentioned plastic modifications of the gray and white matter are not the unique kind of macro-modifications of the brain. Indeed, and emblematically after brain lesions, extended phenomena of functional reorganizations can involve the cortex.

A well-established knowledge concerns the fact that motor and sensory cortices are organized and divided into functional areas. Since each of these functional areas represents a precise part of the body, they are also known as cortical maps. Following a deafferentation, for example the resection of a peripheral nerve of a limb, we can observe, after just a few hours, a reorganization of that cortical area deprived of the sensory input.

In human beings is possible to investigate noninvasively the functional reorganization of motor maps through TMS since this technique allows mapping motor areas. When a magnetic pulse triggers a motor response in a specific part of the body, we can infer a causal relationship between the stimulated motor area and the motor response. Using this method, Pascual-Leone and colleagues (1995) demonstrated an enlargement of specific cortical maps after a motor training consisting of a five-finger exercise. Thus, before the training, the whole area sensitive to the TMS stimulation was smaller than after the training. Interestingly, they found similar effect also in the case participants were trained to mentally perform the same training (Pascual-Leone et al., 1995).

The exact mechanisms underlying the reorganization of cortical maps is still unknown, even if at least three factors could be implicated: unmasking of latent synapses, sprouting, and synaptogenesis.

LTP and LTD - These two phenomena reflect the ability of synapses to change their strength and seem to be basic mechanisms of explicit memory, or declarative memory (Kemp & Manahan-Vaughan, 2007; Nicoll, 2017). The neural mechanisms for the formation of declarative memory (memory for facts and events) are believed to be integrated from processes mediated by

hippocampal long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD are induced by persistent stimulation of synapses at high or low frequency (Nabavi et al., 2014; Nicoll, 2017). Although LTP and LTD have been initially discovered in two different brain sites, respectively the hippocampus (Bliss & Lømo, 1973) and the cerebellum (Ito, 1982), nowadays growing evidence shows that LTP and LTD are present in the neocortex as well (Eder, Zieglgänsberger, & Dodt, 2002; Tsumoto, 1990). The neocortex would be particularly crucial for neural plasticity because it performs sensory, motor, and cognitive tasks. Last but not least, LTP and LTD are among the main mechanisms underlying the modulatory effects of NIBS. For this reason, they will be again mentioned in Chapter 2.

LTP corresponds to a long-lasting enhancement of synaptic transmission that follows high-frequency stimulation (tetanic).

In the hippocampus, the region of CA1 (Cornu Ammonis) receives input from the CA3 subfield through a set of fibers called the Schaffer collaterals. In a typical experiment, the stimulation with a single electrical pulse of a CA3 cell induce an excitatory postsynaptic potential (EPSP) in a CA1 cell. In one of the first demonstration of LTP, Bliss and Lømo (1973) showed that, instead of a single pulse, a tetanic presynaptic stimulation of the CA3 region caused a long-lasting enhancement of EPSPs in postsynaptic cells of the CA1 region. Thus, a tetanic stimulation can modify the synaptic transmission between the CA3 and CA1 regions.

The N-methyl-D-aspartate receptor (NMDA receptor) plays an important role in LTP (Lüscher & Malenka, 2012). Normally, extracellular magnesium (Mg^{2+}) ions bind to specific sites on the receptor, blocking the passage of calcium (Ca^{2+}) ions. However, if the postsynaptic membrane is sufficiently depolarized, Mg^{2+} ions get dislodged from the pore, allowing Ca^{2+} ions to enter in the cell (Nicoll, 2017). The entry of Ca^{2+} ions activates a series of cascade reactions that triggers protein synthesis and, in turn, improves the efficiency of synaptic transmission.

Contrary to LTP, LTD is a long-lasting decrement of synaptic transmission after low-frequency stimulation (Nabavi et al., 2014). The chemical bases of this phenomenon are similar to LTP since also in LTD the NMDA receptors would be involved. However, unlike LTP, in LTD the amount of Ca^{2+} ions is reduced because the low-frequency stimulation of presynaptic cells is not able to sufficiently depolarize the postsynaptic membrane. In LTD, the reduced flow of Ca^{2+} ions triggers another kind of chemical reactions that reduces dramatically the strength of synapses (Gazzaniga, 2004).

So far the main factors involved in neural plasticity have been described: dynamic changes of synaptic structures, neurogenesis phenomena, neurotrophins, macro-modification of gray and white matter, functional reorganization of cortical maps, as well as LTP and LTD. However, for the sake of clarity, other aspects can contribute to change the brain. For example, some environmental factors such as environmental enrichment exposure (Mora, Segovia, & del Arco, 2007; Sale et al., 2014) and sensory deprivation (Bengoetxea et al., 2012; Milshtein-Parush et al., 2017).

Additionally, age seems to play an important role in neural plasticity, both when we consider age as a crucial aspect during the development of the nervous system and when we consider age as an interacting factor with the recovery after a brain lesion. In the first case, considering age as a central factor within the development of the brain, the presence of sensitive periods during the development, in particular, the first years of life, is a proof of the importance of age in the maturation of the nervous system. In line with Bateson (1979), these sensitive periods can be seen as time windows by which the experience determines a proper development of a process. The absence of an adequate stimulation within these periods may cause an atypical development (Fox, Levitt, & Nelson, 2010) and leads to permanent alterations in the neural networks of different brain regions (Ismail, Fatemi, & Johnston, 2017). In the second case, taking the interaction between age and brain lesion into account, different outcomes may derive after a damage, depending on age. An interesting vein of research investigates the effect of brain injury on children (for a review, Anderson, Spencer-Smith, & Wood, 2011). For instance, some authors show a better recovery after a brain injury in childhood, compared to adults with the same lesion (Singh et al., 2013; Woods & Carey, 1979). In fact, the children's brain would be more plastic than the adult's one. Nevertheless, other authors draw a worse prognosis in case the brain injury occurs during the childhood (Anderson et al., 2005; Taylor & Alden, 1997) since in this period the brain is not still well developed and it is particularly fragile (Keenan, Hooper, Wetherington, Nocera, & Runyan, 2007). However, a more recent view (Anderson et al., 2011) suggests that the outcome following the injury in children is not only given by the age at which brain damage occurs, but also by other factors, such as injury-related factors (e.g. nature, severity, and timing of damage), constitutional factors (e.g. developmental stage, cognitive abilities) and environment (e.g. social status, and access to medical/rehabilitation treatments). All of these factors interact with each other, explaining the variable outcomes observed post-early brain damage.

Chapter 2

Drivers of brain modulation

The brain is a wonderful flexible structure. As we have seen, neural plasticity is an intrinsic property of the brain that is present throughout life. Perception of sensory stimuli, stimulus-response associations, memories or motor procedures are all consequences of neural plasticity. Within this theoretical framework, the distinction between a psychological process and an organic process ceases to be informative. In fact, changes in brain functioning can lead to behavioral changes, just as modifications of behavior can induce functional or structural changes in the brain (Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

The possibility to modify our behavior or deeper brain processes is intriguing and several research fields have focused their attention on the fascinating field of brain modulation. A crucial point concerning brain modulation is the "direction" of expected results of modulation. When we conceive to modulate behavior and/or brain functioning, an important issue should be addressed: *What can we expect from modulation?* Depending on the desired outcome, we should consider the proper method. In some cases, the purpose could be to enhance a specific process. For example, an intervention could be focused on improvement of selective attention in patients with traumatic brain injury. On the other hand, the aim could be to downregulate a process, for example with the purpose to reduce an aberrant behavior. Thus, an intervention can act at different levels: to enhance neural plasticity when it plays an adaptive role or to reduce it when it is maladaptive (Hummel & Cohen, 2005).

In this dissertation, the main purpose was to induce **behavioral and neurophysiological modulation**, as well as to investigate error-related processes. In Chapter 4, 5, and 6, we will present three studies aim to modify one or more processes. In particular, in study 1, in order to increase error awareness (error awareness and other error-related processes will be exhaustively described in Chapter 3), performance of a group of elderly and younger adults were incentivized by using rewards, whereas in studies 2 and 3, TMS was used to modulate and investigate error-related processes.

Behavioral modulation: enhancing performance with rewards

Performing a task in a context in which rewards are available contributes to improving performance. Growing evidence shows that this improvement can involve several cognitive processes: working memory, attention, episodic encoding, and decision making (Locke & Braver, 2010; Maddox & Markman, 2010; Pessoa, 2009, 2010; Shohamy & Adcock, 2010). These results suggest an interaction between motivation and cognition. In fact, motivation can modulate ongoing neurocognitive processing (Braver et al., 2014; Hughes & Zaki, 2015).

Motivation-cognition interaction is investigated by different disciplines such as cognitive neuroscience, social and personality psychology, and cognitive-aging research. Since in general these disciplines vary significantly in terms of disciplinary focus, only the perspective of cognitive neuroscience and cognitive-aging research will be considered here, at the expense of the framework of social and personality psychology that is not strictly related to this dissertation.

In cognitive neuroscience, the construct of motivation is often conceptualized as a neural representation of an expected result by which it is possible to predict the effort that an individual will invest in order to reach that result. In other words, motivation can be seen as a process that supports, guides and maintains a goal-directed behavior.

In the domain of cognitive neuroscience, a common approach to investigate motivation is by using reward signals. Motivation is a transient representation triggered by internal or external incentives. Experimental research typically operationalizes motivation as a mental representation evoked by extrinsic incentives (Braver et al., 2014). In a classical experiment, extrinsic incentives (e.g. monetary rewards) can be manipulated and delivered during the execution of a task, in order to investigate their impact on performance (Bonner & Sprinkle, 2002). This approach typically involves various programs of incentives or several types of rewards. Taken together each variation of these parameters may produce different effects on performance. For example, as regards different programs of incentives, a reward could be delivered either before or after a response, namely trial-by-trial. In other cases, a reward could be delivered after a certain number of responses, for example after each block of a task. Even if these programs of incentives seem pretty the same, their impact on performance can be dramatically different.

Depending on cognitive process investigated, age of participants and other factors such as cognitive strategies employed in the execution of a task, we could have diametrically opposite results by changing the program of incentives. It is not surprising, therefore, that several studies show a paradoxical reduction of incentivized performance (Bonner, Hastie, Sprinkle, & Young, 2000; Bonner & Sprinkle, 2002; Camerer & Hogarth, 1999). Thus, it is extremely important to accurately choose when an incentive/reward should be provided.

This paradoxical effect of incentives has been recently discussed in a review of Yu (2015), where mechanisms of incentive-induced performance decrements have been carefully considered. This article raises an important issue: although goals can support strong motivation, at the same time, they may induce a reduction of performance due to a strong psychological pressure. This phenomenon is known as "**choking under pressure**" and efficaciously described failures of performance caused by a high motivation that induces stress and, in turn, poor performance. An emblematic and practical example concerns the performance of football players on the penalty shootout. In major competitions, such as World Cup Games, it is common to observe big fails due to psychological pressure.

Previous accounts have tempted to explain "choking under pressure" phenomenon:

- **the distraction account**
- **the explicit monitoring account**
- **the over-arousal account**

In the distraction account, attention would have a crucial role in explaining failures of performance in stressful scenarios. In fact, the reduction of performance would be a consequence of an attentional shift from skill execution to psychological pressure (Carver & Scheier, 1981; Wine, 1971). Thus, attentional focus is moved to distracting cues, such as the consequences associated with failure.

Differently, the explicit monitoring account claims that pressure would shift mental processes from an automatic to a controlled mode (Baumeister, 1984). Also a well-learned behavior, such as driving a car, had required at the beginning of its acquisition a constant monitoring of performance during its execution. At this stage, when we are still somehow untrained, the level of cognitive resources is high to have an acceptable performance. The transition from a step-by-step monitoring stage to an automatic stage leads an advantage since, in this case, we can maintain

good performance by using a minimal level of resources. According to the explicit monitoring account, high psychological pressure would lead to a sort of regression in which even an automatic behavior would require a high step-by-step control. Therefore, this regression from the automatic stage to the step-by-step monitoring stage would lead performance to the inefficient style of execution at the beginner level.

Finally, the over-arousal account suggests that an optimal level of arousal would contribute to maintain a good performance. In line with this theory, although an enhancement of arousal can improve performance in simple or well-learned task, it can disrupt performance on complex tasks (Yerkes & Dodson, 1908). Even if this theory is popular in psychology, so far the role of arousal on cognition is still debated. Whereas some studies show a positive effect of arousal on cognition (for example, Lambourne & Tomporowski, 2010), other ones reveal an opposite effect. In fact, several studies suggest that arousal, especially high level, can be detrimental on performance (Han, Liu, Zhang, Jin, & Luo, 2013; Moran, 2016), irrespective of the kind of task and the level of expertise (Ariely, Gneezy, Loewenstein, & Mazar, 2009).

Unlike cognitive neuroscience, cognitive-aging research aims to investigate how cognitive processes change in aging, either normal or pathological, as well as to pinpoint underlying neural mechanisms implicated in aging. Many factors can be considered crucial to explain cognitive performance in aging, such as general health condition, education, gray and white matter volume, working memory, and speed processing. However, research points out motivation as a key factor to explain performance in aging as well (Braver et al., 2014; Spaniol, Schain, & Bowen, 2014; Spaniol, Voss, Bowen, & Grady, 2011).

Cognitive-aging studies emphasize how motivation interacts with emotion and *vice-versa*. Interestingly, some studies show a sort of cognitive bias in elderly towards positive stimuli (positive valence) compared to negative stimuli (Carstensen & Mikels, 2005; Reed & Carstensen, 2012).

However, while several studies have investigated how motivational states interact with emotion or, in general, cognitive functioning, little is known about the effects of motivational incentives on the age-related cognitive decline that occurs in normal aging. In an interesting study, Spaniol and colleagues (2014) investigated the effect of remote monetary rewards on episodic memory in two groups of healthy participants, namely younger and older adults. In two different experiments, younger and older adults showed enhanced recognition for high-reward items

compared with low-reward items. In another study, Spaniol and colleagues (2011) investigated the effect of rewards on perceptual age-related decline. In this study, they used symbolic positive and negative rewards in a perceptual discrimination task, in which bicolored stimuli had to be classified according to their dominant color. The valent color was associated with either a positive or negative reward, whereas the neutral color was not associated with a reward. In line with expected results, authors showed that perception of neutral stimuli presented age-related decline, whereas perception of valent stimuli, associated with a positive or negative reward, showed no age difference. Authors interpreted these results in terms of preserved top-down control over the allocation of perceptual processing resources. Interestingly, this demonstrates that motivational incentives can modulate cognition, in particular, contribute to reducing age-related perceptual decline.

Neural mechanisms of motivation–cognition interaction

"Motivation" and "cognition" are typically two labels aimed to define distinct and precise entities. However, the concept of "motivation-cognition interaction" elicits itself a rethinking of these segregated constructs. In order to arbitrarily avoid distinguishing these two processes, the neural mechanisms that will be illustrated are, first of all, common to both processes. Secondly, we will not only talk about single brain structures, but also about brain networks and widespread broadcast systems of neural information involved in motivation-cognition interaction.

Basically the main neural mechanisms involved in motivation-cognition interaction can be summarized as: (1) single brain structures; (2) brain networks; (3) neuromodulatory systems. The figure 2 shows a representation of these mechanisms. For a careful review of this topic, we recommend Braver and colleagues (2014).

Single brain structures - One of the key structures of motivation-cognition interaction is the striatum. In particular, the nucleus accumbens seems to play an important role since it could be the structure able to bridge the gap between the dopaminergic system, widely implicated in motivation, and behavior (Berridge & Waterhouse, 2003). Moreover, the reciprocal connection between the striatum and the frontal cortex could contribute to prevent inappropriate actions and thoughts until the context or the situation is more adequate (O'Reilly & Frank, 2006).

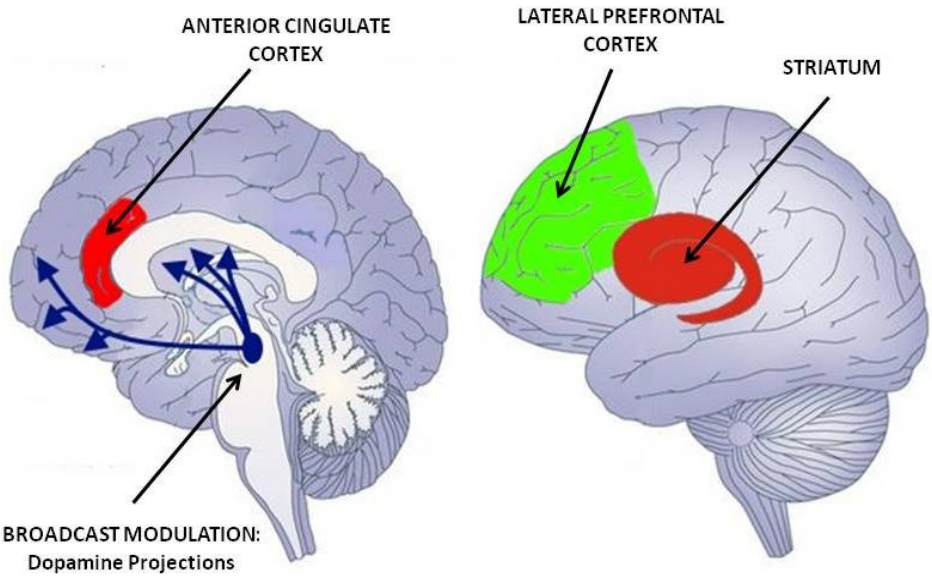

Figure 2 | Neural Mechanisms of motivation-cognition interaction. Inspired by Braver et al., 2014.

Another brain structure has been many times associated with motivation: the anterior cingulate cortex (ACC). This area forms a large region around the rostrum of the corpus callosum and seems to perform several functions that range from motor to motivational processes. For example, by the invasive method of single-unit recording, a study suggested that neurons in the ACC process multiple aspects of reward, such as proximity to the reward within a sequence of actions (Shidara & Richmond, 2002). In addition, the ACC and the prefrontal cortex (PFC), in particular the dorsomedial PFC, are implicated in performance monitoring, as well as in triggering cognitive control in response to motivational variables (Kouneiher, Charron, & Koechlin, 2009).

An interesting theory of Shenhav and colleagues (2013) offers a possible interpretation of these findings, suggesting that the ACC would have a role in both motivation and executive functions. Specifically, the ACC might be crucial in the cost-benefit evaluation of an action, contributing to triggering a proper level of executive control. Thus, after this evaluation, the ACC would send the information to the PFC that would allocate an appropriate level of cognitive control.

The Shenhav and colleagues' theory introduces the third hub described by Braver and colleagues (2014) as central in motivation-cognition interaction: the lateral PFC. In particular, Braver and colleagues claim that the lateral PFC would be a structure that receives and integrates motivational and cognitive information.

Brain networks - So far, the striatum, the ACC, and the lateral PFC have been described as areas strictly related to motivation-cognition interaction. However, as nowadays is well established, any brain process is supported by a combined functioning of structures that are organized in brain networks.

In line with Braver and colleagues (2014), motivation-cognition interaction relies on two networks, namely "task network" and "valuation network". Depending on how these networks interact with each other and exchange information, we can observe two *modes of communication*: direct pathways and reconfiguration of network topology modes. Although distinct, these *modes of communication* are not mutually exclusive.

Direct pathways mode considers each kind of direct connection between task and valuation networks. For instance, the connection between dorsolateral prefrontal cortex (DLPFC) and cingulate regions or between orbitofrontal and lateral PFC.

On the other side, reconfiguration of network topology mode explains motivation-cognition interaction in terms of reorganization of networks. In a network analysis study (Kinnison, Padmala, Choi, & Pessoa, 2012), task and valuation networks were compared during a task in which trials could be presented in two modalities: low versus high reward value. Results showed that while on control trials (no reward) the two networks performed in a modular way and presented a high within-network functional connectivity, on high-reward trials between-network connectivity increased. Thus, the within-between alternation of network connectivity reflected which kind of information was processed.

Neuromodulatory systems - Neuromodulatory systems, including the noradrenergic, serotonergic, dopaminergic, and cholinergic systems have a strong influence on behavior and cognition since they can rapidly influence neuronal activity through broad projections to large portions of the brain. A large amount of literature shows an involvement of dopamine in motivation (Collins & Frank, 2015; Volkow, Wise, & Baler, 2017). Moreover, dopamine is crucial in cognition because it produces spread effects on cellular-level physiology that affect neural excitability (Henze, Gonzalez-Burgos, Urban, Lewis, & Barrionuevo, 2000; Lisman et al., 2011) and enhances the signal-to-noise ratio (Durstewitz & Seamans, 2008; Thurley, Senn, & Lüscher, 2008).

Taken together, these findings support the idea that dopamine might be implicated in motivation-cognition interaction. In other words, dopamine may represent somehow a chemical

modulator of motivation-cognition interaction. However, it is equally true that other widespread neuromodulatory systems may be involved.

In these two paragraphs, some essential aspects of reward-related modulation have been described. Several studies were presented showing how the use of rewards is associated with improved performance in different fields (Locke & Braver, 2010; Maddox & Markman, 2010; Pessoa, 2009, 2010; Shohamy & Adcock, 2010). As anticipated, this modulation would be possible since motivation and cognition are not unrelated processes. Another interesting point concerns the direction of modulatory effects. All the studies previously illustrated were aimed to increase a certain process. However, an extensive literature about reward-related modulation shows cases in which rewards are used in order to reduce specific behaviors, such as hyperactivity in children with attention deficit hyperactivity disorder (ADHD) (Coelho et al., 2015), the negative symptoms of schizophrenia (Gholipour, Abolghasemi, Gholinia, & Taheri, 2012), agitated behaviors in elderly (Billig, 1986), and aggressive behaviors in psychiatric patients (Corrigan, Yudofsky, & Silver, 1993).

The next paragraph will introduce another emerging and promising group of techniques more and more used to modulate brain functioning and behavior: NIBS. Given that a deep examination of these techniques goes beyond the objectives of this dissertation, the next sections will briefly describe the main NIBS, without going into too much detail. Greater attention will be given to TMS, as the technique used in the studies described in Chapters 5 and 6.

Noninvasive brain stimulation

The concept of stimulating the brain dates back thousands of years, but only recently this approach has become a reality. Indeed, the past decade has seen a growing interest in research in the application of NIBS to investigate brain-behavior relations and implement new treatments in neurologic and psychiatric fields. NIBS not only modulates neural activity during application, but can also induce long-lasting modifications of cortical excitability (Polanía, Nitsche, & Ruff, 2018; Yavari, Jamil, Mosayebi Samani, Vidor, & Nitsche, 2017). The growing use of NIBS lies in the fact that this set of techniques represent an advantageous tool for interventional neurophysiology applications, modulating brain activity in specific brain areas or networks, as well as to produce

controlled modulations in behavior. Moreover, NIBS can overcome one of the most limitations of neuroimaging techniques: the difficulty to infer causal relationships between brain areas or networks and cognitive, motor, or perceptual processes. While neuroimaging techniques can reveal correlations, NIBS are able to identify causative relations. Before the introduction of NIBS, the only way to infer a causal implication of an area in a specific task was studying patients with brain damage. However, this approach presents some drawbacks: firstly, brain lesions are rarely restricted to a specific region (Robertson, Théoret, & Pascual-Leone, 2003), and second, after a lesion, the brain undergoes a massive functional and structural reorganization so that every behavioral outcome we observe may depend on these plastic and compensatory phenomena (Veniero, Strüber, Thut, & Herrmann, 2016).

NIBS can affect neural states and behavior through variations of the membrane potentials. This is a common feature that all NIBS share. In fact, in general, NIBS can induce ionic movements and change the membrane potentials and, in turn, foster or reduce spikes. Although, all these techniques can modify the membrane potential of neurons by inducing electric currents, the way through they reach this aim can vary according to the method.

For example, transcranial electrical stimulation (tES) is mainly a **neuromodulatory** method that induces a change in the state of the membrane potential by weak electric current (Miniussi, Harris, & Ruzzoli, 2013). Thus, the neuron may be depolarized or hyperpolarized, depending on the parameters of stimulation and other multiple aspects. However, unlike TMS, tES does not directly induce action potentials, but a subthreshold modulation of neuronal membrane potentials. On the other side, TMS is both a neuromodutory and **neurostimulation** method because it induces a direct depolarization of the membrane and elicits action potentials of the stimulated area.

tES and TMS are two of the most well-known types of NIBS, which affect brain functioning based on different electromagnetic principles. The next sections of the dissertation will explain more in details both these techniques. Firstly, tES will be introduced, by describing several methods that belong to this category of methods and explaining their physiological effects on the brain. Secondly, TMS will be described in order to classify different paradigms of stimulation. Moreover, similarly to tES, the physiological effects of TMS will be deeply elucidated.

Transcranial electrical stimulation

The term tES refers to several methods that require the application of weak electric currents (1-2 mA) directly over the scalp. As already mentioned, tES does not induce an action potential, since the polarization of the membrane is too weak. However, tES can modify intrinsic neuronal excitability leading to variations in synaptic efficacy, even for long period after the stimulation. In general, the stimulation is delivered through two or more electrodes applied over the scalp. The position of the electrodes, as well as their size, are two factors that will contribute massively to determine the effects of tES.

One of the main disadvantages of tES concerns their reduced spatial resolution. In fact, the electric currents applied on the scalp diffuse in a spread way, depending on the electrical resistance produced by a given tissue (e.g. bone, liquor, and gray matter present different level of electric resistance) and modeling and imaging studies suggest diffuse brain modulation (Bikson, Datta, Rahman, & Scaturro, 2010; Datta et al., 2009; Lang et al., 2005). Between tES and TMS, this latter method is without doubts characterized by a higher spatial and temporal resolution than tES. However, contrary to TMS, tES is more easy to operate, cost-effective, and suitable for double-blind, sham-controlled studies (Yavari et al., 2017).

Among tES, we can identify the above-mentioned tDCS, in which the electrical current is direct, and two different methods in which the current is alternating: transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). The figure 3 shows a representation of different kinds of tES.

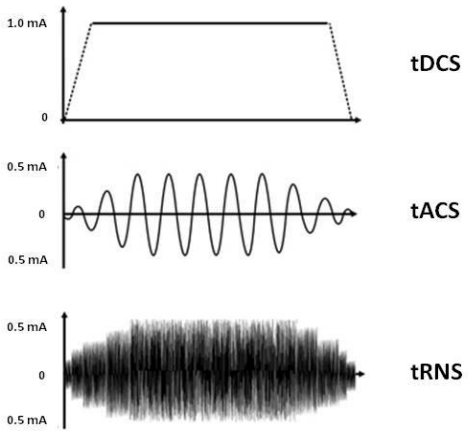

Figure 3 | A representation of tES: tDCS, direct current; tACS, alternating current with a fixed frequency; tRNS, alternating current with random frequencies.

One of the most popular and used tES is tDCS. In the classic setup of tDCS, one of the electrodes (anode or cathode) is placed on the area of interest, while the other is placed in a neutral area, either cephalic or extracephalic. Depending on which electrode is placed over the area of interest, we can have different effects. Studies on animal models have shown that anodal stimulation (anode placed over the area of interest) increases the frequency of spontaneous neuronal discharges, whereas cathodal stimulation (cathode placed over the area of interest) seems to produce an opposite effect (Bindman, Lippold, & Redfearn, 1962; Purpura & McMurtry, 1965). Interestingly, this effect has been replicated on humans as well, by using 10 minutes of tDCS (Nitsche et al., 2008; Nitsche & Paulus, 2000).

Although this evidence shows how anodic stimulation may potentially facilitate a particular process and cathodal stimulation may inhibit it, several studies show that these effects are not always consistent and they seem only valid for the use of tDCS on the motor areas (Nitsche et al., 2008). For instance, in many studies, the stimulation of non-motor areas has shown unexpected behavioral outcomes, with anodal tDCS usually inducing facilitation and cathodal tDCS inducing a range of effects (Jacobson, Koslowsky, & Lavidor, 2012; Wiethoff, Hamada, & Rothwell, 2014).

With regards to tACS, the neuromodulatory purpose is generally to entrain brain oscillations (Amengual, Vernet, Adam, & Valero-Cabré, 2017; Miniussi et al., 2013; Tavakoli & Yun, 2017). Unlike tDCS, in tACS the current is lower and is not direct but alternating with predetermined frequencies that can range between 0.1 Hz, up to 1000 Hz. This method shares with tES all pros and cons, even if the mechanisms by which tACS modulates the brain are still debated.

It has been suggested that tACS may modulate ongoing neuronal activity and behavior through the entrainment of a specific frequency in a certain area. In brief, by the application of tACS on a particular brain area, we could potentially induce that area to oscillate at a particular frequency (Kanai, Chaieb, Antal, Walsh, & Paulus, 2008). Within the theoretical framework of "rhythmic approach" (Miniussi, Brignani, & Pellicciari, 2012; Thut & Miniussi, 2009), tACS can represent a fruitful tool to establish a causal relationship between cognition and brain oscillations, as many cognitive neuroscience studies show. For example, when tACS was applied over the primary motor cortex at different frequencies during a motor task, several authors revealed an improvement of performance at alpha frequency stimulation only (10 Hz) (Antal et al., 2008). In another study, Pogosyan and colleagues (2009) demonstrated in a group of healthy participants that the entrainment of cortical activity at beta frequency stimulation (20 Hz) of the motor cortex

was associated with a slowing of voluntary movements. This result is suggestive because allows drawing a connection between Parkinson's slowing and the exaggerated beta activity found in these patients.

Finally, the third and newest type of tES is tRNS. This kind of stimulation is somehow similar to tACS because in both cases the current is alternating. However, in tRNS, the frequency of oscillation is not stable as in tACS but random. Thus, the frequency of stimulation changes continuously within a spectrum of oscillation that ranges from 0.1 Hz to 640 Hz. Sometimes, some studies adopt smaller ranges, for example low band (0.1–100 Hz) or high band (101–640 Hz).

Given that tRNS is a relatively recent method, so far the underlying mechanisms by which it can modulate the brain are still uncertain (Antal & Herrmann, 2016). A prominent hypothesis suggests that tRNS may be based on the repeated subthreshold stimulations that avoid homeostasis of the system (Fertonani, Pirulli, & Miniussi, 2011). The homeostasis mechanisms are important in the systems like the brain because they allow maintaining the functioning within a normal range. For example, the impact of tDCS could be reduced because of these homeostasis mechanisms. In fact, since tDCS is a direct current, it might produce a disequilibrium in the system and trigger these mechanisms. This possibility could explain some null or unexpected effects find in tDCS studies. Contrary, tRNS is a subthreshold alternating stimulation that may induce mechanisms of temporal summation in neural activity without to activate homeostasis (Miniussi et al., 2013). In line with this theory, Fertonani and colleagues (2011) compared in a study the effect of tDCS (anodal and cathodal) and high-frequency tRNS on the visual cortex. Their results suggest that high-frequency tRNS produce stronger effect on performance than tDCS.

Basic neurophysiology of transcranial electrical stimulation

In this section will be reviewed some studies that describe the neurophysiological bases of tES. The main purpose of this paragraph is a brief presentation of neural mechanisms responsible for the capability of tES to modulate plasticity and cortical excitability, as well as motor and cognition processes. Since tDCS is one of the first tES used in research, most evidence about neurophysiological bases of electrical stimulation derives from this technique (for a review, Yavari et al., 2017).

The duration and direction of tES effects are determined by several stimulation parameters: polarity (only in tDCS), montage of electrodes, current density (i.e. shape of the electrodes), and duration of stimulation. For instance, in tDCS, a stimulation of a few seconds only produces a modulation of the brain during the intervention (Nitsche & Paulus, 2000). However, if we implement a stimulation for a longer period, for example minutes, we can observe long-lasting changes of cortical excitability (Nitsche et al., 2008; Paulus, 2011)

A notable contribution from animal and pharmacological studies has allowed understanding how tDCS induces modulatory effects on the brain. In general, anodal stimulation seems somehow to induce similar effects observed in LTP, whereas cathodal stimulation seems to replicate the effects typically observed in LTD (Monte-Silva et al., 2013; Yavari et al., 2017). Furthermore, first animal studies suggested an involvement of other plastic mechanisms to explain modulation of anodal and cathodal stimulations: changes of intracellular cyclic AMP concentration, gene expression, intracellular calcium level, BDNF concentration, and protein expression (Yavari et al., 2017).

Summarizing the neural mechanisms of tDCS is not simple because different mechanisms may be involved depending on several factors, such as the duration of stimulation. For example, a study investigating the anodal stimulation on-line effects revealed an implication of sodium and calcium channels in the induction of cortical excitability produced by stimulation (Nitsche et al., 2003). In addition, another study excluded the involvement of NMDA and $GABA_A$ receptors in on-line anodal stimulation, again as regards on-line effects. On the other hand, long-lasting aftereffects on cortical excitability seem to reflect other mechanisms. For example, pharmacological studies show that NMDA receptors are crucial for excitatory effects of anodal stimulation. In fact, the blockage of NMDA receptors causes a suppression of cortical excitability, whereas using the partial NMDA receptor agonist d-cycloserine the excitability after anodal stimulation is increased (Nitsche et al., 2003; Nitsche et al., 2004).

A pharmacological intervention has unveiled additional mechanisms of tDCS effects in humans. Indeed, a study has investigated the role of the dopaminergic system. Results showed that low and high L-DOPA administration nullifies tDCS-induced LTP-like and LTD-like plasticity (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010), suggesting that dopaminergic neurotransmission is required for tDCS-induced LTP-like and LTD-like plasticity.

Finally, it has been shown that the long-lasting aftereffects of tDCS are also dependent on calcium. A low and prolonged influx into Ca^{2+} postsynaptic neurons causes LTD, a moderate

increase of influx does not induce synaptic changes, a larger calcium influx increases LTP, and, paradoxically, excessive calcium again induces LTD due to potassium channel-dependent counter-regulation (Lisman, 2001; Misonou et al., 2004).

Transcranial magnetic stimulation

In the next paragraphs TMS will be illustrated, providing essential information aimed to understanding the studies that will be then described in the next chapters of this dissertation (Chapter 5 and 6).

A number of books have been written about TMS and thousands of studies have been conducted using this technique. The reasons for this success are numerous, but probably one of the first concerns the noninvasiveness of TMS. In fact, before the advent of TMS, the procedures able to stimulate the brain, producing a suprathreshold depolarization of neurons, needed invasive interventions. For example, some procedures consisted in delivering electrical currents directly over the surface of the cerebral cortex, therefore after craniotomy (Adrian & Moruzzi, 1939; Patton & Amassian, 1954). Alternatively, without the removing of parts of the skull, the depolarization of neurons could be conducted by delivering of high-voltage electric currents (Merton & Morton, 1980). Although these currents could overcome the natural barrier represented by the skull, they were at the same time extremely intolerable and painful.

The first nonpainful stimulation of the human brain, through the use of magnetic fields, dates back to the 1980s (Barker, Jalinous, & Freeston, 1985). The introduction of TMS has been a turning point for neurosciences because the advantage of this technique lies in the fact that the magnetic field delivered by TMS passes through the extracortical structures without encountering any resistance, unlike the electric currents. Once the magnetic field reaches the cortex, it induces an electric field that causes a rapid depolarization of neurons.

In order to simplify the TMS description, the next sections will be so organized: (1) TMS fundamentals; (2) TMS paradigms; (3) basic neurophysiology of TMS; (4) future role of TMS in research field.

TMS fundamentals

Faraday's law of electromagnetic induction is the physical principle by means TMS can induce electric currents in the brain. An electric pulse, sent through a wire coil (primary conductor), generates a magnetic field. The rate of change of this magnetic field induces a secondary current in a nearby conductor (secondary conductor). An essential aspect of this principle is that a contact between the two conductors is not necessary. In the theoretical framework of Faraday's law, the TMS coil represents the primary conductor and the brain the secondary one. Obviously, in the magnetic stimulation of the brain, the stimulating coil is not directly in contact with the brain tissue. Indeed, the skull is in between the coil and the brain. However, as already explained, the magnetic field passes through both bone and soft tissue without being affected by them.

In TMS, an electric pulse which peaks and diminishes rapidly back to zero in a brief period (< 1 ms) is sent through the coil. The rapid fluctuation of the current generates a magnetic field, perpendicular to the horizontal plane of the coil. The magnetic field rises (up to 2.5 T) and falls rapidly. Consequently, this fluctuation of the magnetic field induces a current flow in the brain tissue nearby the magnetic field. The figure 4 summarizes this cascade of events.

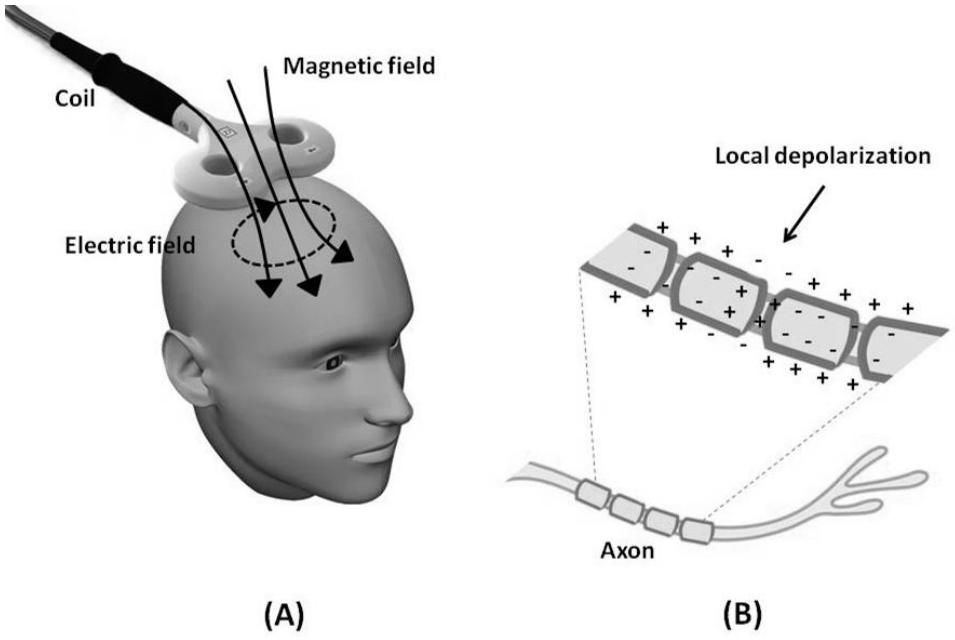

Figure 4 | On the left (A): The coil generates a magnetic field that induces, in turn, an electric field in the brain tissue. On the right (B): at a microscopic level, TMS induces a local membrane depolarization and, consequently, an action potential in the stimulated neurons.

The intensity and focality of stimulation will depend on some factors such as the geometry and size of the coil and its distance from the stimulated site. In the last few years, different types of coils have been developed in order to administrate a proper stimulation according to the aims of investigators or clinicians. For example, in basic research, it is generally preferred the use of coils that induced focal electric fields. On the other hand, less focal coils are often used in clinical practice since they allow an adequate stimulation of the peripheral nerves (indeed, TMS is not only used to stimulate the central nervous system). Among the main coils:

- **Round coil (or circular coil)** - The round coil is the first coil designed for TMS. It is not very focal and it is generally useful for peripheral stimulation.
- **Figure-of-8 coil (or butterfly coil)** - This coil is formed by two circular coils and it is conventionally adopted for academic uses of TMS. It induces a smaller electric field than the round coil, therefore it allows to maintain a better spatial resolution. Although not fully experimentally confirmed, mathematical modeling suggests that a pulse delivered at the 100% of intensity by a standard figure-of-8 coil (70 mm) can stimulate a 2 x 2 cm^2 cortical surface (Deng, Lisanby, & Peterchev, 2013). Nowadays, smaller figure-of-8 coils (50 mm) are used in several experimental fields. They allow a more focal stimulation but, at the same time, less deep.
- **H-coil** - Thanks to a complex and recent coil design, the H-Coil can stimulate deeper and larger areas than usual coils. A study suggests that H-coil could stimulate neural structures up to 6 cm below the cortex (Roth, Amir, Levkovitz, & Zangen, 2007). This type of coil is mainly used in clinical contexts, where the focality can be less precise.

Apart from the geometry of the coil, it is important to keep in mind that the orientation of the coil, as well as the distance between the coil and the brain, are crucial variables that determine the efficacy of TMS. Moreover, even if some coils allow directly stimulating only cortical areas, it is plausible that the effects of TMS can also propagate along white matter tracts and to reach subcortical nuclei.

The administration of single-pulse TMS (spTMS) is a proficient stimulation paradigm highly used in the clinical setting (Rotenberg, Horvath, & Pascual-Leone, 2014) to evaluate, for example, the integrity of the corticospinal tract. This procedure introduces some possibilities offered by the use of spTMS. Using spTMS, it is possible to evaluate various parameters such as the state of

cortical excitability of the primary motor and visual cortices and the conduction time of the motor pathways. For example, a well-known measure related to the motor system is the **motor-evoked potential** (MEP). The MEP is evaluated through the use of the electromyography (EMG), which allows measuring the degree of muscle contraction. When applied to the motor cortex, spTMS can induce contralateral muscle activity which can be recorded by EMG as MEPs. From an electrophysiological perspective, the MEP is considered an indirect index of the integrity of the corticalspinal tract.

An index of cortical excitability, directly associated with the MEP, is the **motor threshold** (MT). The MT is defined as the lowest intensity of the TMS stimulator able to induce, at least in 50% of TMS pulses, MEPs of 50 μV. The standard procedure to measure the MT is in detail described by Rossini and colleagues (2015).

Finally, the **phosphene threshold** (PT) is another index adopted to evaluate cortical excitability, namely the visual cortex excitability (Silvanto, 2013). The PT is not correlated to the MT and is generally higher (Stewart, Walsh, & Rothwell, 2001). However, it cannot be considered an objective measure because it depends on a personal report of the participant that communicate when it is perceiving the phosphene. Thus, the interindividual variability of this measure is an unavoidable consequence.

Importantly, the MT and PT are conventionally used to establish the intensity of stimulation of the brain. However, the MT and PT are related to motor and visual areas, respectively. Thus, if an investigator decides to stimulate nonmotor/nonvisual areas, such as the DLPFC, and the intensity of stimulation is assessed by the above-mentioned indices (MT or PT), it should consider that the intensity could affect this area differently, because the DLPFC, an associative area, is surely different from motor and visual areas (e.g. these areas have a different cytoarchitecture).

TMS paradigms

An important aspect concerning TMS regards its functional versatility. By variation of several paradigms, researchers and clinicians can address interesting questions. In this paragraph, the main paradigms will be described.

Single-pulse TMS - spTMS consists of an isolated pulse applied to a specific cortical site. The main applications of spTMS have already been described, such as the evaluation of the MT and PT. In general, spTMS is used to diagnose or investigate the cortical reaction to each pulse. Moreover, spTMS can be used to affect cognitive functioning during a task. For example, an investigator could administer spTMS in specific time windows while a cognitive process is occurring and to address important questions about the time course of cognitive processes. In Chapter 5, spTMS has been adopted to induce a time-selective modulation of error awareness.

Paired pulse TMS (ppTMS) - the general purpose of this paradigm is to investigate the effect of a first stimulus, or *conditioning stimulus* (S1), on the MEP elicited by a second stimulus, or *test stimulus* (S2). Crucial parameters of this paradigm are the interstimulus interval (ITI) and the stimulus intensity. For instance, in some experiments different kinds of conditioning stimuli are delivered, progressively varying the intensity, whereas the intensity of test stimulus is maintained at 110-120% of the MT. ppTMS is generally used to investigate the cortico-cortical connection between two areas. In this case, the two stimuli are administered to two different cortical regions that are supposed to be connected with each other (Bolognini & Ro, 2010).

Both spTMS and ppTMS are on-line paradigms. This means that stimuli are always delivered while participants are doing something (an action, a computerized task and so on). Theoretically, these paradigms can affect and modulate brain functioning for a brief period (for a review, Sandrini, Umiltà, & Rusconi, 2011). Unlike on-line paradigms, off-line ones are administered before a measurement and, in general, consist in repetitive stimulation in which trains of pulses are delivered at a specific frequency for a certain period. These paradigms are known as rTMS.

Repetitive TMS - When the aim of investigators or clinicians is to produce long-lasting modulation, rTMS is the most proper paradigm. rTMS is characterized by trains of pulses delivered at a fixed intensity over a single brain site.

Typically, after rTMS, a physiological or behavioral variable is measured, in order to evaluate the effect of rTMS on this variable. These paradigms are characterized by two crucial parameters: frequency and duration. Frequency refers to the number of pulses per second. The frequency of stimuli can range between 1 Hz (if ≤ 1 Hz: **low-frequency rTMS**) to 50 Hz (if > 5 Hz: **high-frequency rTMS**). In general, low-frequency rTMS is applied for several minutes, whereas high-frequency

rTMS is applied in a patterned fashion. In this case, brief and high-frequency bursts are spaced by short windows without TMS. For example, rTMS paradigm in the study illustrated in Chapter 6 is a low-frequency paradigm at 1 Hz of frequency. Duration refers to the length of the paradigm in terms of time.

rTMS can induce long-lasting effects, either inhibitory or facilitative, that outlast the stimulation duration itself. In general, the effects last several minutes following a single rTMS session, and days/weeks following several consecutive rTMS sessions (Klomjai, Katz, & Lackmy-Vallée, 2015; Oberman, 2014). Most of the studies investigating the modulatory effects of TMS focused on motor areas, as in the case of tES. In general, low-frequency paradigms seem to induce a cortical inhibition, as evidenced by the peak-to-peak reduction of the MEP amplitudes. On the contrary, high-frequency paradigms produce a cortical facilitation, again highlighted by MEP amplitudes, which in this case are larger (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000).

Theta burst stimulation - Theta burst stimulation (TBS) is a family of recent TMS paradigms. TBS refers to pattern of stimuli that mimics neural oscillatory patterns (Rotenberg et al., 2014). Two types of TBS are mainly known: **continuous TBS** (cTBS) that would replicate the inhibitory effects of low-frequency TMS, and **intermittent TMS** (iTBS) that would replicate the effects of high-frequency TMS (Oberman, 2014). In general, TBS elicits more consistent effects than simple rTMS paradigms (Hoogendam, Ramakers, & Di Lazzaro, 2010).

Basic neurophysiology of TMS

In relation to the immediate effect that TMS can produce, pharmacological interventions shed light on possible underlying mechanisms. Two prominent indices used to on-line assess cortical excitability are the MT and MEP. A study shows that the MT is affected by agents blocking voltage-gated sodium channels, that are essential in regulating axon excitability (Hodgkin & Huxley, 1990). Contrary, other neuromodulator systems do not affect the MT, such as dopamine, norepinephrine, GABA, acetylcholine, and serotonin (Klomjai et al., 2015). Differently, MEP amplitude is increased after both the administration of dopamine and norepinephrine agonists, and reduced by modulators of $GABA_A$ receptors (Ziemann, 2004).

The neurophysiological bases of rTMS are still debated (Hoogendam et al., 2010; Klomjai et al., 2015). However, more and more evidence suggests that a plausible explanation of long-term effects of rTMS might base on processes like LTP and LTD (Esser et al., 2006; Korchounov & Ziemann, 2011). In fact, an incontrovertible evidence concerns the fact that rTMS is able to produce effects that go beyond stimulation. The facilitative and inhibitory effects that rTMS can induce are somehow connected to LTP and LTD, respectively.

Several research fields provide findings of an involvement of LTP and LTD in TMS-induced modulation of the brain and behavior. The effects of rTMS on motor cortex have already been described in terms of MEP modulation. In addition to these effects, neuroimaging and electroencephalography (EEG) studies contribute to confirming the implication of LTP and LTD in long-term effects of TMS. These findings consist in alteration of cerebral blood flow, different BOLD activation patterns, or EEG modifications (Hoogendam et al., 2010).

Some parameters of rTMS such as intensity, frequency, and duration are crucial to determine a specific effect. However, an aspect that is sometimes neglected, but that is likewise important, is the **state of the system** before the stimulation (Miniussi et al., 2013). For example, a priming stimulation (i.e. a pretreatment exposition with a brief stimulation) can affect the results of the following stimulation (i.e. the treatment). In line with this statement, Iyer and colleagues (2003) tested 25 healthy participants using the MEP as an index of cortical excitability. They hypothesized that because in vitro LTD is increased by pretreatment of synapses with higher-frequency stimulation and rTMS inhibition had common mechanisms with LTD, higher-frequency priming would enhance it as well. Thus, a subthreshold rTMS (6 Hz) was used to prime the motor cortex and afterward a suprathreshold 1 Hz stimulation for 10 min was administered. Authors showed that the 6-Hz pretreatment enhanced the inhibitory effect of the subsequent 1-Hz rTMS.

Again, according to the importance of the state of the system before the stimulation, some authors demonstrated that specific factors before the stimulation lead to longer effects. Kujirai and colleagues (2006) demonstrated this phenomenon by a paired associative stimulation (PAS) paradigm that combines: (1) a repetitive stimulation of peripheral nerve afferents of the target muscle, and (2) TMS over its motor area. Importantly, in this kind of paradigms is crucial the interstimulus interval (ISI) between the peripheral stimulation and the cortical stimulation. In this study, results suggested that the facilitative effects of PAS (ISI = 25 ms) lasted longer only when the peripheral muscle was contracted respect to when it was relaxed (Kujirai et al., 2006).

The studies just now described (Iyer et al., 2003; Kujirai et al., 2006) suggest an analogy between LTP and LTD and long-term effects of TMS. As in LTP and LTD, also in TMS a priming stimulation would support stronger neural plasticity. Thus, the aftereffects of stimulation seem sensitive to prior activation of cortical circuits (Hoogendam et al., 2010).

Animal models and pharmacological interventions have contributed to unveil the neurophysiological mechanisms of rTMS. An interesting study combine these two approaches. Kim and colleagues (2006) compared four groups of rats under different conditions. The first three groups were administered a specific treatment (see below) and subsequently, all groups were exposed to a stressful condition, namely the forced swim test (FST). In this test, the immobility is an index of depression, so higher immobility is associated with higher depression. The fourth group was a control group composed of naive rats that were not treated and were not exposed to the FST. To summarize the four groups:

- *Group 1* - 7-day treatment with 10 Hz rTMS + FST
- *Group 2* - 7-day treatment with sham stimulation + FST
- *Group 3* - 7-day treatment with fluoxetine (antidepressant drug) + FST
- *Group 4* - no intervention

This study reported two interesting results. Firstly, rats treated with rTMS showed less immobility than the sham group. No relevant improvement of immobility time in rats administered with fluoxetine. Secondly, whereas LTP was suppressed in fluoxetine and sham groups, rTMS and no-intervention groups presented LTP. Since is known that the stress can disrupt LTP (Foy, Stanton, Levine, & Thompson, 1987), this result shows that 7-day treatment with rTMS can reverse the negative effect of stress on synaptic plasticity.

Future role of TMS in research field

TMS is a versatile tool that allows the neurostimulation and neuromodulation of the brain. The main advantage of this technique is that it can induce a depolarization of neurons nearby the magnetic field, without causing pain. Therefore, TMS is considered a completely noninvasive technique.

Among NIBS, TMS has some exclusive prerogatives. For example, contrary to tES, TMS allows investigating the time course of cognitive processes, thanks to the use of specific on-line

stimulation paradigms. By means the ability to modulate brain functioning for a period that outlasts the stimulation, TMS has gradually attracted the attention of clinicians who have begun to exploit this remarkable aspect in order to treat psychiatric and neurological disorders. Nowadays, the clinical applications of TMS are so varied that listing them would lead to the inevitable consequence of not mentioning someone.

However, despite this success, TMS should still be considered a complementary tool and not a substitute for conventional treatment. In fact, there are no standard protocols that allow a systematic use of TMS in the clinical field. Unfortunately, each study is characterized by multiple methodological differences ranging from the type of stimulation paradigm adopted, the duration of the intervention, up to the outcomes taken into consideration to evaluate the modulatory effects of TMS.

Nowadays, only the prefrontal TMS therapy is US Food and Drug Administration (FDA) approved for treating a specific condition, namely major depressive disorder in adults who have not responded to prior antidepressant medications (Perera et al., 2016). In all other cases, the research for the best stimulation parameters, or the most suitable stimulation targets, is still ongoing.

In recent years, an interesting approach is gathering many favors in TMS research. It concerns the combined use of TMS with other neuroscientific techniques such as fMRI, positron emission tomography (PET) and EEG. The combined use of TMS and neuroimaging techniques is a promising tool to shade light on unsolved questions regarding the brain cognition-behavior relationship. The main advantage of coregistration lays on the fact that TMS can compensate for the limits of neuroimaging techniques and *vice-versa*.

One of the most unsolved aspects of TMS regards its complex physiological mechanisms. As mentioned before, despite the widespread use of TMS in research, its underlying mechanisms of action are poorly known. For this reason, neuroimaging techniques can help to understand how TMS can modulate the brain. An example derives from the TMS-EEG coregistration that provides an important electric marker: **TMS evoked potential** (TEP). Some characteristics of TEP such as latency, polarity, amplitude, and waveform allow evidencing the physiological state of the stimulated brain site.

Another advantage of the coregistration consists in investigating several aspects of the same process, by collecting data from different sources (e.g. behavioral and electrophysiological data). A

TMS-dependent behavioral modulation is not always noticeable. Sometimes, modulation cannot reach a sufficient threshold to produce a significant effect on behavior. In these cases, if the gathered measure is only a behavioral marker, investigators will not able to infer anything from the manipulation and the result will be only a null effect. By the combined use of TMS and other techniques, in addition to behavioral effects, it is also possible to reveal neurophysiological effects of TMS, even in cases in which the behavioral outcome does not seem to be influenced by stimulation. In Chapter 6, a combined use of TMS and EEG allowed us to evidence a significant effect of TMS on an event-related potential (ERP) associated with error-related brain activity, even if the behavioral results did not show a related modulation.

As just now discussed, despite the widespread use of TMS, many questions are still opened and need answers. Especially the therapeutic use of TMS will require important research efforts in order to assess the effectiveness of the technique and to develop standardized protocols that can maximize the plasticity mechanisms when they play a positive role. An intriguing solution may lay on the coregistration between TMS and other neuroscientific techniques. TMS and neuroimaging are two complementary methods whose combined use will be probably more widespread in the future.

Chapter 3

Error-related processes

In the previous chapters, two topics have been addressed. In Chapter 1, neural plasticity has been illustrated as a general ability of the brain to functionally and structurally change. Afterward, in Chapter 2, some typical interventions used to modulate behavior and brain functioning have been described. In Chapter 3, the focus will be moved on a set of processes that are core in this dissertation, namely error-related processes. The three studies described in the next chapters will share a general aim: **the modulation of error-related processes through the use of behavioral techniques and NIBS**. By means the previous premises, it will be easier to understand how it is possible to modify a process, either behavioral or physiological, and which are the hypothesized mechanisms underlying this modulation.

Let me to start this paragraph by asking a question: *What does an error represent in our daily life?* The easiest and most obvious answers could be that an error is a nuisance, an unexpected event, an obstacle that requires to review our actions. Probably none of these answers is wrong because they capture some aspects intrinsically connected to an error. An error is perceived as something with a negative valence, but this attribution may push to improve ourselves and therefore it may have a motivational role in our daily life. Furthermore, an error is a rare and unexpected event, therefore particularly salient and easily detectable. Finally, an error requires an adjustment of our actions, since it signals us that something has gone wrong.

Contrary to common sense, this question is the affliction of many cognitive neuroscientists because to empirically explain the functional role of an error is not easy at all. In general terms, our behavior is constantly monitored by a set of cognitive processes that allow performing goal-directed actions. This set of processes is called **performance monitoring** and it is crucial for keeping action performance as optimum as possible by ongoing monitoring of the course and outcome of actions (for a review, Ullsperger, Danielmeier, & Jocham, 2014).

Once an individual has identified a goal, for example reaching some food in order to feed itself, an appropriate action is implemented. The performed action will produce results that will be evaluated in terms of changes in the state of the individual and the environment, for instance the

extinction of hunger. Performance monitoring aims to reveal a mismatch between the performed action and the planned action by monitoring before, during and after the execution of the action. In the event that the performance monitoring identifies a mismatch between executed and planned action (an error), it triggers a series of reactions aimed to correct the action or avoid similar errors in the future (Laming, 1968; Ullsperger, Fischer, Nigbur, & Endrass, 2014). These reactions range from motor adjustments, up to cognitive adaptations.

Thus, an errors has a double meaning: (1) it represents the failure of the planning or monitoring of the action; (2) it provides information on the purpose, direction, and necessity of adjustments aimed to avoid the same error is repeated again. Moreover, an error can also result in an immediate change while the action is being performed to allow the achievement of the planned goal.

Besides these considerations, performance monitoring is therefore a very general term that encompasses a wide range of processes. These include a set of processes that intervene after the commission of the error, namely error-related processes.

In experimental settings, errors are a useful way to test the integrity of performance monitoring and to study how error-related processes affect behavior. Tasks developed for investigating error-related processes, although they are different with each other, share generally the fact that are demanding task and induce a participant to commit a certain number of errors. The number of errors is one of the most critical aspect of research on error-related processes. In fact, an ideal experimental task requires a subtle tradeoff between the number of correct responses and the number of errors. A reduced number of errors leads to a reduction in statistical power, whereas an excessive number of errors, for example higher than correct responses, produces atypical effects in which the error is processed somehow differently, as Notebaert and colleagues (2009) highlighted in an elegant study. To complicate matters further, the study of error awareness requires that the task elicits a sufficient number of unaware errors. In the next section, the main paradigms used to satisfy these requirements will be described.

In order to simplify and make more comprehensible the description of error-related processes, they will be divided into two groups: behavioral and neurophysiological correlates of error-processes. Specifically, among the behavioral correlates, we will be described **error awareness** and **post-error adjustments**, whereas among the neurophysiological correlates, two

ERP components will be illustrated, namely the **error-related negativity** (ERN) and the **error positivity** (Pe). These processes have been investigated in studies describe in Chapter 4, 5, and 6.

Behavioral correlates of error-related processes: error awareness

First of all, before defining error awareness, a terminological distinction is necessary in order to avoid confusion. Indeed, in the literature, different terms can indicate the same processes. Studies that investigate the consequences of an error are divided between those that explore in general the process of error monitoring (or error processing) and studies that investigate specifically error awareness (or error detection). This paragraph will focus only on these latter studies.

Human beings base their knowledge on awareness. This aspect characterizes and distinguishes humans from other living beings. However, the term "awareness" can assume various meanings and be used in a more or less extended way. In our case, error awareness is a component of awareness that specifically refers to the conscious detection of an error during the course of an action. Thus, error awareness is a metacognitive process somehow.

The ability to detect an error has an adaptive role in everyday life. Although humans can act in absence of a proper action monitoring (e.g. when they perform well-learned actions), in general, being aware of errors supports an effective goal-directed behavior. In fact, as previously introduced, an aware error triggers a series of adjustments that allow correcting and avoiding the same error in the future (Laming, 1968; Ullsperger et al., 2014). In line with this statement, two studies show that aware errors induce larger behavioral adjustments than unaware errors (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; Wessel, Danielmeier, & Ullsperger, 2011). However, not all studies seem to confirm this result. For example, van Gaal and colleagues (2012) review studies showing that also unconscious information triggers cognitive reactions. Similarly, Cohen and colleagues (2009), in a Go/No-go task, reported a significant post-error slowing (PES) effect after unaware No-go errors.

Responses to aware errors are not only confined to behavioral reactions: also vegetative changes can be observed. A crucial point is whether these autonomous changes are a cause or reflect a consequence of error awareness. Several studies demonstrated that errors can elicit a response of the autonomic nervous system. A typical consequence of an aware error is a heart rate deceleration (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005). This phenomenon could

be explained if considering an error as a significant internal event that evokes a response resembling the orienting response (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012; Łukowska, Sznajder, & Wierzchoń, 2018). In addition, other indices of the autonomic system, such as changes in pupil diameter and skin conductance, are correlated to error (Hajcak, McDonald, & Simons, 2003; O'Connell et al., 2007).

Research on error awareness requires experimental paradigms that allow a manipulation and an assessment of error awareness. A task should take at least two points into account: (1) produce a good number of errors; (2) elicit both aware and unaware errors. In the literature, three types of paradigms are successfully adopted to investigate error awareness (Klein, Ullsperger, & Danielmeier, 2013). The first type of tasks progressively manipulates the perception level of stimuli, for example through a degradation of the stimulus visibility or masking stimuli (Scheffers & Coles, 2000; Steinhauser & Yeung, 2010). These manipulations contribute to producing a sort of "stimulus uncertainty" that increases the rate of unaware errors. The second type of tasks involves the detection of eye movements. A typical task is the anti-saccade task in which participants are asked to inhibit an automatic saccade towards a particular stimulus (Endrass, Reuter, & Kathmann, 2007). The anti-saccade task induces unaware errors because the saccade towards the prohibit stimulus are so short and immediately corrected that the error is often unnoticed. Finally, the third type of tasks includes complex paradigms with competing and constantly to-be-monitored rules (Klein et al., 2013). Several authors accomplished these rules by using Go/No-go tasks with different No-go conditions, in order to increase the task difficulty.

The **error awareness task** (EAT; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005) belongs to the third group of tasks. The EAT is the paradigm we adopted in the studies presented in this dissertation. In the EAT, color words are presented at the center of a computer screen. Participants are asked to press a Go button, as soon as possible, when word and its font color are congruent (Go trial). On the contrary, participants have to withhold the response in two conditions: (1) when the same colored word was repeated on two consecutive trials (repeat No-go trial), or (2) when the word and its font color were incongruent (Stroop No-go trial). Moreover, participants are instructed to signal an error commission, both Stroop and repeat errors, by pressing an "awareness button". Although in all our studies the general structure of the EAT was maintained, some features were varied to tailor the EAT to different purposes and methods of the studies. These variations will be described in detail.

So far the debate on what makes the difference between aware ad unaware errors is still heated. Probably it depends on a combination of exogenous and endogenous factors (Klein et al., 2013). For example, the nature of error itself can be relevant for its conscious detection. Typically, when errors occur in routine situations (e.g. action slips or lapses) are more easily detected than other kinds of errors, such as mistakes of planning (Reason, 1990). Moreover, overwhelming task situations contribute to determining unaware errors. Another possible context in which unaware errors are more probable is in the case of weak perceptual information that can determine a low confidence in own responses. In addition, a decrement of arousal may lead to unaware errors, as confirmed in a study in which a boring task reduced the number of aware errors (Shalgi, O'Connell, Deouell, & Robertson, 2007). Finally, also age plays a crucial role in error awareness. In fact, some studies show a decline of error awareness in normal aging (Harty, Murphy, Robertson, & O'Connell, 2017; Harty, O'Connell, Hester, & Robertson, 2013; Masina, Di Rosa, & Mapelli, 2018a).

Altogether, these factors contribute, in a normal situation, to detecting an error or not. The comprehension of these interacting factors is essential because they allow characterizing error awareness deficits in neurological and psychiatric patients. From a clinical point of view, the modulation of error awareness could be relevant to reduce patient's deficits. In fact, some neurological patients present a reduction of awareness, such as in anosognosia, whereas in some psychiatric disorders error awareness seems excessive, such as in obsessive-compulsive disorder (Klein et al., 2013). In general, patients affected by obsessive-compulsive disorder pay excessive attention to their errors (Endrass et al., 2010). Furthermore, cannabis and cocaine users show a poor error awareness as well (Hester, Nestor, & Garavan, 2009; Hester, Simões-Franklin, & Garavan, 2007).

With regards to the neural bases of error awareness, recent evidence suggests that the neural response to errors involves a network of areas. Specifically, examining the neural correlates of error awareness, several brain regions would have a crucial role in this process: the anterior inferior insula (AIC), the posterior medial frontal cortex (pMFC), the DLPFC, the ACC, and the thalamus.

The insula is a part of the cortex that is deeply located within the Sylvian fissure, between the temporal and frontal lobes. Its functions are complex and heterogeneous because the insula is engaged in motor functions, language-related auditory processing, vestibular processes, visceral sensory processes, and interoceptive awareness (Klein et al., 2013). Especially the AIC seems

related to error awareness, as some authors show. In fact, the AIC has been associated with the detection of novel salient stimuli (Menon & Uddin, 2010). Thus, somehow, it is plausible that the AIC can have a central role in error awareness since an error is surely a salient event and an aware error is obviously more salient than an unaware error (Hester et al., 2009).

Whether the pMFC is implicated in error awareness or not, it is not still clear. In fact, while in some studies the pMFC did not discriminate between aware and unaware errors (Hester et al., 2005; Klein et al., 2007), more recent studies show that it was selectively activated by aware errors (Hester et al., 2009; Orr & Hester, 2012).

Similarly to the pMFC, also the role of the DLPFC is not fully confirmed. Actually, the DLPFC seems related to error awareness, but it is not clear whether only the right DLPFC, as demonstrated by (Harty et al., 2014), or without lateralization, as shown in a recent study (Masina, Vallesi, Di Rosa, Semenzato, & Mapelli, 2018b) that revealed an implication of both the right and left DLPFC in error awareness. This study will be described in Chapter 5. Apart from these considerations about a possible lateralization of error awareness, the DLPFC will be crucial in this dissertation because in TMS studies described later, our hypotheses concerned the fact that this area could be involved in error awareness.

Hester and colleagues (2009) observed a deficit of error awareness in chronic cannabis users. In addition, the researchers observed in the experimental group a reduction in activity both in the ACC and in the right insular cortex. These results are consistent with previous findings showing that in chronic drug users there would have a reduction in cognitive control and monitoring of interoceptive awareness. Given that the ACC has been reported in the majority of studies investigating error awareness, a general opinion is that the ACC activity may be necessary, but not exclusive, for error awareness.

In a study (Seifert, von Cramon, Imperati, Tittgemeyer, & Ullsperger, 2011), patients with thalamic lesions, in particular the ventral anterior and ventral lateral anterior nuclei, showed impaired error awareness, suggesting a role of thalamus in this process. Seifert and colleagues (2011), observed in these patients difficulties in reporting their errors during a flanker task. Participants were asked to press a button to report their own errors. Compared to the control group (healthy people), which indicated an average of 85% of their errors, the experimental group of patients indicated on average only 39% of their errors. Although prominent, this result has been questioned because the task proposed by the authors presented some disadvantages that could be responsible for the result. In fact, since patients generally tended to produce a slower motor

response than controls, some of their unaware errors could simply reflect an omission in signaling the error, so due to difficulties not related to an impairment in error awareness.

Behavioral correlates of error-related processes: post-error adjustments

Error awareness promotes correction, adaptation, and optimization of behavior. An interesting consequence after an error conceives a set of behavioral adjustments that are extensively investigated. These forms of adaptations range from fast and immediate compensatory reactions (Danielmeier & Ullsperger, 2011) to long-term strategic changes in behavior (Ullsperger et al., 2014). In particular, in this dissertation, the focus will be on **"trial-by-trial" mechanisms**, namely adjustments that are an immediate consequence of an error. These adjustments are measured at the level of the trial immediately following the error and therefore appear to occur simultaneously. The main post-error adjustments are:

- **Post-error improvement in accuracy (PIA)**
- **Post-error reduction of interference (PERI)**
- **Post-error slowing (PES)**

PIA is defined as an improvement in accuracy that occurs after the commission of an error. Post-error adjustments, such as PES, were thought to be necessary to allow people learning from own errors and improve their performance (accuracy). However, by evaluating accuracy in post-error trials and in trials after correct responses, results for improved post-error accuracy are not unequivocal. In fact, the performance is not always improved after an error and PIA and PES do not always occur together (Danielmeier & Ullsperger, 2011). This result suggests that PES and PIA are two distinct processes.

The separated nature of these mechanisms is remarked by a study in which these behavioral adjustments followed different time intervals. A study that examined the effects of different stimulus-response intervals (RSI) on PES and PIA, found that PES is greater with short intervals between the error and the following stimulus, whereas it decreases with longer intervals (Jentzsch & Dudschig, 2009). Differently, PIA is reduced with short RSI, whereas it improves with longer RSI.

In some cases, it is very difficult to observe PIA. Indeed, this effect occurs only when participants have the real possibility to improve their post-error performance. If the purpose of a task is to produce a large number of errors, participants might be unable to improve their accuracy (Danielmeier & Ullsperger, 2011).

PERI has been observed for the first time by Ridderinkhof (2002). In tasks such as the Flanker task, we generally observe an interference expressed in terms of increasing of reaction times in incompatible trials compared to compatible trials. What the author observed was a reduction of interference in trials that followed an error. PERI seems to reflect cognitive control processes. An increased allocation of cognitive control would explain how the system can reduce interference in post-error trials (Danielmeier, & Ullsperger, 2011).

PERI phenomenon, as well as PES, are considered post-error adjustments guided by the pMFC. However, PES and PERI are implemented in different neuronal networks. While PES is related to motor activity, regardless of the activity in progress, PERI is correlated with activity in areas relevant to that task (Ullsperger et al., 2014). This suggests that the resolution of the interference depends on the specific brain areas for the task.

Pharmacological interventions confirm that PERI and PES have different neural bases. In a study, the administration of lorazepam suppressed only PERI, without to produce a modulation of PES. Thus, PES seems immune to $GABA_A$-modulating drugs (Danielmeier & Ullsperger, 2011).

PES is the motor slowing that usually occurs after errors, and was described for the first time in 1966 by Rabbitt, who reported significant slower reaction times after erroneous responses than mean reaction times of all correct responses. Nowadays, other studies have reported PES in different kind of tasks, for instance Stroop, Flanker, Simon, or categorization tasks (Danielmeier and Ullsperger, 2011; Wessel & Aron, 2017).

PES is probably the post-error adjustment more frequently observed and studied. However, despite this large piece of knowledge, the functional role of PES is still not clarified. In general, two veins of research consider alternatively PES either an adaptive or a maladaptive phenomenon (Wessel & Aron, 2017). On the one hand, the **adaptive theories** suggest that PES contributes to improving ongoing behavior (Donald Richard John Laming, 1968). This view often associates PES and PIA. In these terms, PIA would reflect the positive and functional consequence of PES. On the other hand, the **maladaptive theories** claim that PES would be a detrimental effect of an error. For

instance, Notebaert and colleagues (2009) suggest an interesting interpretation of PES. In their study, the authors observed that it was not the error itself that produced a slowdown, but the frequency of the responses. Specifically, when participants made few errors, PES was very pronounced. On the contrary, if the errors were numerous, greater than correct responses, the slowdown was surprisingly observed after correct responses. When the error rate increased, approaching the frequency of correct responses, PES was reduced or absent. The authors interpreted these results as a consequence of an infrequent and surprising event. Apart from erroneous or correct responses, an infrequent event would capture attention (a sort of orienting response) and would produce a slowdown of the system.

The magnitude of PES is sensitive to several factors, such as the frequency of errors, the salience of an error, the RSI between an error and the following stimulus (Danielmeier & Ullsperger, 2011; Ullsperger et al., 2014). Interestingly, PES seems to be a relatively stable phenomenon along the lifespan. In a recent study, by testing three age-groups (children, younger, and older adults), no difference was found (Masina et al., 2018a).

From a clinical point of view, alterations of PES have been found in children with attention-deficit/hyperactivity disorder (ADHD). For example, in a recent meta-analysis, PES appears to be reduced in children with ADHD compared to healthy children (Balogh & Czobor, 2016).

Regarding the neural bases of PES, Danielmeier and colleagues (2011) have shown that the phenomenon is linked to an inhibitory network comprising the pMFC and other structures linked to performance monitoring. In fact, the activity of this inhibitory network in post-error trials predicts the decrease in the activity of motor areas in post-error trials. This latter, in turn, is associated with PES. Thus, less activation of the motor areas induces an increase of PES. The decreased motor activity following errors may reflect an increased response threshold, hence, motor inhibition (Ridderinkhof, 2002; Ullsperger et al., 2014).

Neurophysiological correlates of error-related processes: the ERN

In a classic event-related potential (ERP) experiment, trials in which participants make an error are generally rejected. However, by comparing these trials to ones associated with correct responses, it is possible to learn something about how the brain computes an error.

It has been almost 30 years since the first evidence of an event-related brain potential component associated with error commission (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Coles, Meyer, & Donchin, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). This component, called ERN (or error negativity, in the early Falkenstein's studies), was initially observed in choice reaction tasks. Currently, the ERN seems to be task-independent (Wessel, 2012), as well as stimulus-independent, in fact both auditory or visual stimuli elicit the ERN (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000).

The ERN is an ERP component characterized by a negative deflection more prominent at the fronto-central sites where it reaches its greatest amplitude. It peaks around 50-100 ms after the commission of an error (figure 5). One of the most validated interpretations sees the ERN associated with the detection of a cognitive conflict, which typically occurs when an error is committed. Moreover, it has been suggested that the ERN reflects the activity of a system that either monitors responses or is sensitive to conflict between planned and executed actions (Kappenman & Luck, 2012; Luck, 2005; Wessel, 2012)

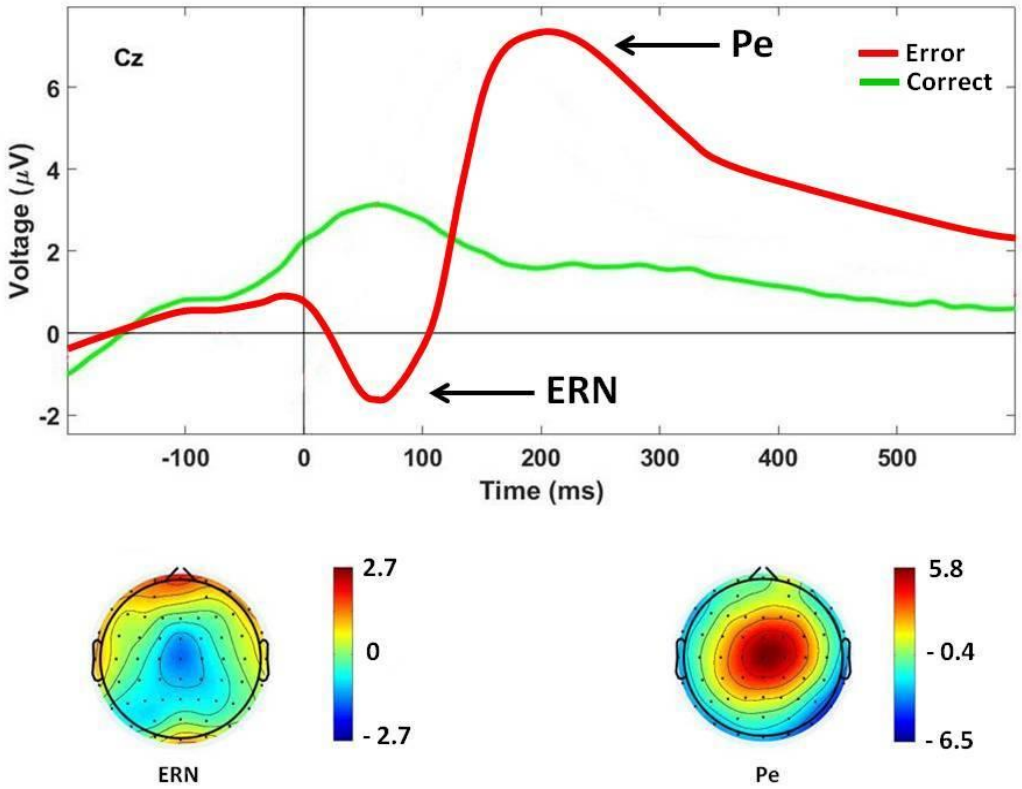

Figure 5 | Top: Graphical representation of the neurophysiological correlates of error-related brain activity (extracted by Cz). The green line shows the waveform after correct responses, whereas the red line the waveform after errors. Bottom: Topographic distribution of the ERN and Pe components.

Although the neural generator of the ERN is not yet known with certainty, several areas have been supposed to participate in its genesis. The main candidate is the ACC that is constantly mentioned by investigators. Several fMRI studies suggest that the ERN occurs in the ACC (Iannaccone et al., 2015; Ito, Stuphorn, Brown, & Schall, 2003; Ullsperger & Von Cramon, 2001), in line with evidence provided by a brain electromagnetic source analysis (BESA) (Dehaene et al., 1994). A subsequent BESA modeling study has supported an ACC locus as well (van Veen & Carter, 2002). In addition, neuropsychological research shows results that partially confirm the involvement of the ACC as a source of the ERN. However, the presence of wide lesions and the differences between groups make difficult to compare these studies with each other (Kappenman & Luck, 2012). Thus, further work is still needed before to confirm the role of the ACC in the ERN. Moreover, as for other ERP components, it is likely that the ERN has multiple neural generators (Kappenman & Luck, 2012).

A rich corpus of studies have investigated the relationship between the ERN and error awareness. Scheffers & Coles, (2000) were the first to point out the sensitivity of the ERN amplitude to error awareness. In this study, participants were involved in a modified version of the Flanker task. Of interest, after each trial, participants had to assess their confidence in their response on a five-point scale ranging from "sure correct" to "sure incorrect". Results showed that the ERN amplitude was positively correlated with growing error awareness. These findings are in line with a prominent theory in which the ERN would reflect a conflict response and, in turn, that conflict tends to be higher on aware errors (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Nick Yeung, Botvinick, & Cohen, 2004).

However, a second study, by using an anti-saccade task, revealed the opposite effect, namely a null implication of the ERN on error awareness (Nieuwenhuis et al., 2001). In line with Nieuwenhuis' study, Endrass and colleagues (2005) contradicted the association between the ERN and error awareness, in this case through another task: a stop-signal task.

Unfortunately, the subsequent studies did not clarify the role of the ERN in error awareness. On the contrary, divergent data seemed to complicate everything. In fact, as Wessel (2012) reports in a detailed review, in the following five years some studies confirmed Scheffers & Coles' results, whereas others Nieuwenhuis' ones.

Several factors can be called into question to explain these discrepancies (Wessel, 2012). For example, a first point concerns the tasks used to quantify the ERN. As emerges from previous studies, different tasks lead to different findings. An explanation for these discrepancies can

depend on the stimuli presented in these tasks. Some studies that failed to find an association between the ERN and error awareness used degraded stimuli (Scheffers & Coles, 2000; Steinhauser & Yeung, 2010). Although the manipulation of stimulus perception, by a gradual degradation of it, can increase the number of unaware errors, degraded stimuli might also induce a lower ERN amplitude. Another salient aspect should be considered as a mediator between the ERN and error awareness: the modality by which authors have operationalized aware errors. In some studies, participants have to report the error by pressing an "awareness button". Others require participants to indicate the level of awareness by using a scale with different points of judgment. Furthermore, while in some tasks participants have to signal their awareness within a narrow time window, other ones do not require a fast signaling. Finally, the sample size may be a crucial aspect that contributes to increasing the type-2 error probability. Thus, it is plausible that not all the tasks allow eliciting the ERN and therefore it may be difficult to highlight a relationship between this component and error awareness.

A promising vein of research concerns the use of clinical markers to improve the diagnosis and treatment of several disorders. Apart from the controvert role of the ERN in error awareness, without doubts, the ERN is a reliable index of error monitoring. This process seems aberrant in some clinical conditions. Olvet & Hajcak (2008) review a significant bunch of clinical studies investigating the relationship between the ERN and psychopathology. For instance, Gehring and colleagues (2000) showed some differences between patients with obsessive-compulsive disorder and controls. In this study, patients had increased ERNs (Gehring et al., 2000).

Also in depression, the ERN appears to be different compared to controls. The rationale for studying the ERN in depression is that these patients show an abnormal sensitivity to errors and negative feedback (Elliott, Sahakian, Michael, Paykel, & Dolan, 1998; Steffens, Wagner, Levy, Horn, & Krishnan, 2001). Thus, in depression, the different way by which the brain processes the error information may be at the base of some symptoms typically observed in these patients. In line with this possible processing bias, patients with depression exhibit abnormal error-related brain activity. For example, in a Stroop task, these patients showed greater ERN than controls after errors (Holmes & Pizzagalli, 2008).

Taken together, these studies show that both anxiety and depression seem to be characterized by an increased sensitivity to committing errors (Olvet & Hajcak, 2008).

Neurophysiological correlates of error-related processes: the Pe

The ERN is followed by a positive deflection, peaking around 200-400 ms after the erroneous response. This component is called Pe and has a centroparietal distribution (figure 5). Unlike the ERN, the Pe is more prominent after an aware error than an unaware error. For this reason, the Pe seems a reliable electrophysiological marker of error awareness (Endrass et al., 2007; Murphy, Robertson, Allen, Hester, & O'Connell, 2012; O'Connell et al., 2007). A recent study demonstrates that the ERN and the Pe may reflect two different mechanisms of human error monitoring (Di Gregorio, Maier, & Steinhauser, 2018). Their results are particularly important because for the first time reveal that the Pe is independent of the emergence of the ERN, namely the ERN is not necessary for the emergence of the Pe. Thus, they refute a previous assumption that saw the ERN and the Pe as consequential processes of error monitoring.

Besides the relationship between the Pe and error awareness, other two interesting functional interpretations of the Pe are suggested: that it is a marker of adaptive strategies following an error and that it represents a sort of affective response to an error (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005).

The Pe can be divided into two sub-components (figure 6): the initial fronto-central positive deflection that immediately follows the ERN is called **early Pe**, whereas the deflection that settles around 300-500 ms after the erroneous response, with a maximum amplitude on parietal electrodes, is defined **late Pe** (van Veen & Carter, 2002). Especially this latter component would be modulated by error awareness (Wessel et al., 2011).

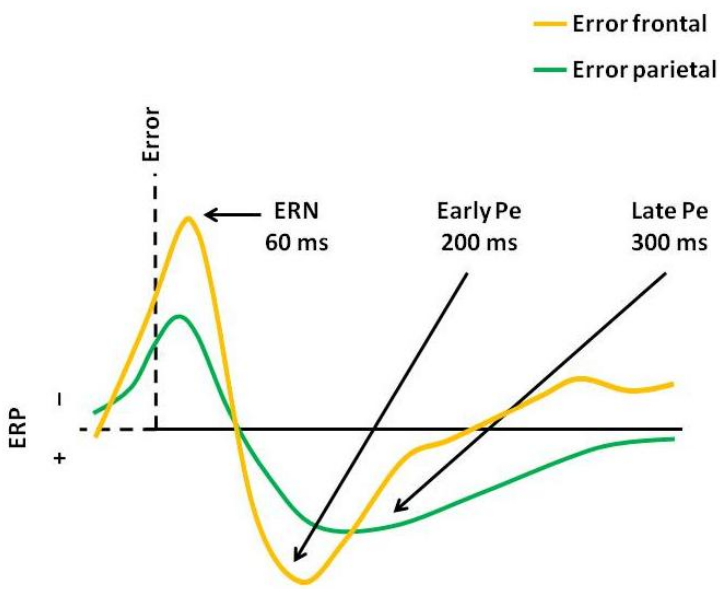

Figure 6 | Response-locked components related to an error in the frontal (yellow line) and parietal (green line) sites. Along the yellow waveform is clearly evident the ERN, followed by the early Pe, whereas along the green waveform is detectable the late Pe. Inspired by Ullsperger, Fischer, Nigbur, & Endrass (2014).

Pharmacological studies provide further information about the Pe. In fact, it seems that this component is not dependent on the dopaminergic system. Except for caffeine, several substances that directly or indirectly modulate dopaminergic activity are able to produce effects only on the ERN, without producing effects on the Pe (Overbeek et al., 2005).

The Pe seems also influenced by age, as reported from previous developmental studies. While no difference in terms of Pe amplitude was found between children and younger adults, a reduction of the Pe characterized older adults when compared to younger adults (Overbeek et al., 2005). Similarly, Harty and colleagues (2017) show a reduction of Pe amplitude in a group of older adults respect to younger adults.

From clinical studies emerge that Pe seems to be partly preserved in many clinical conditions, unlike the ERN (Overbeek et al., 2005). However, if present, the alteration of the Pe reveals awareness deficits. In fact, patients with traumatic brain injury and reduced Pe amplitude showed less awareness of abilities (measured in terms of the discrepancy between patient and significant-other ratings on the Frontal Systems Behavior Scale) (Larson & Perlstein, 2009). This data contributes to reinforcing the hypothesis that the Pe is a marker of awareness processes, such as error awareness. Interestingly, the Pe may be somehow a correlate of metacognitive processes.

Chapter 4

Study 1 - Motivation and error awareness

Introduction

As previously stated, the ability to detect an error is fundamental in our life. Even if an error can be perceived as an annoying event, it is informative because it indicates that the level of our performance has not been adequate to expectations and, therefore, a replanning or adjustment of our actions is necessary.

Error awareness can be theoretically viewed as a function represented along a continuum where at the extreme points we observe an excessive or absent awareness. In Chapter 3, some clinical conditions have been mentioned since they present a symptomatic picture that refers to an over-expressed or reduced error awareness. Some neurological conditions and cannabis and cocaine users present a reduction of error awareness, whereas in some psychiatric disorders error awareness seems excessive, such as in obsessive-compulsive disorder (Hester et al., 2009, 2007; Klein et al., 2013).

Although in normal aging error awareness is not dramatically absent, it seems reduced. A number of studies show that older adults tend to be less aware of their errors than younger adults. To test this hypothesis, Harty and colleagues (2013) compared a group of younger adults (age-range 18-34 years) with a group of older adults (age-range 66-90 years). Participants performed different tests aimed to evaluate self-awareness, namely the ability to assess own level of functioning. In particular, Harty and colleagues measured self-awareness in two ways: (1) a computerized task (the EAT, Hester et al., 2005) to evaluate the on-line ability to detect an error; (2) questionnaires, in particular, the discrepancy between self-reports and informant reports on questionnaire measures of daily functioning to measure self-awareness in daily contexts. In this study, two important results emerged. The first one confirmed the presence of a decline in error awareness in elderly, as already seen in a previous study (Rabbitt, 1990). Second, the authors observed a correlation between on-line error awareness and awareness of daily functioning. Thus,

results suggest that performance on laboratory measurements, such as the EAT, are representative of awareness in real-world contexts (Harty et al., 2013).

Error awareness impairment can have a negative impact on daily life. Being unaware of personal limitations can lead to risky behaviors for the individual, for example by an overestimation of own abilities. Furthermore, some authors show an increased care-given burden, poor compliance treatment, and a poor general prognosis (David, 1992; Fleming, Strong, & Ashton, 1996; Malec & Moessner, 2000; Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007).

Since healthy older adults exhibit a decline in performance monitoring (Palmer, David, & Fleming, 2014; Schreiber, Pietschmann, Kathmann, & Endrass, 2011), it is plausible to suppose that this impairment may produce negative consequences on error awareness and, more generally, on error monitoring. On the other hand, it is also possible an opposite scenario in which the impairment of error awareness and error monitoring causes the reduction of performance monitoring.

As already described, error awareness is reduced in elderly as confirmed by Rabbitt (1990) and Harty and colleagues (2013). Actually, a recent study suggests a U-shaped ontogenetic trajectory of error awareness that describes an increase of the process from childhood to early adulthood and a progressive reduction advancing age in late adulthood (Masina et al., 2018a).

As regards the decline of error monitoring, growing evidence shows an impairment of this process in older adults. A proficient vein of research investigates the ERP correlates of error monitoring showing, in several cases, a reduction of the ERN in older adults compared to younger adults (Falkenstein, Hoormann, & Hohnsbein, 2001; Schreiber et al., 2011; Themanson, Hillman, & Curtin, 2006).

In line with these previous studies, it is clear that error awareness, error monitoring, and performance monitoring decline in elderly may affect the ability to on-line monitor performance. In turn, this difficulty to monitor performance may depend on the decline of two crucial cognitive processes that it is well-know are reduced in older adults: working memory and vigilance.

Since older adults have difficulty to maintain and update information in working memory, it is possible that in demanding situations, for example during a dual-task, the system can be prone to momentary failures. In this case, the consequences may be several: a general reduction of performance, a failure to detect an error, a reduction of the behavioral adjustments normally triggered by an error.

Vigilance is negatively affected by normal aging as well. Interestingly for the present study, a number of findings show a relationship between vigilance and error awareness (Masina et al., 2018b; Shalgi et al., 2007). This evidence suggests that an appropriate level of vigilance could support an adequate ability for detecting errors.

In Chapter 2, some methods widely used in research to modulate the behavior and underlying neural processes have been described. Among these methods, the use of rewards seems to be an effective tool capable of improving performance in a number of cognitive domains, such as working memory, attention, episodic encoding, and decision making (Locke & Braver, 2010; Maddox & Markman, 2010; Pessoa, 2009, 2010; Shohamy & Adcock, 2010). These results suggest that motivation can affect ongoing neurocognitive processing (Braver et al., 2014).

Despite these interesting findings, no studies have explored the effects of motivational rewards in error awareness, leaving this interesting and relevant research field still lacking of evidence. Thus, in order to contribute to fill this gap, **the purpose of study 1 was the modulation of error awareness in a group of healthy older adults. Specifically, this study aimed to increase error awareness in a group of older adults compared to younger adults, by using rewards.** To the best of our knowledge, the present study is the first that directly uses rewards with the aim of modulating error awareness.

The previous considerations about error awareness have been extremely precious to plan the present study because they have helped us to think about which kind of intervention could be more efficient to modulate error awareness. As explained in Chapter 2, reward-related modulation requires to take some points into considerations to avoid unexpected results, such as a paradoxical reduction of performance which is expected to be improved by an intervention. Moreover, considering the decline of older adults in some cognitive domains such as working memory and vigilance, a manipulation should consider these processes as well. For example, in the view of using a computerized task to assess error awareness, it should not be extremely demanding, to avoid an overload of working memory. Moreover, considering the reduction of vigilance in older adults, an experiment should be characterized by breaks, in which participants can have time to take a rest.

Taken together these considerations and with the aim to conduct a manipulation as efficiently as possible, the following points have been carefully considered in study 1:

- **Task** - The tasks generally used to evaluate error awareness are very different and can lead to different results. Therefore, in the present study, we have decided to use the same task that Harty and colleagues (2013) have shown to be fitted for measuring error awareness in a group of healthy older adults. However, considering the difficulties that older adults may encounter while performing a task such as the EAT, in the present study we have tried to further simplify the procedure. In particular, in our task, after each trial, a prompt was presented to explicitly check the accuracy of participants. We hypothesized this prompt would have supported participants in monitoring trial-by-trial own performance.
- **Reward** - Assuming to confirm the reduction of error awareness in elderly, in our study we rewarded error awareness with the aim to improve it. All participants performed a task in which the performance was supported by virtual monetary incentives. After each trial participant received a feedback about her/his accuracy, as well as a reward. In particular: (1) a big reward, after a correct response; (2) a small reward, after a signaled error; (3) no reward, after an unnoticed error. With this program of incentives, we expected to increase both accuracy and error awareness.

Method

Participants[1]

Sixty-one healthy participants were recruited in the study 1: 30 younger adults aged 19-35 (mean = 25.4; *SD* = 5; men = 10) and 31 older adults aged 61-83 (mean = 69.7; *SD* = 5; men = 12). Exclusion criteria were a history of neurological or psychiatric diseases, use of neurological or psychiatric medications, and a score at the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) under the Italian cut-off (Conti, Bonazzi, Laiacona, Masina, & Coralli, 2015; Santangelo et al., 2015). All participants had normal or corrected-to-normal vision. Written informed consent was obtained from all participants. The Table 1 shows the main demographics of the sample. The study 1 was conducted in accordance with the Helsinki Declaration on human rights and was approved by the Ethics Committee of the School of Psychology at the University of Padova.

[1] Post hoc power analysis has demonstrated that in study 1 the sample size was adequate to the analyses conducted (Effect size = 0.25, Power = 0.99).

Table 1. Participant demographics and MoCA scores.

	Younger Adults	**Older Adults**
Mean Age (*SD*)	25.4 (5)	69.7 (5)
Education	15.1 (3)	11 (6)
MoCA score (*SD*)	28.1 (2)	25.7 (2)

Note. *SD*: Standard Deviation; MoCA: Montreal Cognitive Assessment test.

Tasks and procedure

Participants performed two different versions of the EAT (Hester et al., 2005), a motor Go/No-go response inhibition task in which participants are presented with a serial stream of single-color words. In both the versions of the EAT, participants were asked to respond with a single-speeded button press ("3" on the keyboard), using their left index finger, when the word and its color font matched (Go trial). On the contrary, participants were trained to withhold their response in two circumstances: (1) when the word and its color font were incongruent (Stroop No-go trial); (2) when the same word was presented twice, namely in two consecutive trials (repeat No-go trial). In the case of participants realized to have committed an error, namely to avoid withholding their response in the No-go trials (Stroop and repeat No-go), they were trained to signal the error by pressing an "error awareness" button (space bar), with their right index finger. Participants were required to respond as fast and accurate as possible, without to prioritize speed or accuracy.

Structurally, each trial started with the color word that was presented at the center of the screen, on a black background, for 750 ms, followed by a second black screen that appeared for 750 ms. Afterward, a prompt was presented for 1000 ms with the following question: "*Did you make a mistake?".* During this time window, participants were instructed to signal a supposed error. Through this prompt, the task was simplified compared to the original version (Hester et al., 2005), because participants were asked explicitly to monitor trial-by-trial own performance.

So far, both the versions of the EAT shared the same characteristics. However, the screen that followed the prompt changed according to which version of the task participants were performing. In the **Classical EAT** version, a white screen was presented for 750 ms, whereas in the **Motivational EAT** this screen showed a reward message for 750 ms (figure 7).

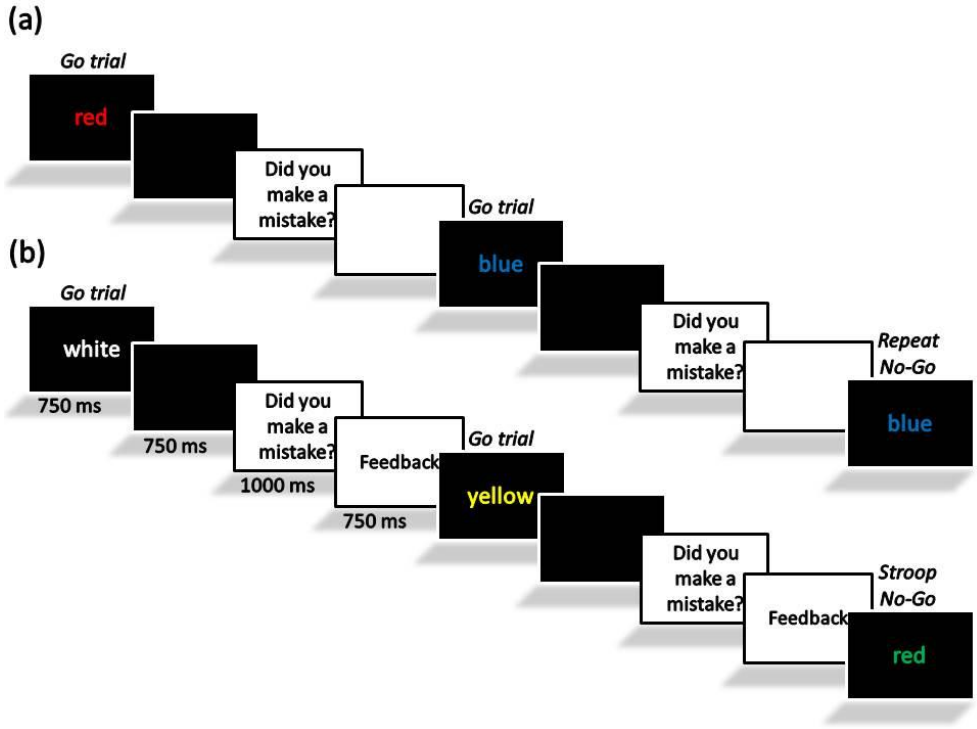

Figure 7 | The figure shows both the tasks: (a) the Classical EAT and (b) the Motivational EAT. As clearly represented by the figure, the only difference between the tasks was the screen that followed the prompt "Did you make a mistake?". Only in the Motivational EAT participants received a feedback and a reward, according to their performance on the task. Instead, in the Classical EAT, after the prompt participants saw a white screen.

In order to investigate the effect of rewards on error awareness, in the Motivational EAT after each trial participants received a feedback ("correct" or "wrong") and, related to their accuracy or error awareness, a symbolic performance-contingent reward. Specifically, after each correct response and after each correctly signaled error, participants received a virtual monetary reward: a correct response was rewarded with a win of €0.50, whereas a signaled error was rewarded with €0.10. No penalty in case participants committed errors. The total virtual budget was updated trial-by-trial and it was shown at the bottom of the reward screen.

In both versions of the task, 675 trials were presented, in three blocks of 225 (200 Go trials and 25 No-go trials, of which 12 Stroop No-gos and 13 repeat No-gos). Each participant was tested with both experimental tasks, Classical EAT and Motivational EAT, which were administered in a counterbalanced order across participants. Each task was performed on a different day and before the beginning of each task, it was ensured all participants were well-trained and correctly understood the instructions. The experiment was run by E-Prime software (version 2.0 Psychology Software Tools, Pittsburgh, PA) installed on a personal computer equipped with a 17''monitor.

Figure 8 summarizes the experimental design of study 1. Each participant took part in two sessions in two different days. The session was so planned: (1) a training phase to guarantee participants had understood the task instructions; (2) a phase in which participants performed a full version of the EAT, either Classical or Motivational EAT (counterbalanced order).

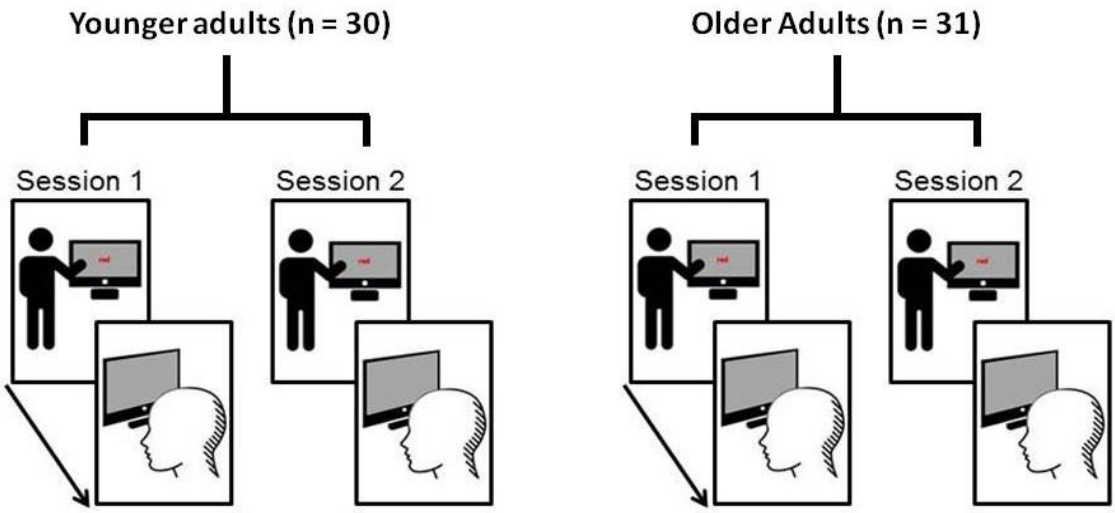

Figure 8 | The experimental design of study 1.

Measures and data analysis

According to the aims of study 1, participant's performance was evaluated through different dependent variables, which were calculated and analyzed as following.

Reaction times and accuracy - Average performance indices was assessed in term of mean reaction times and mean accuracy (calculated as the ratio of correct withholds on No-go trials) in both Classical and Motivational EAT. Reaction times under 100 ms were removed from analyses. To evaluate differences on mean reaction times, a mixed 2 x 2 x 2 ANOVA was conducted with *task* (Classical Vs Motivational EAT) and *response type* (correct Vs error) as within-subjects variables and *group* (younger Vs older adults) as between-subjects variable.

Differences in mean accuracy were computed by a mixed 2 x 2 ANOVA with *task* (Classical Vs Motivational EAT) as within-subjects variable and *group* (younger Vs older adults) as between-subjects variable.

Error awareness - Mean error awareness was calculated as the percentage of correctly signaled errors on the total number of commission errors (O'Connell et al., 2009).

A mixed 2 x 2 ANOVA was conducted with *task* (Classical Vs Motivational EAT) as within-subjects variable and *group* (younger Vs older adults) as between-subjects variable

Post-error slowing - PES was computed according to Dutilh and colleagues (2012) by the difference between the reaction times that follows and precedes each error. This difference was compared with the difference between the reaction times that follows and precedes each correct inhibition. Unaware errors were excluded from the analyses of PES as well as reaction times under 100 ms. We performed a mixed 2 x 2 x 2 ANOVA with *task* (Classical Vs Motivational EAT) and *target response* (aware error Vs correct inhibition) as within-subjects variables and *group* (younger Vs older adults) as between-subjects variable. For these analyses, the sample size was reduced to 59 participants (30 younger adults and 29 older adults) because 2 older adults did not signal any error during a particular task (so it was impossible to calculate PES for aware errors).

The Bonferroni correction was always applied to multiple comparisons and post-hoc analyses and a corrected alpha-level of 0.05 was considered. Finally, effect sizes were estimated by partial eta squared (η^2_p).

Results

Reaction times and accuracy - The mean of reaction times and accuracy are shown in Table 2. Analyses on mean reaction times showed a main effect of *task* [$F(1,59) = 7$, $p < 0.05$, $\eta^2_p = 0.1$], *response type* [$F(1,59) = 40.1$, $p < 0.001$, $\eta^2_p = 0.4$], and *group* [$F(1,59) = 64.7$, $p < 0.001$, $\eta^2_p = 0.5$]. Post-hoc comparisons showed that participants were faster when performed the Classical EAT than the Motivational EAT (550 ms Vs 567 ms; $p < 0.05$). Moreover, error reaction times were faster than correct reaction times (548 ms Vs 570 ms; $p < 0.001$). Generally, younger adults were faster than older adults (480 ms Vs 638 ms; $p < 0.001$). No interaction was found.

As regards mean accuracy, a main effect of *group* was found [$F(1,59) = 4.4$, $p < 0.05$, $\eta^2_p = 0.1$]. Post-hoc comparisons showed that younger adults made more errors than older adults (52% Vs 62%; $p < 0.05$).

Table 2. Mean and standard deviations (*SD*) of performance indices on the Classical and Motivational EAT for younger and older adults.

	Classical EAT		**Motivational EAT**	
	Younger Adults	**Older Adults**	**Younger Adults**	**Older Adults**
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Correct reaction times (ms)	483 (60)	636 (94)	500 (77)	659 (89)
Error reaction times (ms)	464 (63)	619 (89)	472 (75)	639 (103)
Accuracy (%)	52 (22)	64 (19)	51 (25)	60 (17)
Error awareness (%)	89 (8)	57 (20)	81 (14)	53 (27)

Error awareness - The mean error awareness percentages are presented in Table 2. revealed a main effect of *task* [$F(1,59) = 4.6$, $p < 0.05$, $\eta^2_p = 0.1$] and *group* [$F(1,59) = 54.1$, $p < 0.001$, $\eta^2_p = 0.5$]. Post-hoc comparisons showed that participants were more aware of their errors when performed the Classical EAT than the Motivational EAT (73% Vs 67%; $p < 0.05$). Moreover, we observed by post-hoc comparisons that younger adults had generally a higher error awareness than older adults (85% Vs 55%; $p < 0.001$). No interaction between *task* x *group* was observed ($p = 0.5$) (figure 9).

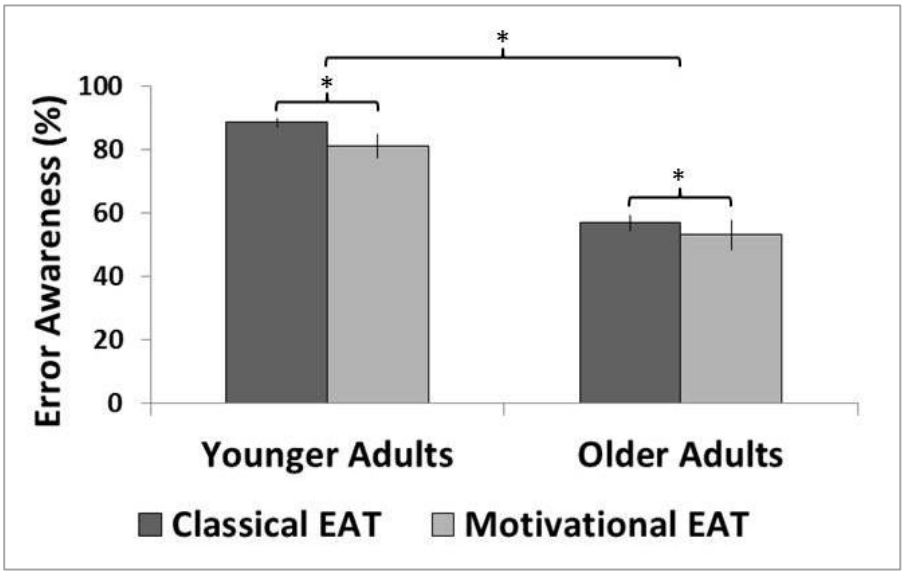

Figure 9 | The figure shows mean error awareness scores in both the Classical and Motivational EAT. Error bars represent standard errors of the mean. Note: * ($p < 0.05$).

Post-error slowing - The mean of reaction times following and prior an aware error or a correct inhibition are shown in Table 3. The analyses showed a main effect of *task* [$F(1,57) = 4.8$, $p < 0.05$, $\eta^2_p = 0.1$] and *target response* [$F(1,57) = 196$, $p < 0.001$, $\eta^2_p = 0.8$]. The paired sample comparisons indicated that participants showed a lower slowing (independently from the response) when performed the Classical EAT than the Motivational EAT (32 ms Vs 48 ms; $p < 0.05$). Furthermore, the difference between post- and pre-target response was greater when the target response was an error than a correct inhibition (105 ms Vs -25 ms; $p < 0.01$). In addition, the analyses revealed a *target response* x *group* interaction [$F(1,57) = 10.4$, $p < 0.01$, $\eta^2_p = 0.2$]. Younger adults showed a lower slowing after errors than older adults (83 ms Vs 127 ms; $p < 0.01$). The figure 10 shows clearly PES effect and the *response* x *group* interaction.

Table 3. Means and standard deviations (*SDs*) for post- and pre-target responses computed as a function of target response (aware error and correct inhibition) and group.

	Classical EAT		**Motivational EAT**	
	Younger Adults	**Older Adults**	**Younger Adults**	**Older Adults**
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Post-target (aware error)	546 (104)	724 (126)	561 (107)	766 (150)
Pre-target (aware error)	463 (59)	610 (97)	476 (72)	624 (86)
Post-target (correct inhibition)	463 (60)	596 (97)	495 (70)	632 (107)
Pre-target (correct inhibition)	489 (62)	637 (93)	503 (78)	658 (91)

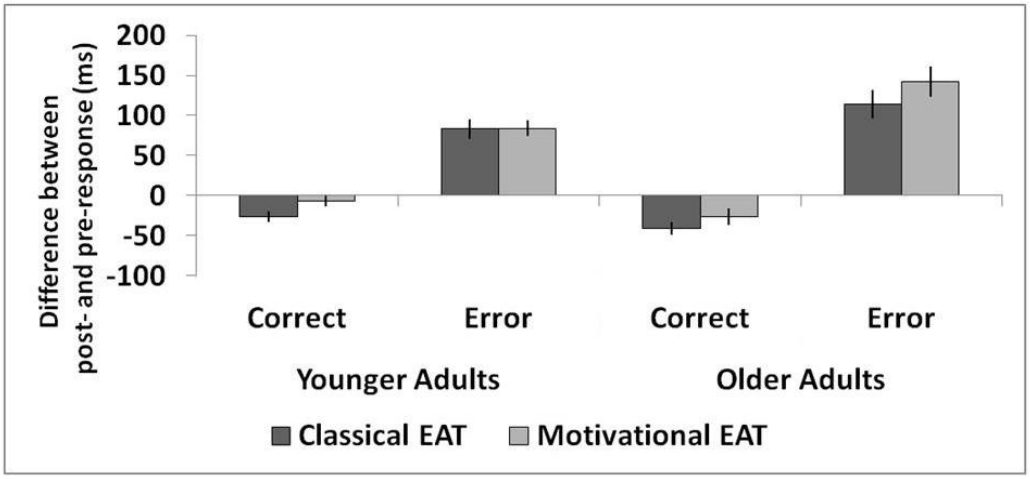

Figure 10 | The figure shows the difference between reaction times following and prior an aware error or a correct inhibition for each group. Post-error slowing is clearly visible after an aware error, as well as the *response* x *group* interaction in which older adults were slower after an error compared to younger adults. Error bars represent standard errors of the mean.

Discussion

The purpose of the present study was to investigate the role of motivational rewards in error awareness through the comparison of two groups (younger and older adults). Each participant took part in two sessions in which a different version of the EAT was presented: a version similar to the original task, called Classical EAT, and a version characterized by incentives, called Motivational EAT.

First, the results on average performance on the EAT showed that older adults were generally slower than younger adults. However, in terms of accuracy, older adults were more accurate than younger adults. These findings are in line with prior studies that show a different **speed-accuracy tradeoff** between younger and older adults. While younger adults are generally faster but less accurate, older adults are slower but more accurate (Dutilh, Forstmann, Vandekerckhove, & Wagenmakers, 2013; Starns & Ratcliff, 2010). This phenomenon seems to reflect different strategies used to tackle a task. Perhaps older adults are more caution than younger adults because a lifetime of experience can have suggested that a correct response requires a sufficient time for the deliberation (Starns & Ratcliff, 2010).

Second, our results confirm the presence of an age-related reduction of error awareness. This reduction seems independent from the difficulty of the task since our tasks, both Classical and Motivational EAT, were designed so that the error signaling procedure was more simple than the version used by Harty and colleagues (2013). Interestingly, this evidence was present despite older adults were generally more accurate than younger adults. Thus, it does not seem that elderly have had difficulty performing the task itself, but it seems that they have had difficulty in the detection of errors. This result adds further confirmation about the decline in error of awareness in normal aging (Harty et al., 2013; Masina et al., 2018a; Rabbitt, 1990).

As discussed in Chapter 3, error awareness involves several brain regions such as the AIC, the pMFC, the DLPFC, the ACC, and the thalamus. Moreover, the association between the PFC and awareness decline suggests that the PFC is a crucial component of self-awareness and, probably, metacognition. Since the PFC is particularly vulnerable to the effects of aging (Hof & Morrison, 2004; Raz, 1997) and considering the role of PFC in error awareness, it is plausible to suppose that the age-related decline of error awareness may lay on the alteration of the prefrontal neural circuits.

The third result is particularly interesting. In the present study, the main purpose was to improve error awareness in older adults. With the aim to reach this objective, participants performed a motivational version of the task, in which both the correct responses and the detection of an errors were rewarded by symbolic economic wins. Contrary to our expectations, the effect produced by rewards was counterproductive: error awareness was significantly reduced in the condition in which error awareness was rewarded, in both younger and older adults. Although this result can seem paradoxical, previous studies suggest several possible explanations.

In Chapter 2, we have described the effect of motivation on cognition. In general, a rewarded performance is associated with an improvement of accuracy. However, some authors point out that the use of rewards to modulate cognition should be carefully considered. In fact, sometimes rewards can produce a reduction of performance (Yu, 2015), as in our study. This unexpected effect may be addressed by several explanations that share an important point: a reward can be stressful and, in turn, distracting because it induces psychological pressure.

A first view, the distraction account, claims that attention would have a crucial role in explaining the failures of performance. The reduction of performance would be a consequence of an attentional shift from skill execution to psychological pressure (Carver & Scheier, 1981; Wine, 1971). In the Motivational EAT, participants would have focused their attention on distracting cues, such as the consequences associated with failure, instead of focusing their attention on the task. A second plausible explanation of our result may be corroborated by the monitoring theory. According to this view, high psychological pressure would lead to a sort of regression in which even an automatic behavior would require a resource-demanding control. Therefore, this shifting from the automatic to controlled information processing would produce a performance reduction (Baumeister, 1984). Finally, the over-arousal account, suggests that an excessive level of arousal, caused by psychological pressure, may have detrimental effect on performance (Yerkes & Dodson, 1908).

Apart from the over-arousal account, both the distraction and monitoring account may partially contribute to explain the error awareness reduction that we found. The over-arousal theory is not plausible because, in general, an increase of arousal is accompanied by a reduction of reaction times. However, this is not our case since we found an opposite effect, namely faster responses in the Classical EAT than the Motivational EAT. Moreover, against the over-arousal account, in a previous study, participants were stressed to provide speeded responses. This manipulation, besides to produce an increase of arousal, namely a reduction of reaction times and

accuracy, was associated with an enhancement of error awareness (Shalgi et al., 2007). Therefore, authors concluded that error awareness can be enhanced in arousal-inducing conditions (Shalgi et al., 2007).

Unfortunately, except from the over-arousal account, this study does not allow to establish which theory, distraction or monitoring, can be responsible for results. This limitation points out the necessity for further investigations.

A limitation of this study concerns the fact that the manipulation of reward was not comprehensive. Considering that the manipulation of incentives can produce different effects on behavior, other reward schedules could be employed. For example, the administration of rewards through non-visual modalities may result less distracting. Moreover, it should be considered that participants were reinforced with different rewards according their accuracy. Since participants received more virtual money for correct responses than signaled errors (€0.50 vs. €0.10), they could be biased toward reporting a correct response instead of signaling an error. This might account for lower error awareness in the reward condition.

Finally, our last result concerns the age-related modulation of PES. This phenomenon has been highly investigated as a correlate of error monitoring and error awareness (for a review, Danielmeier & Ullsperger, 2011), therefore our analyses could not neglect this crucial phenomenon. First of all, also in this study, PES was confirmed, as expected when the difference between post- and pre-reaction times after aware errors was compared with the difference between post- and pre-reaction times after correct inhibitions. Thus, the EAT, especially our modified versions, can elicit a significant PES. This aspect is not trivial because PES seems highly task-dependent and, in particular, it seems affected by the duration of RSI. The shorter is RSI, the higher PES will be (Ullsperger et al., 2014). In our study, the interval between erroneous response and the next stimulus was longer than 750 ms. In a previous study, Danielmeier & Ullsperger, (2011) showed that with RSI longer of 750 ms, PES was not observed anymore. However, this evidence is not consistent in the literature and some fMRI studies found a substantial PES even after RSIs of 4–5 seconds (Danielmeier et al., 2011; King, Korb, von Cramon, & Ullsperger, 2010).

A second important result concerns the *target response* x *group* interaction we found. This result is coherent with a previous study that showed a more pronounced PES in older adults (Dutilh et al., 2013). In our opinion, this result may be interpreted both in terms of different strategies used by younger and older adults to perform a task and in terms of differences in error-related processing. As regards the first hypothesis, some investigators agree that older adults

slowdown because they are more cautious than younger adults. Thus, elderly need more evidence, and so, more time, before they are willing to make a decision. The second possibility takes changes in error-related processing into consideration. This hypothesis is also plausible because, as previously shown, some error-related components, such as the ERN, seems affected by aging, indicating a general reduction of error processing in older adults (Colino et al., 2017; Hoffmann & Falkenstein, 2011). However, further confirmations are necessary to corroborate or not these statements since the reduction of a specific error-related process cannot suggest a generalized reduction of error processing in older adults. In fact, some processes could be differently affected by aging.

Conclusion

In study 1, the main topic was the modulation of error awareness through the use of behavioral techniques, namely rewarding performance. The use of rewards to facilitate, or reduce specific behaviors is not new. As discussed in Chapter 3, these techniques are already widely used, even in clinical settings.

In the present study the introduction of rewards to incentivize error awareness was detrimental. The reasons could be multiple and, as described above, other authors have observed counterproductive effects of rewards. Although results of this study show a paradoxical effect of incentives on error awareness, they allow at the same time to raise an important issue. Despite the promising applications of rewards to modulate performance, the efficacy of these methods is not always guaranteed.

For this reason, and in particular because the literature on the topic "modulation of error awareness" is still rather scanty, future studies should investigate the possibility of modifying error awareness. This research field may facilitate the conception of new interventions in clinical settings, especially for patients with error awareness deficits.

Study 2 - The role of dorsolateral prefrontal cortex in error awareness: insights from single-pulse TMS

Introduction

The objective of study 1 was to improve error awareness by supporting the process through virtual monetary incentives. However, as in Chapter 2 it has been highlighted, the modulation of behavior or underlying neural processes can also be induced by NIBS. NIBS is a set of brain stimulation methods in which current flows are induced into the brain to produce changes in brain plasticity. These techniques are important in the field of neuroscience since they allow identifying possible causative relationships between the brain and the investigated process. Moreover, they are able to produce long-term modification of brain activity. This feature is perhaps one of the most important aspect of NIBS and makes it an excellent tool for inducing modulation.

TMS is probably one of the best known NIBS. The application of TMS ranges from the study of very short brain effects induced by single pulses to long-lasting effects induced by repetitive paradigms of stimulation. In study 2, spTMS will be used to investigate some aspects of error awareness, specifically the time-course of the process and its neural bases.

Indro Montanelli, a famous Italian journalist, wrote: "*Among errors, there are those that stink of sewage and the ones that smell of laundry"* (Montanelli, 1992). Although this aphorism can only seem romantic and poetic, it expresses in a couple of words the value and functional meaning of errors. The detection of an error is essential because it forces us to adapt our behavior as a function to our goals. Moreover, from our errors, we can learn how to avoid future erroneous and potentially detrimental actions.

The behavioral and neural effects produced by errors have been broadly studied in the literature. In many studies, the focus is generally on the ability of the brain to process the error-related information, in other cases, a number of studies specifically investigate the

ability to consciously perceive an error. While in the first case we talk about error monitoring, in the second one we refer to error awareness.

Error monitoring refers to a multi-componential system that contributes to refocus attention to the task, triggering behavioral adjustments and emotional reaction following an error (Taylor, Stern, & Gehring, 2007), regardless of whether the error made was aware or not. Differently, error awareness indicates more specifically a metacognitive process that allows the conscious detection of an error (Ullsperger et al., 2014).

In Chapter 3, we have illustrated many studies showing how error monitoring is not a synonym of error awareness (for example, Endrass et al., 2005). For instance, ERP studies have established that an error is processed by at least two independent and parallel processes: a first process seems dedicated to a rough processing of error, and a second one, more related to a proper evaluation and conscious detection of error (Di Gregorio et al., 2018; Wessel, 2012). Two ERP components seem to reflect these distinct processes. On the one hand, the ERN, i.e. a fronto-central deflection that peaks between 20 and 100 ms after an erroneous response, is more related to the first process, whereas on the other hand, the Pe, namely a more posterior positive deflection that peaks 100-200 ms after an erroneous response, is modulated by error awareness. In particular, the Pe is generally larger for aware error than unaware error (Endrass et al., 2007; Nieuwenhuis et al., 2011).

Similarly to ERP studies, MRI and fMRI evidence confirms that the processing of aware and unaware error is different. As mentioned before, the ACC (Hester et al., 2009; Maier, Di Gregorio, Muricchio, & Di Pellegrino, 2015; van Veen & Carter, 2002), the thalamus (Seifert et al., 2011), the anterior insula (Klein et al., 2007; Klein, Ullsperger, et al., 2013), and the PFC (Hoerold, Pender, & Robertson, 2013) seem selectively activated by aware errors. Complementary to these findings, several EEG studies using source analyses have identified cortical structures correlated with error awareness. For example Charles and colleagues (2013) have revealed a relationship between aware errors and the activity of the posterior cingulate cortex, as well as a correlation between unaware errors and the dorsal anterior cingulate cortex.

Although these results contribute to improve the knowledge about the neural bases of error awareness, they share the fact that the information obtained with ERP, neuroimaging, and EEG methods, despite their good spatial or temporal resolution, do not allow to establish

a causal relationship between structure and function, because they provide only correlational evidence.

With the aim to overcome these methodological limitations, NIBS has recently been employed, obtaining promising results. In particular, in a tDCS study, Harty and colleagues (2014) revealed a causal relationship between error awareness and the DLPFC, a brain area associated with awareness of cognitive functioning (Fleming, Huijgen, & Dolan, 2012). In their study, authors tested a group of healthy older adults (65–86 years), who were involved in four different experiments, in order to test the effect of both anodal and cathodal stimulation over the right and left DLPFC. Interestingly, the authors observed in Experiment 1, and confirmed in Experiment 4, that only anodal tDCS over the right DLPFC induced an improvement of error awareness in their participants. This result is crucial because is the first evidence that establishes a causal relationship between the right DLPFC and error awareness.

However, the method that Harty and colleagues (2014) used in their study, namely tDCS, presents two important limitations. Firstly, tDCS is characterized by low spatial resolution and this limitation does not allow establishing which brain area was modulated. According to a recent study (Cieslik et al., 2013), at least from a functional point of view, the DLPFC can be divided into two subregions: an anterior subregion, more associated with attention and cognitive control, therefore more related to error awareness, and a posterior subregion, more associated with working memory. Thus, considering this evidence, results of Harty and colleagues (2014) does not allow clarifying which part of the right DLPFC was really involved in error awareness. Moreover, aside from this consideration, the study of Cieslik and colleagues (2013) is relevant because it may provide an explanation for results provided by Harty and colleagues (2014). In line with Cieslik and colleagues (2013), the anterior subregion of the right DLPFC seems to be functionally connected with the ACC, another brain area strongly related to error awareness (Hester et al., 2009; Maier et al., 2015; van Veen & Carter, 2002). Therefore, it is plausible to suppose that Harty and colleagues (2014), by the stimulation of the right DLPFC may indirectly have modulated the ACC.

Secondly, this study cannot provide any temporal information about error awareness, specifically when the activity of the right DLPFC is crucial in error awareness. Again, this limitation depends on tDCS that, unlike TMS, does not allow to study the time-course of the process under investigation.

In order to overcome these limitations, in the present study we decided to employ TMS. Specifically, through on-line TMS we aimed to investigate temporal information about error awareness. Unlike tDCS, in on-line TMS paradigms, pulses are discrete events that produce a punctual neuronal depolarization (Wagner, Valero-Cabre, & Pascual-Leone, 2007) and can, therefore, be used to infer information about the time-course of neural and cognitive events.

The purpose of the present study was to confirm the involvement of the right DLPFC in error awareness, as well as to investigate the timing of error awareness. In this study, three experiments were conducted: a paired-pulse and a single-pulse on-line stimulation paradigms were employed respectively in Experiments 1 and 3, whereas a control test was conducted without stimulation (Experiment 2). All three experiments were conducted according to the declaration of Helsinki and were approved by the Ethics Committee of the School of Psychology, University of Padua. All the participants[2] enrolled in experiments were volunteers and did not receive any reimbursement. Before experiment, participants gave their written informed consent and were checked for TMS exclusion criteria (Rossi, Hallett, Rossini, & Pascual-Leone, 2011) (see appendix). Extra exclusion criteria were a history of neurological or psychiatric diseases, use of neurological or psychiatric medications. The adopted safety procedures were in line with the guidelines for the use of TMS (Rossi et al., 2009).

[2] Post hoc power analysis has demonstrated that in study 2 the sample size of each experiment was adequate to the analyses conducted (Effect size = 0.25, Power = 0.84).

Experiment 1

Method

Participants

Twenty volunteers participated in Experiment 1 (6 male, 22.5 ± 3.2 years, range: 19-30). All participants had a normal or corrected-to-normal vision and were right-handed. Each participant took part in three experimental sessions carried out on different days (3 days on average were left between each session). During each session, only a brain site was stimulated (e.g. Session 1: right DLPFC, Session 2: left DLPFC; Session 3: Vertex). Figure 11 summarizes the experimental design of study 2. Each participant took part in three sessions in three different days. The session was so planned: (1) a training phase to guarantee participants had understood the task instructions; (2) a phase in which participants performed a full version of the task, namely the EAT (Hester et al., 2005), while on-line TMS was administered.

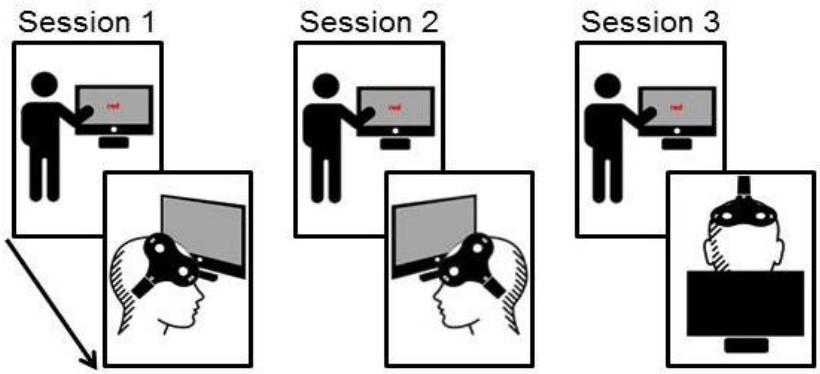

Figure 11 | The figure represents three hypothetical sessions during which each participant, after a brief training, performed the EAT (Hester et al., 2005) while on-line TMS was delivered. In this figure the order of stimulated brain sites was: (1) right DLPFC; (2) left DLPFC; (3) Vertex. This is only an example because the order was randomly determined.

Task

In order to evaluate error awareness, a modified version of the EAT was adopted. Similarly to study 1, participants were trained to respond as fast and accurate as possible (without to prioritize speed or accuracy), with a single-speeded press of a button ("3" on the keyboard),

with the left hand, when the semantic meaning of the word and its font color were congruent (Go trial), while they were asked to withhold the response in two circumstances: (1) when the semantic meaning of the word and its font color were incongruent (Stroop No-go trial); (2) when the word presented on the current trial was the same as the one presented previously (repeat No-go trial). Moreover, participants were instructed to signal an error commission, both Stroop and Repeat errors, by pressing the space bar with the right hand.

Unlike the EAT versions used in study 1, in the present study the EAT differs for two important points. Firstly, in line with previous studies (Harty et al., 2014; Murphy et al., 2012; O'Connell et al., 2009), participants could signal an error immediately after its commission, instead of delaying this response for a fixed time as it was the case for other studies in which the EAT was used (Harty et al., 2013; Hester et al., 2009; Shalgi et al., 2007). This aspect allowed measuring the timing of error awareness (*error awareness reaction time*) as well as the error awareness itself. The second aspect, similarly to a prior study (Harty et al., 2013), concerns the implementation of an adaptive staircase approach to maintain the number of errors between subjects as similar as possible (figure 12). To this aim, in the present study, the task difficulty was based on the participants' accuracy on No-go trials. In this way, any potential variation of error awareness would have been related to our manipulation, namely TMS, instead of depending on accuracy.

Initially, the word was presented for 750 ms with an ISI of 1250 ms. These parameters were maintained if the accuracy was between 50% and 60%. If the accuracy on No-go fell under 50%, the presentation of the word and ISI were both set to 1000 ms, whereas if the accuracy on No-go exceeded 60%, the presentation of the word and ISI were respectively set to 500 ms and 1500 ms. During the task, this check of accuracy was computed after each No-go trial. Stimuli appeared at the center of the screen on a black background. The total number of trials in the task was 1150, specifically 1000 Go trials, 75 Repeat No-go trials, and 75 Stroop No-go trials. The task was divided into five blocks including 230 trials each. It was ensured that all participants were well-trained and fully understood the instructions of the task before they began experiment. Participants rested their head on a table-mounted head-rest which fixed their distance at 60 cm from a 19-inch monitor for the duration of the task. The response device was a PS2 standard keyboard. Stimulus presentation was controlled by E-Prime software (Psychological Software Tools, Pittsburgh, PA, USA; version 2.0.8.90).

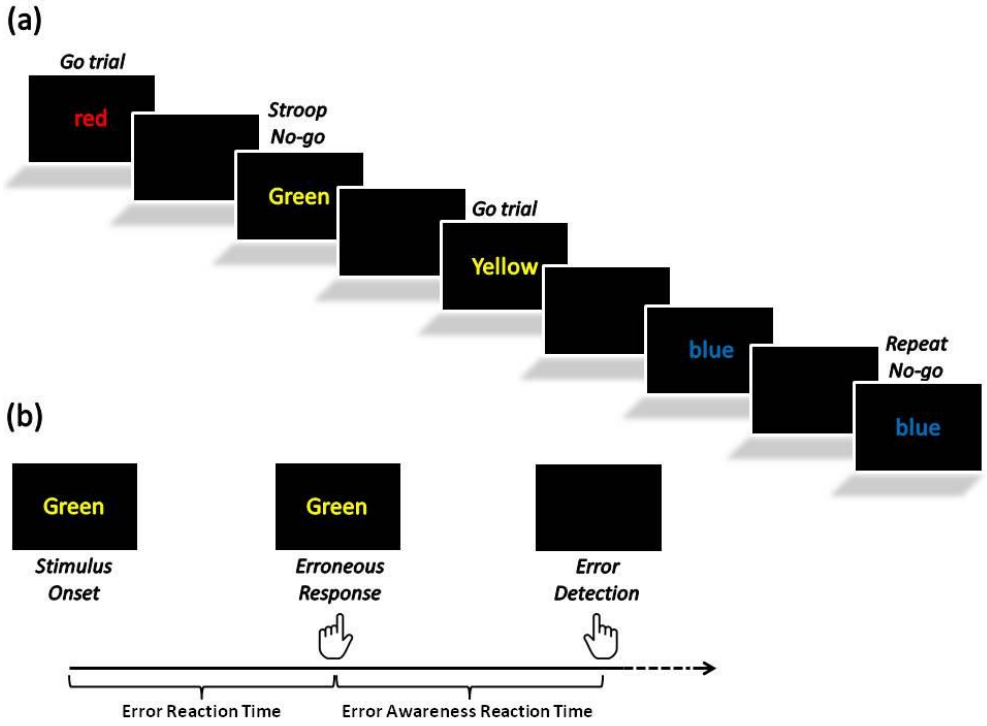

Figure 12 | A representation of the EAT. (a) A serial stream of single color words in which all the three kinds of trial are shown: Go trial, Stroop No-Go, and Repeat No-go. (b) This part of figure shows the typical scenario when a participant made an error and, afterwards, signaled it. In this case two measures were collected: error reaction time and error awareness reaction time.

TMS

TMS pulses were delivered via a Magstim Rapid^2 TMS stimulator (Magstim Company, Whitland, UK). A 70-mm figure-of-eight stimulation coil was fixed in space thanks to well-trained operators over target brain sites. In both the right and left DLPFC sessions the coil was oriented with the handle at 45° to the mid-sagittal line. In the Vertex session, the coil was positioned with the handle pointing backwards parallel with the midline. Since TMS over the frontal sites could be annoying, the intensity of magnetic stimulation was prudentially set 5% below the individual motor threshold. The intensity was estimated by the observed movement motor threshold (OM-MT) method (Pridmore, Fernandes Filho, Nahas, Liberatos, & George, 1998). The stimulation targets were identified with Brainsight frameless stereotaxic system (Rogue Research, Montreal, Canada) and spatial transformation was used to adjust the MRI template (the non-linear ICBM-152 template by the Montreal Neurological Institute) to individual head shapes. According to Cieslik and colleagues (2013), the coordinates of the right and left DLPFC were ±30, 43, 23 (MNI coordinates). Since one of the aims of the study was to confirm the involvement of the right DLPFC in error awareness, the

left DLPFC was a control area, as well as the Vertex. For this reason, we decided to target the left DLPFC by using the same coordinates we adopted to identify the right DLPFC (MNI coordinates: 30, 43, 23), but changing only the x-parameter (MNI coordinates: -30, 43, 23), a strategy to select a control site that has already been used in previous TMS studies (Herwig et al., 2003; Vallesi, Shallice, & Walsh, 2007). The Vertex corresponded to the Cz site of the international 10-20 system (Steinmetz, Fürst, & Meyer, 1989). The order of the stimulation sites was randomly assigned to each participant, for example, PARTICIPANT_1 (Session 1: right DLPFC, Session 2: left DLPFC; Session 3: Vertex), PARTICIPANT_2 (Session 1: left DLPFC, Session 2: right DLPFC; Session 3: Vertex), and so on. In total, in Experiment 1, we collected data from 60 TMS sessions (20 participants x 3 sessions).

During the task, pairs of TMS pulses (with 40 ms between the two pulses) were delivered with the aim to produce greater effects than spTMS, as previous studies reported (Bardi, Kanai, Mapelli, & Walsh, 2012; O'Shea, Muggleton, Cowey, & Walsh, 2004). This delay, as suggested in these two studies, guaranteed an adequate spatial resolution (longer delay would have reduced the spatial resolution of TMS). In order to investigate the time-course of error awareness, TMS pulses were delivered in two possible time windows after an error commission: 20-60 ms or 170-210 ms (figure 13).

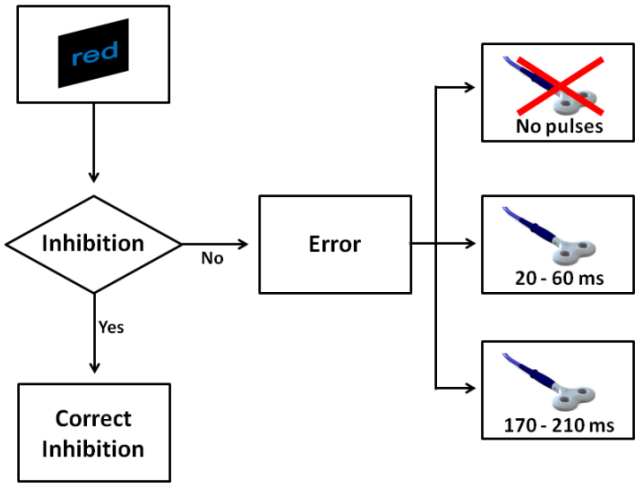

Figure 13 | The figure shows four possible scenarios after a No-go trial. If participant withheld the response, TMS was not delivered. Contrary, if participant committed an error, three scenarios could occur: (1) a couple of TMS pulses was delivered at 20 and 60 ms; (2) a couple of pulses was delivered at 170 and 210 ms; (3) no TMS pulse was delivered.

Furthermore, pairs of TMS pulses were also delivered at 110-150 ms after a correct response, so that participants avoided to associate TMS pulses with error commission.

Notably, TMS pulses were always triggered by a response, but not all the responses triggered TMS pulses. In fact, the delivery of TMS pulses was predetermined. Specifically, only 80% of No-go trials and 40% of Go trials triggered TMS pulses. Different percentages allowed maximizing the probability that an error was associated with TMS (80% of errors) and, on the other hand, reducing the probability that a Go response was associated with TMS (40% of Go trials), especially considering the different number of trials (150 No-go trials vs. 1000 Go trials).

Measures and data analysis

Error awareness - The *mean error awareness* was computed dividing the number of aware errors by the total number of errors (O'Connell et al., 2009). As in study 1, error awareness for Stroop and Repeat errors was computed separately. Therefore, we performed a repeated-measures 2 x 3 x 3 ANOVA *trial type* (Stroop Vs repeat), *timing of TMS pulses* (no pulse, 20-60 ms, and 170-210 ms), and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors. In this analysis, the sample size was reduced to 18 participants because 2 of them did not commit any repeat errors within some conditions of the analysis. Since the reduction of the sample size can increase the Type 2 error rate, we decided to conduct two different repeated-measures 3 x 3 ANOVAs, in order to evaluate separately the effect of TMS on Stroop and repeat errors.

The first 3 x 3 ANOVA (sample size: n = 20) considered only the Stroop errors with *timing of TMS pulses* (no pulse, 20-60 ms, and 170-210 ms) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors. The second 3 x 3 ANOVA (sample size: n = 18) took only the repeat errors into consideration, again with *timing of TMS pulses* (no pulse, 20-60 ms, and 170-210 ms) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors.

Error awareness reaction times - This measure was computed as the time between the erroneous response and its detection (figure 12). A repeated-measures 3 x 3 ANOVA was conducted with *timing of TMS pulses* (no pulse, 20-60 ms, and 170-210 ms) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors.

Mean reaction times and accuracy - *Mean reaction times* referred to correct responses and errors and they were analyzed in a repeated-measures 2 x 3 ANOVA considering *kind of response* (Go reaction times Vs error reaction times) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors. Finally, *accuracy* was calculated as the ratio of correct withholds on No-go trials. The *mean accuracy* was analyzed by a repeated-measures ANOVA with *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factor.

Before data analyses, reaction times above and below 2 *SD* from the mean were excluded and a logarithm transformation was applied on the remaining reaction times, in order to improve normalization. In every analysis, the Bonferroni correction for multiple comparisons was applied and a corrected alpha-level of 0.05 was considered. Finally, effect sizes were estimated by partial eta squared (η^2_p).

Results

The behavioral measures of Experiment 1 are presented in Table 4.

Table 4. Mean and standard deviation (*SD*) of performance indices on the EAT for right DLPFC, left DLPFC, and Vertex stimulation.

	Right DLPFC	**Left DLPFC**	**Vertex**
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Stroop awareness (%)	94 (10)	95 (10)	94 (10)
Repeat Awareness (%)	83 (10)	82 (20)	81 (20)
Error awareness reaction times (ms)	407 (95)	408 (94)	407 (92)
Go reaction times (ms)	471 (66)	482 (56)	479 (70)
Error reaction times (ms)	448 (56)	453 (55)	449 (62)
Accuracy (%)	51 (20)	52 (20)	52 (20)

Note: DLPFC, Dorsolateral prefrontal cortex.

Error awareness - The number of errors in each condition is shown in Table 5.

Results from the first 2 x 3 x 3 ANOVA showed a main effect of *trial type* [$F(1,17) = 13.8$, $p < 0.01$, $\eta^2_p = 0.4$]. As observed in study 1, participants were more aware for Stroop than Repeat

errors. No other main effect or interaction reached statistical significance (lowest *p*-value = 0.1). When we performed two separate repeated-measures 3 x 3 ANOVAs, both models did not reveal main effects or interactions (lowest *p*-value = 0.4).

Error awareness reaction times - This analysis did not show any effect of TMS on *error awareness reaction times* (lowest *p*-value = 0.3).

Table 5. Mean and standard deviation (*SD*) of the number of errors in each condition.

Condition	**Right DLPFC**	**Left DLPFC**	**Vertex**
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Errors	72 (30)	71 (25)	70 (30)
Stroop Errors	44 (17)	43 (12)	43 (16)
Stroop Errors_no pulse	7 (3)	7 (2)	7 (3)
Stroop Errors_20-60 ms_TMS	18 (7)	18 (5)	19 (7)
Stroop Errors_170-210 ms_TMS	18 (7)	18 (5)	17 (7)
Repeat Errors	29 (16)	28 (15)	27 (16)
Repeat Errors_no pulse	6 (3)	5 (3)	4 (3)
Repeat Errors_20-60 ms_TMS	11 (7)	11 (6)	11 (7)
Repeat Errors_170-210 ms_TMS	12 (7)	12 (6)	12 (7)

Note: DLPFC, Dorsolateral prefrontal cortex.

Reaction times and accuracy - The analysis of *mean reaction times* showed a significant difference between Go reaction times and error reaction times [$F(1,19) = 73.7$, $p < 0.001$, $\eta^2_p = 0.8$], indicating that error reaction times were faster than Go reaction times. No main effect or interaction with the factor *stimulation site* was found (lowest *p*-value = 0.3). Finally, no significant effect of TMS was found on *accuracy* (lowest *p*-value = 0.8).

Discussion

Contrary to our expectations, results of Experiment 1 showed no significant effect of paired-pulse TMS over either left or right DLPFC on error awareness. Although this evidence seems to not confirm a previous finding (Harty et at., 2014), namely the role of the right DLPFC in error awareness, alternative explanations could be involved to explain null results we found.

The first one could depend on the inadequacy of the target area. Thus, the right DLPFC may not be implicated in error awareness. Although this explanation is the most obvious, it should be carefully considered to avoid a false negative. In fact, Harty and colleagues (2014) confirmed the involvement of the right DLPFC in error awareness twice. A second plausible cause may derive from the stimulation paradigm we used in this experiment. This latter point needs a brief discussion of some nonspecific effects that TMS can produce.

TMS can produce a direct modification of brain activity through the depolarization of neurons. However, since TMS generates somatosensory sensations that can nonspecifically alter task performance (Robertson et al., 2003) it contributes partially to introduce noise, namely producing effects that are not strictly related to the brain site stimulated in a specific circumstance. In Experiment 1, participants may have moved their attention from the task to TMS pulses. In this experiment, the paradigm consisted of paired pulses delivered during the execution of the task. Although TMS is generally painless, it is plausible to suppose that paired pulses delivered during the execution of a task could have been perceived as annoying. In turn, this uncomfortable sensation may have increased the arousal of participants. This hypothesis is not new in literature because, among others, also Dräger and colleagues (2004) revealed an increase of arousal caused by TMS.

Taken together these considerations, we believed that a fruitful strategy to disambiguate confounding nonspecific effects of TMS from specific effects induced by this technique was to compare Experiment 1 with a second experiment in which TMS was not delivered.

Experiment 2

Method

Participants

In Experiment 2, 20 healthy participants were recruited. All participants were right-handed and had normal or correct-to-normal vision. Because of an unusual *mean error awareness* (< 30%), a participant was excluded from the analyses. As a result, the final sample consisted of

19 participants (5 men, 23.8 ± 3.3 years, range: 19-29). Each participant performed the EAT and received the same instructions as in Experiment 1. All participants were tested in one experimental session without TMS.

Measures and data analysis

Experiment 2 aimed to compare the behavioral measures collected from this experiment with the measures of Experiment 1. Since participants in Experiment 1 performed the EAT three times (once for each session), in order to avoid practice effect, we compared the behavioral measures of Experiment 2 with the measures at the first session of Experiment 1. For the sake of clarity, in Experiment 1, sites of stimulation in the first session were so distributed: right DLPFC (n=7), left DLPFC (n=7), Vertex (n=6).

Error awareness, error awareness reaction times, mean reaction times and accuracy from both experiments were compared by one-way ANOVAs with *group* (Experiment 1 Vs Experiment 2) as between-subject factor. As in Experiment 1, reaction times above and below 2 *SD* were not included in the analyses. Moreover, a logarithm transformation was used on the remaining reaction times, to increase normalization. A corrected alpha-level of 0.05 was considered in each analysis and the effect sizes were estimated by partial eta squared (η^2_p).

Results

The behavioral measures of both experiments are shown in Table 6.

Table 6. Mean and standard deviation (*SD*) of performance indices on the EAT for the first and second experiment.

	Experiment 1 - TMS (first session)	**Experiment 2 - no TMS**	
	Mean (*SD*)	Mean (*SD*)	*F*-values
Stroop Awareness (%)	93 (10)	91 (10)	0.6
Repeat Awareness (%)	82 (20)	79 (20)	0.3
Error Awareness reaction times (ms)	**445 (101)**	**503 (92)**	**4.3**
Go reaction times (ms)	515 (50)	496 (115)	1.2
Error reaction times (ms)	462 (50)	451 (116)	0.7
Accuracy (%)	53 (20)	58 (20)	0.5

Note: In bold, statistically significant differences between groups ($p < 0.05$).

The statistical analyses revealed that error awareness reaction times were different between groups, [$F(1,38) = 4.3$, $p < 0.05$, $\eta^2_p = 0.1$]. Participants in Experiment 1 were faster to signal their errors than participants in Experiment 2. The other one-way ANOVAs did not reveal differences between groups (lowest p-value = 0.3).

Discussion

In Experiment 2, participants performed the EAT without TMS. Measures from this experiment were then compared to measures from the first sessions of Experiment 1 (TMS experiment).

The comparison between experiment 1 and 2 shows an interesting result. Regardless of the stimulation site, in experiment 1 TMS induced a significant reduction of *error awareness reaction times*. This result highlights how TMS can interfere with performance in a nonspecific manner, namely inducing effects independently from the stimulation site. Corroborating this result, previous studies reported a speeding effect associated with TMS (Campen, Keuken, Wildenberg, & Ridderinkhof, 2013; Terao et al., 1997). Thus, this nonspecific TMS-induced effect on reaction times is not unusual.

However, how can TMS affect reaction times, independently from the stimulation site? A previous study may provide a response. In fact, Dräger and colleagues (2004) revealed that TMS can increase the arousal in participants involved in a task. Since a TMS pulse produces a noticeable sensation on the head and a clicking sound, it plausible to suppose that these somatosensory sensations could affect task performance, cause an attentional shift from the task to TMS and, furthermore, increase the arousal.

This previous evidence might support an explanation for null findings we found in Experiment 1. If this explanation was correct, in Experiment 1 the paradigm of stimulation may have increased the level of arousal, submerging any specific effect of TMS on error awareness. Thus, null results of Experiment 1 may depend on the inadequacy of the paradigm of stimulation. This consideration points out an important aspect that investigators should consider if interested to adopt TMS (or more in general NIBS) in their studies: a careful reflection about the chosen of the stimulation paradigm. In Experiment 1, we expected that the paradigm of stimulation would have maximized the behavioral effects of TMS on error

awareness (Bardi et al., 2012; O'Shea et al., 2004). Unfortunately, contrary to our expectations, the high number of pulses delivered during the task may have been the reason for the increase of the arousal, that in turn would have submerged specific effects of TMS. This consideration is plausible if considering that error awareness is particularly sensitive to arousal (Robertson, 2014; Shalgi et al., 2007).

Aside from this interpretation, two crucial questions are still open, because both Experiment 1 and 2 cannot shed light on brain regions involved in error awareness and its time-course. In fact, these experiments can only provide information about nonspecific effects that TMS induced in Experiment 1.

Thus, with the same purposes of Experiment 1, namely **to confirm the involvement of the right DLPFC in error awareness, as well as to investigate the timing of error awareness,** we decided to implement the third experiment, setting a paradigm of stimulation characterized by fewer pulses than the paradigm in Experiment 1, in order to minimize the hypothesized impact of the arousal on error awareness.

Experiment 3

Method

Participants

Twenty right-handed healthy individuals, with a normal or corrected-to-normal vision, participated in Experiment 3 (5 men, 24.6 ± 2.9 years, range: 21-31). The experimental design was the same of Experiment 1. Each participant took part in three sessions in three different days. The session was so planned: (1) a training phase to guarantee participants a good familiarization with the task; (2) a phase in which participants performed a full version of the task, namely the EAT (Hester et al., 2005), while on-line TMS was administered (figure 11). During each session, only a brain site was stimulated (e.g. Session 1: right DLPFC, Session 2: left DLPFC; Session 3: Vertex). All participants performed the EAT. Structure and instructions of the task were the same as Experiment 1 and 2.

TMS

TMS stimulator, type of coil, placing of the coil, and method to measure the individual motor threshold were identical to those of Experiment 1. In Experiment 3, the TMS intensity was set at 100% of the individual motor threshold, to increase a possible effect of TMS and also in the light that here the TMS protocol was overall less intensive than Experiment 1 (single pulse Vs paired pulse). In Experiment 3, we collected data from 60 TMS sessions (20 participants x 3 sessions).

Since the purposes were the same of Experiment 1, in Experiment 3 we maintained the same stimulation sites. Thus, the MNI coordinates of the right and left DLPFC were ±30, 43, 23 (MNI coordinates). Again, the control sites were the left DLPFC and the Vertex. In addition, in Experiment 3, the cortical location of sites was visually verified by Brainsight frameless stereotaxy (Rogue Research, Montreal, QC, Canada) on T1-weighted MRIs of 11 participants. Images were acquired using a 3-T Philips Ingenia whole-body scanner with a 32-channel head-coil at the Neuroradiology Unit, University-Hospital of Padova, Italy. MRIs were then registered to the MNI template. For the extra 9 participants, the localization of sites was based on individualized MRI template by a magnetic resonance-based head model, as all participants in Experiment 1.

Importantly, in Experiment 3, we maintained same procedures of Experiment 1, apart from the paradigm of stimulation. As mentioned before, in Experiment 3 we implemented a stimulation paradigm that we thought may be more suitable to investigate error awareness. In this case, to minimize a possible confound of nonspecific effects of TMS and to reduce the impact of a supposed increase of the arousal level induced by TMS, in Experiment 3 we adopted a single-pulse paradigm, instead of a paired-pulse. This paradigm of stimulation was characterized by an overall reduced number of TMS pulses per session (50%) than the paradigm adopted in Experiment 1. Similarly to Experiment 1, we delivered the pulse in two possible time windows: 50 ms or 200 ms after the commission of an error (figure 14). Furthermore, a spTMS was also delivered at 125 ms after a correct response. As in Experiment 1, the probability to receive a TMS pulse after an error was 80% and 40% after a Go trial.

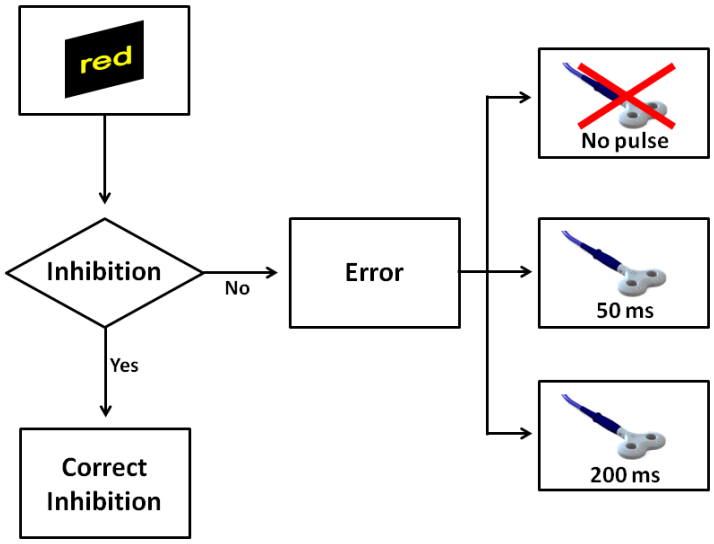

Figure 14 | The figure shows four possible scenarios after a No-go trial. Similarly to Experiment 1, if participant withheld the response, TMS was not delivered. However, unlike Experiment 1, in Experiment 3, if participant committed an error, three scenarios could occur: (1) a single pulse was delivered at 50 ms; (2) a single pulse was delivered at 200 ms; (3) no TMS pulse was delivered.

Measures and data analysis

Error awareness - The analyses on *error awareness* were the same as Experiment 1. Initially, an *omnibus* repeated-measures 2 x 3 x 3 ANOVA was conducted, with *trial type* (Stroop Vs Repeat), *timing of TMS pulses* (no pulse, 50 ms, and 200 ms), and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors. As in Experiment 1, this analysis yielded to a reduction of the sample size (n = 15) because 5 participant did not commit any Repeat commission errors within some conditions of the analysis. Therefore, exactly for the same reasons of Experiment 1, namely to avoid an increase of the Type 2 error rate, we evaluated separately the effect of TMS on Stroop and Repeat commission errors by means of two models. The first model, a 3 x 3 ANOVA (sample size: n = 20), considered only the Stroop commission errors with *timing of TMS pulses* (no pulse, 50 ms, and 200 ms) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors. Since this analysis showed a borderline significant interaction, we decided to reduce the model and collapse the factor *timing of TMS pulses* (no pulse, 50 ms, and 200 ms) in a dichotomous factor *TMS* (no pulse Vs TMS pulse). Finally, the second model, a 3 x 3 ANOVA (sample size: n = 15), included only the

Repeat commission errors, with *timing of TMS pulses* (no pulse, 50 ms, and 200 ms) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors.

Error awareness reaction times - A repeated-measures 3 x 3 ANOVA with *timing of TMS pulses* (no pulse, 50 ms, and 200 ms) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors was performed.

Reaction times and accuracy - *Mean reaction times* were analyzed in a repeated-measures 2 x 3 ANOVA considering *kind of response* (Go reaction times Vs error reaction times) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors. Finally, *accuracy* was analyzed by a repeated-measures ANOVA with *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factor.

As in Experiment 1 and 2, reaction times above and below 2 *SD* were excluded from the analyses and a logarithm transformation was applied on the remaining reaction times. The Bonferroni correction was applied to post hoc analyses. Effect sizes were calculated in terms of partial eta squares (η^2_p).

Results

The behavioral measures of Experiment 3 are summarized in Table 7.

Table 7. Mean and standard deviation (*SD*) of performance indices on the EAT for right DLPFC, left DLPFC, and Vertex stimulation.

	Right DLPFC	**Left DLPFC**	**Vertex**
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Stroop Awareness (%)	96 (0)	95 (10)	97 (10)
Repeat Awareness (%)	79 (10)	79 (20)	81 (10)
Error awareness reaction times (ms)	384 (82)	398 (89)	415 (76)
Go reaction times (ms)	462 (61)	467 (56)	458 (39)
Error reaction times (ms)	436 (46)	442 (42)	435 (36)
Accuracy (%)	58 (10)	55 (10)	58 (10)

Note: DLPFC, Dorsolateral prefrontal cortex.

Error awareness - The number of errors in each condition is presented in Table 8.

Table 8. Mean and standard deviation (*SD*) of the number of errors in each condition.

Condition	Right DLPFC	Left DLPFC	Vertex
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Errors	59 (20)	63 (18)	59 (20)
Stroop Errors	38 (11)	41 (10)	38 (11)
Stroop Errors_no pulse	5 (2)	5 (2)	5 (1)
Stroop Errors_50 ms_TMS	15 (4)	17 (3)	16 (4)
Stroop Errors_200 ms_TMS	17 (6)	19 (5)	16 (6)
Repeat Errors	21 (11)	21 (11)	21 (11)
Repeat Errors_no pulse	4 (2)	4 (3)	5 (3)
Repeat Errors_50 ms_TMS	9 (5)	8 (5)	7 (5)
Repeat Errors_200 ms_TMS	8 (5)	10 (5)	9 (5)

Note: DLPFC, Dorsolateral prefrontal cortex.

The first *omnibus* repeated-measures 2 x 3 x 3 ANOVA revealed a main effect of *trial type* [$F(1,14) = 37.4$, $p < 0.001$, $\eta^2_p = 0.7$]. As in Experiment 1, participants were more aware for Stroop than Repeat errors. No other main effect or interaction was found (lowest *p*-value = 0.3).

When we split this analysis into two different models, the first 3 x 3 ANOVA on Stroop errors shown a main effect of *timing of TMS pulses* [$F(2,38) = 8.1$, $p < 0.01$, $\eta^2_p = 0.3$]. The corrected paired sample comparisons indicated that participants were more aware when they did not receive any TMS pulse after an error commission (no pulse condition) than the condition in which the pulse was delivered at 200 ms after an error commission (respectively 98% Vs 95%; $t_{(19)} = 4$, $p < 0.01$) (figure 15).

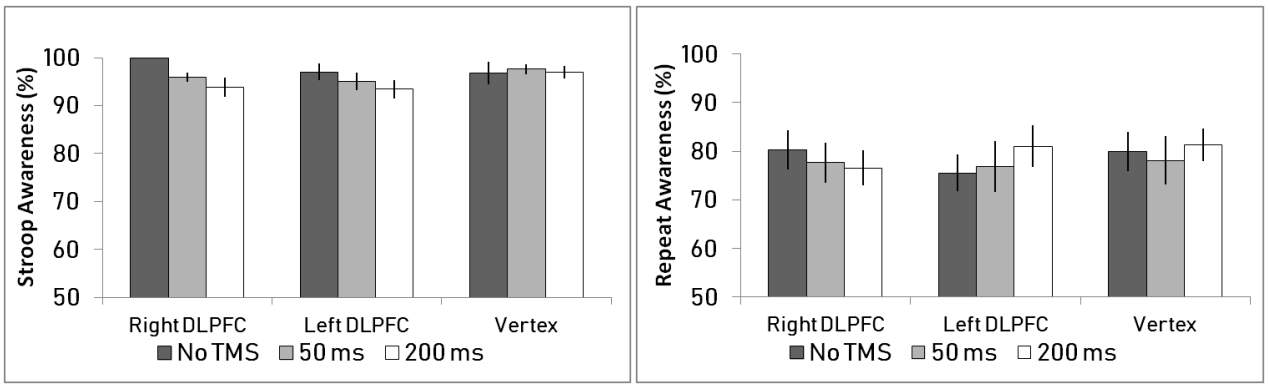

Figure 15 | The panel on the left refers to Stroop Awareness, whereas the panel on the right Repeat Awareness. Error bars represent standard errors of the mean.

No other main effect or interaction was found (lowest *p*-value = 0.1). However, after collapsing the factor *timing of TMS pulses* (no pulse, 50 ms, and 200 ms) in a dichotomous factor *TMS* (no pulse Vs TMS pulse), the analysis for Stroop Awareness showed a significant interaction between *TMS* x *stimulation site* [$F(2,38) = 3.61$, $p < 0.05$, $\eta^2_p = 0.2$]. Corrected paired sample *t*-tests indicated that the interaction was driven by a reduction of Stroop Awareness in both the right and left DLPFC stimulation sessions: participants were less aware for Stroop errors when they were stimulated on prefrontal sites than on Vertex (right DLPFC vs. Vertex: $t_{(19)} = 4.2$, $p < 0.01$; left DLPFC vs. Vertex: $t_{(19)} = 2.3$, $p < 0.05$), (figure 16).

The second 3 x 3 ANOVA on Repeat errors did not reveal any effect or interaction (lowest *p*-value = 0.5).

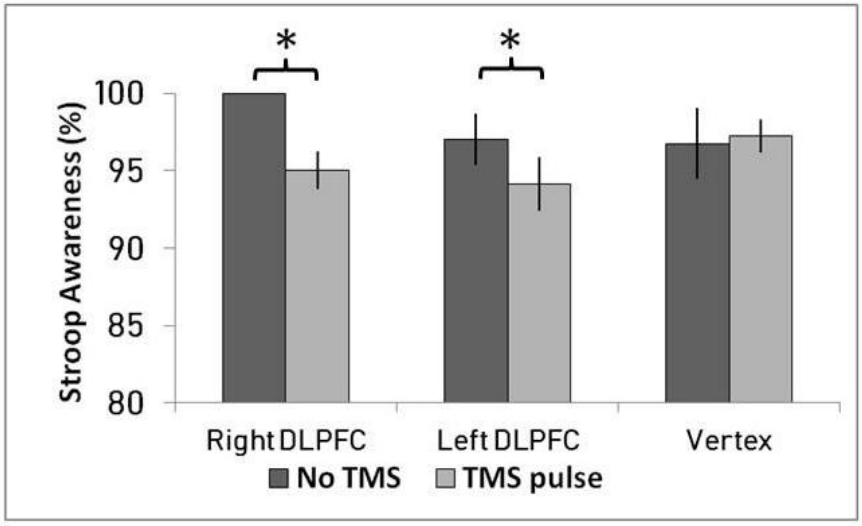

Figure 16| Figure shows Stroop Awareness (%) after collapsing the factor *timing of TMS pulses*. Error bars represent standard errors of the mean. Note: * ($p < 0.05$).

Error awareness reaction times - The analyses did not show any effect of TMS on *error awareness reaction times* (lowest *p*-value = 0.1).

Reaction times and accuracy - As expected, the analysis of *mean reaction times* revealed a significant main effect of *kind of response*, [$F(1,19) = 38.6$, $p < 0.001$, $\eta^2_p = 0.7$]. Error reaction times were faster than Go reaction times, as in Experiment 1. No main effect or interaction with the factor *stimulation site* was found (lowest *p*-value = 0.8). Finally, similarly to Experiment 1, no significant effect of TMS was found on *accuracy* (lowest *p*-value = 0.3).

Discussion

The general purposes of this study were to investigate the relationship between the right DLPFC and error awareness, as well as identify crucial time-windows within which this process occurs. With the aim to shed light on these aspects, on-line TMS was employed in two experiments.

In Experiment 1, results failed to confirm our hypothesis about an implication of the right DLPFC in error awareness. As above discussed, these null findings may have several explanations. Firstly, these null findings could depend on the target area, namely the right DLPFC. The most simple explanation consists in refusing an implication of this brain region in error awareness. Unfortunately, despite this explanation can be the easiest and the most convenient interpretation, other alternative views should be considered, especially because null findings in NIBS studies are frequent and a number of authors encourage to report and productively interpret null results (Munafò & Neill, 2016) so that they can methodologically guide the design of future TMS research (De Graaf & Sack, 2011).

In a previous study, Harty and colleagues (2014) had strongly demonstrated in two experiments the involvement of the right DLPFC in error awareness and this evidence encouraged us to search a different explanation for null findings revealed in Experiment 1. We thought that a plausible reason may depend on the inadequacy of the paradigm of stimulation used in Experiment 1. Interestingly, when we compared Experiment 1 with Experiment 2 results showed that in Experiment 1 TMS induced a reduction of *error awareness reaction times*, regardless the stimulation site. Thus, participants were surprisingly faster to signal their errors in Experiment 1 than in Experiment 2. This aspect could be ascribable to an increase of the arousal in participants that were stimulated with TMS. In fact, as confirmed in previous studies (Dräger et al., 2004; Terao et al., 1997), TMS can enhance the arousal level, inducing nonspecific effects on performance of a task.

An aspect we strongly stressed in this study is the fact that is reasonable to assume that in Experiment 1 the paired-pulse TMS paradigm may have maintained the participants' arousal high during the task because a paired pulse, constantly delivered on the head, is somehow an activating situation.

In order to control this nonspecific effect of TMS, in Experiment 3, a spTMS paradigm was employed. Experiment 3 was identical to Experiment 1, except form the paradigm of

stimulation. In fact, in Experiment 3, participants received only a single pulse instead of two, as in Experiment 1. We hypothesized that the spTMS paradigm could be a less arousal-inducing paradigm than the paired-pulse.

Of interest, Experiment 3 revealed an implication of the DLPFC in error awareness, without evidence for lateralization. Even if this finding was not generalized on error awareness, but only for Stroop Awareness, it provides two important evidence: firstly, we confirm an involvement of the DLPFC in error awareness, secondly, both the right and left DLPFC seem implicated in error awareness. The study of Harty and colleagues (2014) depicted a different scenario because they found a selective role of the right DLPFC in error awareness. However, considering they used another technique, namely tDCS, different results are not so surprising. In fact, TMS and tDCS differ from their spatial resolution (Priori, Hallett, & Rothwell, 2009), physical, and physiological effects (Miniussi et al., 2013). Furthermore, in their study, the sample was composed of older adults, whereas in the present study our samples were composed of younger people. The age difference may contribute to explain the difference in terms of effect size between these studies. In fact, while in our study we evidenced a small effect of TMS, Harty and colleagues (2014) showed a strong modulation of tDCS on error awareness. Taken together these differences, we suppose that it may be easier to modulate (improve) error awareness in older adults, in which error awareness is normally reduced (see study 1) than to modulate the process in younger adults that present higher level of error awareness. Moreover, it should be considered that tDCS induces a more diffuse brain modulation (Bikson et al., 2010; Datta et al., 2009; Lang et al., 2005) compared to the TMS stimulation. This aspect can account for the difference in terms of modulatory effects between Harty's study and the present study.

Regarding the second objective of the study, namely to provide evidence about specific time windows within which error awareness would occur, neither Experiment 1 nor Experiment 3 showed significant results. A possible explanation may rely on the fact that the pulse timings were delivered too late after the commission of an error.

In this study some limitations should be considered. In fact we must acknowledge that other possible explanations may apply to the null result found in Experiment 1, besides the nonspecific increase of the arousal we suggested. For example Experiment 1 and 3 differed for the intensity of stimulation. In Experiment 1, it was lower than Experiment 3 (95% of participants' motor threshold, instead of 100%). Although weak, this difference may have

affected our results. Second, a potential limitation of the study concerns the theoretical comparison between Experiment 1 and 3. In fact, the paired-pulse and the single-pulse on-line TMS paradigm we employed were substantially different and, also in the case we had found similar effects of TMS, it would have been difficult to disambiguate any effect, especially because the paradigms were characterized by different timing. Finally, and more important, in Experiment 3 we only found a small effect of TMS on Stroop Awareness, instead of a generalized effect on error awareness.

Conclusion

Although the purposes of study 2 did not completely achieve, this study contributes to shed light on error awareness. In fact, results show that the right and left DLPFC are implicated in this process. Moreover, study 2 raises an important issue that deserves to be discussed: subtle changes in stimulation parameters can lead to different results. In Experiment 1 we saw how a paired-pulse paradigm failed to modulate error awareness. The only modification achieved was nonspecific and certainly did not concern an area-related modulation. However, through a simple modification of the paradigm, we observed that in experiment 3 a single-pulse paradigm was able to produce a modulation of error awareness, in line with our expectations.

Nowadays, TMS is widely used as a treatment for neurological and psychiatric disorders. Its applications cover several disorders such as, among others, depression, obsessive-compulsive disorder, schizophrenia, Parkinson's disease, aphasia, attentional disorders, memory deficits, dystonia (writer's cramp), epilepsy and related disorders, and tic disorder. Although TMS is a versatile method highly used in clinical contexts, a consensus about which parameters of stimulation and target brain areas are recommended for effective treatments is not still reached. Actually, only in the treatment of major depressive disorder, the effort of research seems to converge toward a consensus. In fact, the most effective treatment consists in the high frequency stimulation (around 10 Hz) of the left DLPFC, for a period of 4-6 weeks (Perera et al., 2016). Obviously, this goal has been achieved thanks to a powerful research focused on the study of depression treatment by using unconventional techniques, such as TMS. For example, in the last few years, fifteen meta-analyses have confirmed the

efficacy of TMS in the treatment of depression, as well as a number of systematic reviews (Perera et al., 2016).

In light of our results, we wish to stress the fact that small variations in the parameters can induce null or unpredictable effects. Therefore, the use of TMS in clinical settings requires careful consideration of the choice of parameters.

Finally, another point relative to possible cognitive side effects of TMS, or more in general NIBS, should be argued. As highly discussed, NIBS is a set of methods able to modulate behavior and brain functioning in a safe manner, by respecting of guidelines on these methods, of course. Although in the past investigators have focused their studies on safety and physical side effects of NIBS (Poreisz, Boros, Antal, & Paulus, 2007), few studies have studied possible cognitive side effects of NIBS. For example, in a recent study, Iuculano & Cohen Kadosh (2013) showed that cognitive enhancement induces by tES can occur at the expense of other cognitive functions. Thus, although the enhancement of cognitive function is an intriguing and promising tool in neuroscience, at the same time it is naive to think that modulation of a process produces only positive effects without, for example, to trigger forms of maladaptive plasticity.

Taken together these considerations underline the necessity, somehow, to monitor the effects of NIBS. Most NIBS studies use only behavioral measures to evaluate the effects of these techniques. For example, in clinical field, can a questionnaire consisting of a handful of items be considered a sufficient method to assess the impact of NIBS on the investigated disorder? The disadvantages of using only behavioral measures concerns the impossibility of: (1) to highlight neural modulation, even in the absence of behavioral modulation; (2) to investigate the neural mechanisms underlying a possible behavioral modification.

In recent years, thanks to a growing improvement of neuroscientific techniques, an interesting approach allows combining NIBS with other methods such as fMRI, PET, and EEG. The combined use of NIBS and neuroimaging techniques, namely coregistration, is a promising tool because it can compensate for the limits of neuroimaging techniques and *vice-versa*, as well as to provide further evidence about the functioning of NIBS.

As already argued, one of the most unsolved aspects of TMS regards its complex physiological mechanisms. Despite the widespread use of TMS in research, its underlying mechanisms of action are poorly known and, crucially, behavioral measures are not sufficient to investigate the effect of

TMS on brain functioning because they leave unsolved several questions. For this reason, neuroimaging techniques can help to understand how TMS modulates the brain. Moreover, coregistration is crucial because allows investigating several aspects of the same process, by collecting data from different sources (e.g. behavioral and electrophysiological data).

To conclude, despite the widespread use of TMS, many questions are still opened and need answers. Research into clinical applications for TMS requires important research efforts in order to assess the effectiveness of the technique and to develop standardized protocols that can maximize the adaptive plasticity mechanisms and to avoid maladaptive plasticity mechanisms. A promising solution may involve coregistration between TMS and other neuroscientific techniques.

Chapter 6

Study 3 - Modulation of error-related processes: a combined TMS-EEG study

Introduction

Study 2 was aimed at modulating error awareness through on-line TMS protocols. The generated modulation was weak, with a small effect size. This could be due to the use of a single-pulse or a paired-pulse paradigm, which were not able to produce a sufficient effect on brain activity. In order to cope with this limitation in the present study an off-line rTMS protocol was adopted. A prominent advantage of TMS is that the effects of every single pulse or single-train can summate with repeated application, leading to long-lasting effects (Hallett, 2007; Ridding & Rothwell, 2007; Rossi & Rossini, 2004). For this reason, rTMS is used to transiently modulate brain functions beyond the time of stimulation. This stimulation protocol would have contributed to maximize the effect of TMS, in terms of modulatory effects, and to avoid nonspecific effects induced by on-line paradigms. Importantly, in the present study, in order to better quantify the modulatory TMS effects, the EEG signal was recorded soon after the rTMS session, simultaneously with the task execution. Therefore, in study 3, besides the classical behavioral measures already analyzed in this dissertation (i.e. error awareness and PES), included neurophysiological measures. Specifically, we combined TMS with EEG technique, in order to investigate TMS-induced brain modulation of error-related processes.

We have seen in previous chapters that our everyday life is scattered by minor errors that do not generally produce significant consequences. James Reason defined these errors “slips”, pointing out all kinds of minor errors characterized by a mismatch between the execution of an action and a planned action (Reason, 1990). However, also a minor error can have important consequences, for example, a driving distraction. Thus, it is not surprising that human error has broadly investigated by several subjects, such as Cognitive Science, Psychology, and Neuroscience.

These disciplines have studied human error from different points of view, through the use of own methodologies and techniques. Nevertheless, what these different approaches share, it is

probably the focus on which they have addressed their attention. Since an error is a distinct event occurring at a precise time, we can distinguish, somehow, two lines of research: (1) studies that investigate antecedents of an error, that are the causes of the error itself, and (2) studies that examine the consequences after an error, namely the impact and the effects an error produces within a system or the reaction of a system following an error. In particular, related to this last line of research, Psychology and Neuroscience have broadly studied the behavioral and neural effects following the commission of an error.

At a behavioral level, an interesting aspect concerning the commission of an error is its detection. We have described this phenomenon in previous chapters. Although a clear definition of error awareness is not present, in the literature error awareness seems to be considered both a metacognitive process (Dockree, Tarleton, Carton, & FitzGerald, 2015; N. Yeung & Summerfield, 2012), and/or a component of executive functions (Simões-Franklin, Hester, Shpaner, Foxe, & Garavan, 2010).

Another interesting behavioral phenomenon, already described in 1966 by Rabbit and colleagues, evidences how the responses associated with a correction of an error are faster than the correct responses (Rabbitt, 1967; Rabbitt, 1966, 1968). Moreover, individuals generally tend to slow down their response on the next trial after committing an error (Rabbitt, 1966). As previously discussed, this phenomenon, highly investigated in the literature, is known as PES (Danielmeier and Ullsperger, 2011; Ullsperger et al., 2014).

From the neural perspective, a rich corpus of EEG studies has investigated the electrophysiological correlates of error monitoring (see Chapter 3). Two ERPs seem particularly involved in error monitoring. The first one, the ERN, occurs at or shortly before an erroneous response and peaks around 50-100 ms after. The ERN has a frontocentral radial voltage distribution on the scalp (Falkenstein et al., 1991; Gehring et al., 1990). Immediately after the ERN, a second positive potential emerges between 200-400 ms after error onset, which is called the Pe. The scalp distribution of the Pe shows a maximum at centroparietal sites (Falkenstein et al., 1991; Overbeek et al., 2005). Several authors found a relationship between the behavioral and ERP correlates of error monitoring: PES seems positively correlated to the Pe (Hajcak et al., 2003; Nieuwenhuis et al., 2001; Overbeek et al., 2005) and, unlike the ERN, the Pe is also strongly observed when an individual detects an error (Endrass et al., 2007; O'Connell et al., 2007; Overbeek et al., 2005).

Although a large piece of knowledge has made possible to understand the effects of an error on our behavior or on the brain, few studies have tried to directly modulate these error-related processes. With regard to PES and error awareness, two studies have succeeded in producing an increase in these processes. In particular, Sellaro and colleagues (2015), by applying transcutaneous vagus nerve stimulation, observed an increase in PES in healthy young individuals, whereas Harty and colleagues (2014) increased error awareness through the use of tDCS in a group of elderly.

As behavioral measures, ERP correlates of error monitoring have been found to be sensitive to NIBS. For example, Rollnik and colleagues (2004) produced a modulation of the ERN and the Pe by means of TMS. In this study, the authors showed how a low-frequency (0.9 Hz) rTMS on medial frontal regions produced a reduction of the ERN amplitude and an increase of the Pe. The authors suggested that the stimulation of the medial frontal regions can have modulated a crucial area associated with the ERN, namely the ACC. Unfortunately, we think that by means of a conventional figure-of-8 coil is pretty improbable to directly modulate deep brain areas such as the ACC.

Taken together, these studies suggest the possibility to modulate error-related processes also in the clinical context, where such processes seem impaired (Klein et al., 2013; Larson, Perlstein, Demery, & Stigge-Kaufman, 2006). However, so far the absence of a strong evidence does not allow defining which approach can be the best choice to modulate error-related processes. In fact, no standardized areas and protocols have been identified and, consequently, future studies are necessary to shed light on this important aspect.

The main purpose of study 3 was the modulation of error-related processes through a low-frequency rTMS paradigm. We opted for a low-frequency rTMS paradigm with the aim of inhibiting the processes associated with error commission. In particular, a 1-Hz rTMS protocol is known to reduce cortical excitability in targeted brain areas for several minutes after the end of stimulation (R. Chen et al., 1997). Specifically, we targeted the DLPFC bilaterally. This regions has been shown to be involved both in error awareness (Harty et al., 2014; Masina et al., 2018b) and in PES (Kerns et al., 2004; Magno, 2006; Mansouri et al., 2016). However, the exact role of this area in error processing is still unclear and, as far as we know, its contribution to error-related ERPs has not been investigated yet. Our working hypothesis was that if the DLPFC contributes to

the error awareness process the low-frequency rTMS paradigm would have produced fewer aware errors and/or reduced PES. Simultaneously, the stimulation would have induced an attenuation of the error-related potentials, namely of the ERN if the DLPFC acts on earlier stage of error detection, of the Pe if it intervenes at later stages.

Method

Participants[3]

Fifteen right-handed healthy participants aged 20-34 (mean = 24.3; SD =3.6) were included in this study (9 females). All participants had normal or corrected-to-normal visual acuity. Exclusion criteria were a history of neurological or psychiatric diseases, and use of neurological or psychiatric medications. Moreover, before experiment, participants gave their written informed consent and were checked for TMS exclusion criteria (Rossi et al., 2011). The adopted safety procedures were in line with the guidelines for the use of TMS (Rossi et al., 2009). The study was approved by the Ethics Committee of School of Psychology, University of Padua. The experimental procedure was in accord with the ethical principles of the 1964 Declaration of Helsinki.

TMS

Repetitive TMS was performed using a Magstim Rapid^2 TMS stimulator (Magstim Company, Whitland, UK) with a 70-mm figure-of-eight stimulation coil. The stimulation targets were identified with Brainsight frameless stereotaxic system (Rogue Research, Montreal, Canada) and the position of the coil was maintained in real-time by the optical tracking system Polaris Vicra (NDI, Waterloo, Canada).

EEG

[3] Post-hoc power analysis has demonstrated that in study 3 the power was pretty low (0.7). This should be recognized as a limitation of study 3. However, as Luck (2005) explains, ERP experiments with a homogeneous group in terms of cognitive abilities, generally cooperative and able to stay focused on the task, usually have an N of 12-16 subjects per experiment.

The EEG signal was recorded by means of 64 Ag/AgCl sintered electrodes mounted on an elastic cap according to the International 10-20 system (EASYCAP GmbH, Germany). Compared to standard electrodes, they are specifically designed to be compatible with TMS. Their material and C-shape avoid overheating during stimulation and eliminates any risk for participants. Furthermore, their thickness is thinner than standard ones (i.e., < 4 mm), reducing the space between the TMS coil and participant's scalp (figure 17). The cap was connected to an AC amplifier (Micromed SD MRI, Micromed Srl., Mogliano Veneto, Italy). The amplifier was optically connected to a PC and Brain-Quick System Plus software allowed monitoring EEG during every session.

The EEG recordings were referenced to FCz electrode, while the ground electrode was placed on AFz. The sampling frequency was 512 Hz.

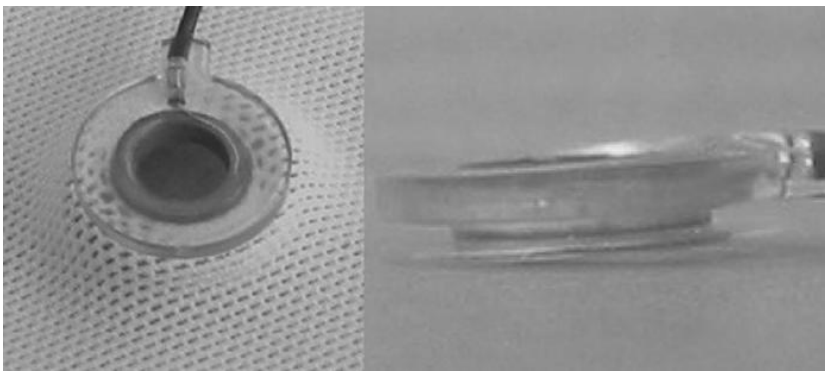

Figure 17 | An example of an electrode mounted on the EEG recording system.

Task

During EEG recording, participants performed an adapted version of the EAT (Hester et al., 2005). In this task, a serial stream of single color words was presented at the center of the screen on a gray background. Participants were trained to respond as fast and accurate as possible (without to prioritize speed or accuracy), with a single-speeded press (“3” on the keyboard), when the word and its color form were congruent (Go trial). They were asked to withhold this response when the word and its color font were incongruent (Stroop No-Go trial), or when the word was presented in two consecutive trials (Repeat No-Go trial). In case that participants failed to withhold their responses in either No-Go conditions (Stroop and Repeat), they were instructed to signal as soon as possible the error commission by pressing a different button (the space bar). In line with the study 2, we measured the timing of error awareness (error awareness reaction time), namely

the interval between the onset of an error and its signaling.

Accordingly with the previous study, in order to maintain the number of errors between participants as similar as possible, we adopted an adaptive staircase approach. Specifically, the task difficulty was based on the participants' accuracy on No-go trials. We manipulated the duration of ISI so that the time required to retain the previous word was modulated as a function of accuracy. By means of this manipulation, longer ISIs would have induced more commission errors on repeat trials. At the beginning of the task, the word was presented for 200 ms with an ISI of 1800 ms. ISI durations could change according to three scenarios: (1) if the accuracy was below 50%, the ISI duration was set at 1700 ms; (2) if the accuracy was higher than 60%, the ISI duration was set at 2000 ms; (3) if the accuracy was between 50% and 60%, the ISI duration was set at 1800 ms, as at the beginning of the task. During the task, this check of accuracy was computed after each No-go trial. The task was divided into two equal blocks and each block lasted 10 minutes. The total number of trials in the task was 668, specifically 468 Go trials, 100 Repeat No-go trials and 100 Stroop No-go trials. Participants rested their head on a table-mounted head-rest which fixed their distance at 60 cm from a 19-inch monitor for the duration of the task. Stimulus presentation was controlled by E-Prime software (Psychological Software Tools, Pittsburgh, PA, USA; version 2.0.8.90).

Procedure

Each participant was involved in three sessions, carried out on different days. The study was divided into three sessions because a different brain site was stimulated by the TMS during each session. In order to ensure an appropriate washout period, at least 24 hours had to pass in between two sessions. The stimulation sites were the right DLPFC, the left DLPFC, and the Vertex. The order of the stimulation sites was randomly assigned to each participant, in order to control for training and fatigue effects or at least to avoid systematic influences of these effects in our experimental design (e.g., Participant_1: I session-right DLPFC, II session-left DLPFC, III session-Vertex; Participant_2: I session-Vertex, II session-left DLPFC, III session-right DLPFC ... and so on). Overall, each session was divided into three phases: (1) task training; (2) EEG cap placement and rTMS; (3) task during the EEG recording (figure 18).

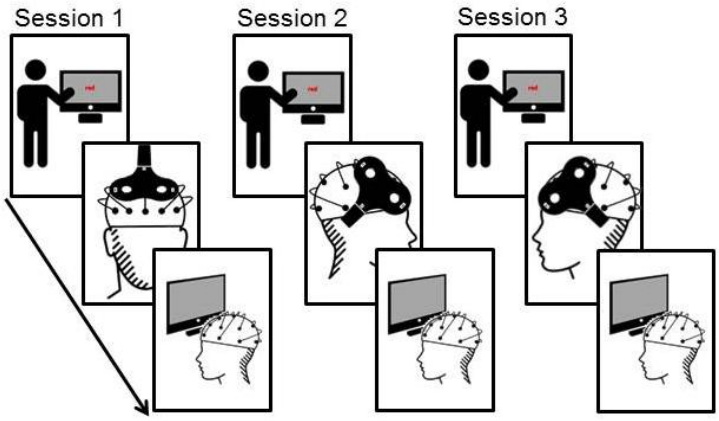

Figure 18 | An example of experimental session where the order of the stimulation sites were Vertex, right DLPFC, and left DLPFC is depicted.

In the first phase (task training), it was ensured that all participants were well-trained and fully understood the instructions of the task. In this phase, participants performed a short version of the task that lasted 5 minutes. Furthermore, participants familiarized with TMS. Some TMS pulses were delivered so that participants could experience the somatic somatosensory sensation and the clicking sound that TMS produces.

In the second phase (EEG placement and TMS), the EEG cap was placed on participants' head. Electrode impedances were kept below 5 kΩ. Afterward, the participants' resting motor threshold (RMT) was determined in line with the standardized procedure (Rossini et al., 2015).

Afterward, the stimulation targets were identified with Brainsight frameless stereotaxic system (Rogue Research, Montreal, Canada) and spatial transformation was used to adjust the MRI template (the non-linear ICBM-152 template by the Montreal Neurological Institute, MNI) to individual head shapes. According to Cieslik and colleagues (2013), the MNI coordinates of the right DLPFC were 30, 43, 23, whereas the MNI coordinates of the left DLPFC were -30, 43, 23. The position of the Vertex was the Cz site of the International 10-20 system.

Finally, rTMS was administered over the stimulation site, randomly chosen for that session. Stimulation parameters were frequency of 1 Hz, 0.1-millisecond pulse duration, and field intensity of 90% of RMT. In total, in each session, 1200 TMS pulses were delivered for 20 minutes. During the stimulation, the coil was oriented with the handle at 45° to the mid-sagittal line, when the right and left DLPFC were stimulated. In the Vertex session, the coil was positioned with the handle pointing backwards parallel with the midline.

In the third phase (task during the EEG recording), at the end of the stimulation, we ensured the impedance was still below 5 kΩ. Only after this check, the EEG was recorded while participants performed the task. The shortest interval passed between the stimulation and the beginning of the EEG recording, in order to ensure that possible modulatory effects of TMS were present while participants performed the EAT.

Behavioral analysis

Participant's performance was evaluated in terms of reaction times, accuracy, error awareness and PES.

Reaction times and accuracy - Reaction times below 100 ms were removed. A repeated-measure 2 × 3 ANOVA was performed, with *response type* (correct vs. error) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within subjects variables. Accuracy (withholding accuracy) was analyzed by a repeated measures ANOVA with *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within subjects factor.

Error awareness - Mean error awareness was calculated as the percentage of correctly signaled commission errors on the total number of commission errors (O'Connell et al., 2009). Error awareness for commission errors on Stroop and Repeat trials was computed separately since previous studies using the EAT have found higher error awareness for Stroop compared with Repeat errors (Harty et al., 2014; Hester et al., 2009; O'Connell et al., 2007). Therefore, a repeated-measure 2 x 3 ANOVA with *trial type* (Stroop vs Repeat) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors was conducted.

Error awareness reaction times - A repeated-measures ANOVA with *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factor was performed.

Post-error slowing - This index was computed according the Dutilh method, namely by the difference in reaction times between post-error trials and the associated pre-error trials (Dutilh et al., 2012).

Unaware errors were excluded from the analyses of PES as well as reaction times under 100 ms. We performed a mixed 2 x 2 x 3 ANOVA with *response* (post vs. pre No-Go target response), *target response* (aware error vs. correct inhibition) and *stimulation site* (right DLPFC, left DLPFC, and Vertex) as within-subject factors.

The Bonferroni correction was always applied to multiple post-hoc analyses and a corrected alpha-level of 0.05 was considered. Finally, effect sizes were estimated by partial eta squared (η^2_p).

ERP analysis

Data were offline analyzed using custom routines in EEGLAB v14 (Delorme & Makeig, 2004) running on Matlab R2017b (The Mathworks Natic, MA, USA).

The continuous EEG trace was filtered with a windowed sinc FIR filter, with a cut-off frequency 40 Hz, a Kaiser Window type with a beta of 5.65, a maximum passband deviation of 0.01 and a transition band of 20 Hz. To visually inspect stimulus-locked waveforms, epochs from 200 before and 2150 ms after stimulus onset were extracted from the continuous EEG signal. Baseline correction was performed by subtracting the mean voltage of a window from 200 to 0 ms before the stimulus onset. In response-locked analysis, epochs from 200 before and 1000 ms after the response (when participants pressed "3" on the keyboard) were extracted from the continuous EEG signal. Baseline correction was performed by subtracting the mean voltage of a window from 200 to 100 before the response onset. Epochs contaminated with artifacts (eye blinks and muscle activity) were identified using the independent component analysis (ICA) function on EEGLAB. The identified components were visually inspected in terms of scalp distribution, frequency, timing and amplitude and removed with ICA (Chaumon, Bishop, & Busch, 2015). Unaware errors were excluded from the analyses because an insufficient number of trials allowed a reliable analysis. Since participants made more than 5 aware errors in each condition, the ERN and Pe could be quantifies (Olvet & Hajcak, 2008; Pontifex et al., 2010). Finally, data was re-referenced off-line to the mean of channels.

The ERN was defined as the most negative deflection from -50 ms to 0 ms from the erroneous button press. Since the ERN is typically distributed over fronto-central regions (Falkenstein et al., 1991; Gehring et al., 1990), the ERN amplitude was examined over the FCz electrode site; furthermore, the scalp distribution of the component was confirmed by means of topographical maps. For statistical analysis, in order to evidence difference related to the stimulation site, we

performed point-by-point ANOVAs on the entire epoch, from 200 before and 1000 ms after the response.

The Pe was defined as the most positive deflection after an erroneous button press. Since the Pe is typically distributed over central regions (Falkenstein et al., 1991; Overbeek et al., 2005) , the Pe was analyzed at electrode Cz. Topographical maps confirm the scalp distribution of the Pe. In line with the analysis on ERN, to evidence difference related to the stimulation site, we performed ANOVAs on the entire epoch.

If Mauchly's Sphericity Test indicated that the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied.

Results

Behavioral analysis

Reaction times and accuracy - The mean of reaction times and accuracy are shown in Table 9. The 2 (*response type*) × 3 (*stimulation site*) ANOVA on reaction times showed a main effect of *stimulation site* [$F(2,28) = 3.9$, $p < 0.05$, $\eta^2_p = 0.2$]. Post-hoc comparisons showed that participants were slower when rTMS was administered on the right DLPFC than the left DLPFC, regardless their response (571 ms vs. 526 ms; $p < 0.05$). No other main effect or interaction was found. As regards *accuracy*, the analysis did not show significant differences.

Error awareness - The mean percentage of error awareness is presented in Table 9. The 2 (*trial type*) x 3 (*stimulation site*) ANOVA, revealed a main effect of *trial type* [$F(1,14) = 31$, $p < 0.001$, $\eta^2_p = 0.7$]. The post-hoc comparisons indicated that participants signaled more often a commission error on a Stroop trial than on a Repeat trial (98% vs. 71%; $p < 0.001$). This model did not reveal a significant effect of *stimulation* site.

Table 9. Mean and standard deviation (*SD*) of performance indices on the EAT for right DLPFC, left DLPFC, and Vertex stimulation.

	Right DLPFC	**Left DLPFC**	**Vertex**
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Accuracy (%)	86 (6)	84 (6)	84 (6)
Stroop Awareness (%)	98 (5)	99 (3)	97 (5)
Repeat Awareness (%)	71 (22)	69 (21)	72 (30)
Go reaction times (ms)	574 (65)	532 (51)	553 (66)
Error reaction times (ms)	567 (68)	519 (73)	537 (91)
Error awareness reaction times (ms)	500 (75)	475 (115)	461 (98)
Post-error reaction times (ms)	592 (69)	550 (55)	577 (71)
Pre-error reaction times (ms)	570 (55)	532 (63)	535 (72)
Post-inhibition reaction times (ms)	550 (63)	511 (53)	528 (68)
Pre-inhibition reaction times (ms)	562 (60)	507 (67)	530 (76)

Note: DLPFC, Dorsolateral prefrontal cortex.

Error awareness reaction times - The repeated-measure (*stimulation site*) ANOVA did not reveal a significant effect of *stimulation site*.

Post-error slowing - The mean of reaction times following and prior to an aware error and a correct inhibition are shown in Table 9. The 2 (*response*) x 2 (*target response*) x 3 (*stimulation site*) ANOVA showed a main effect of *response* [$F(1,14) = 13$, $p < 0.01$, $\eta^2_p = 0.5$], *target response* [$F(1,14) = 12$, $p < 0.01$, $\eta^2_p = 0.5$], and *stimulation site* [$F(2,28) = 3.7$, $p < 0.05$, $\eta^2_p = 0.2$]. The post-hoc comparisons indicated that reaction times following a No-Go trial were slower than reaction times prior to a No-Go trial (551 ms vs. 539 ms; $p < 0.01$). Moreover, reaction times were slower, without a distinction between post and pre No-Go target response, when participants committed an error than a correct inhibition (559 ms vs. 531 ms; $p < 0.01$), and slower when rTMS was administered on the right DLPFC than the left DLPFC, (568 ms vs. 525 ms; $p < 0.05$). Finally, a *response x target response* interaction was found [$F(1,14) = 12.2$, $p < 0.01$, $\eta^2_p = 0.5$]. This interaction confirmed a PES effect, namely a slowing after an aware error (post-error reaction times = 573 ms vs. pre-error reaction times = 530 ms; $p < 0.001$), without to evidence a difference after a correct inhibition (post-inhibition reaction times = 546 ms vs. pre-inhibition reaction times = 533 ms; $p = 0.26$).

ERP analysis

Grand average stimulus-locked ERP waveforms at electrode Cz as a function of response (correct response, inhibition, error) and stimulation site (right DLPFC, left DLPF, Vertex) revealed differences between the waveforms (figure 19).

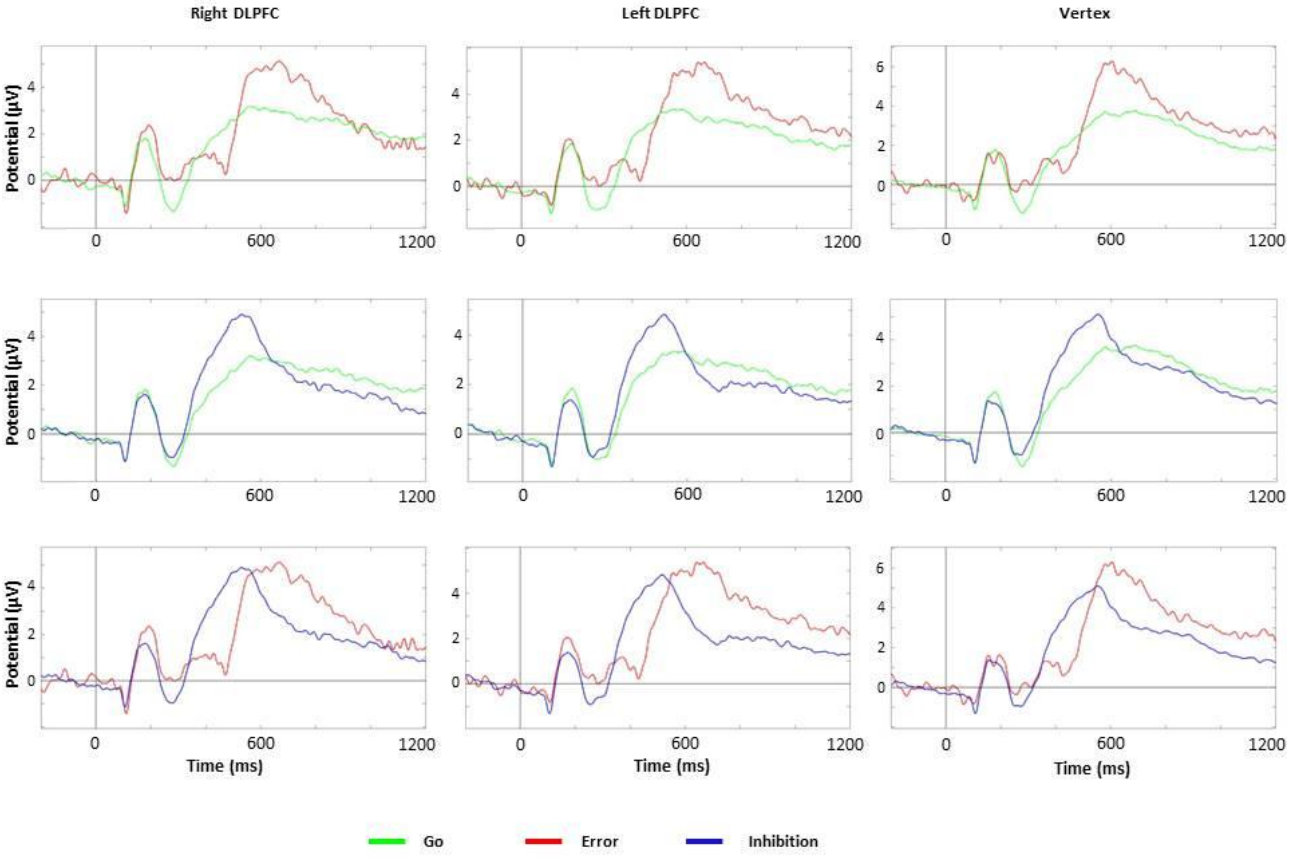

Figure 19 | Stimulus-locked ERP data at electrode Cz (the zero point corresponds to stimulus onset). Grand average waveforms for correct responses (green line), inhibitions (blue line), and aware errors (red line).

As shown, a large difference emerged between the ERPs evoked by erroneous responses and the ERP evoked by correct responses (Go trials) or inhibitions (No-go trials). A negative deflection is present around the time point of erroneous button press, not in the correct responses or inhibitions. This deflection represents the ERN potential. Afterwards, a positive deflection emerged, only on erroneous trials, which reach up to 7 V amplitude on average and that represents the Pe potentials. The visual inspection of topographical maps of these two components showed that, in line with literature, the ERN had a more fronto-central distribution,

especially localized over FCz (see Figure 20B), whereas the Pe had more central distribution, especially localized over Cz (see Figure 21B).

Grand average response-locked ERP waveforms and scalp topographies of the ERN and Pe components are shown in Figure 20A and 21A, respectively. As depicted in Figure 20A, no differences in amplitude across stimulation sites were found. The point-by-point ANOVA performed over the entire epoch, from -100 to 1000 ms, confirmed this observation. Also, when the effect of the stimulation site was examined on mean ERN amplitude over the entire window the ANOVA did not show significant differences.

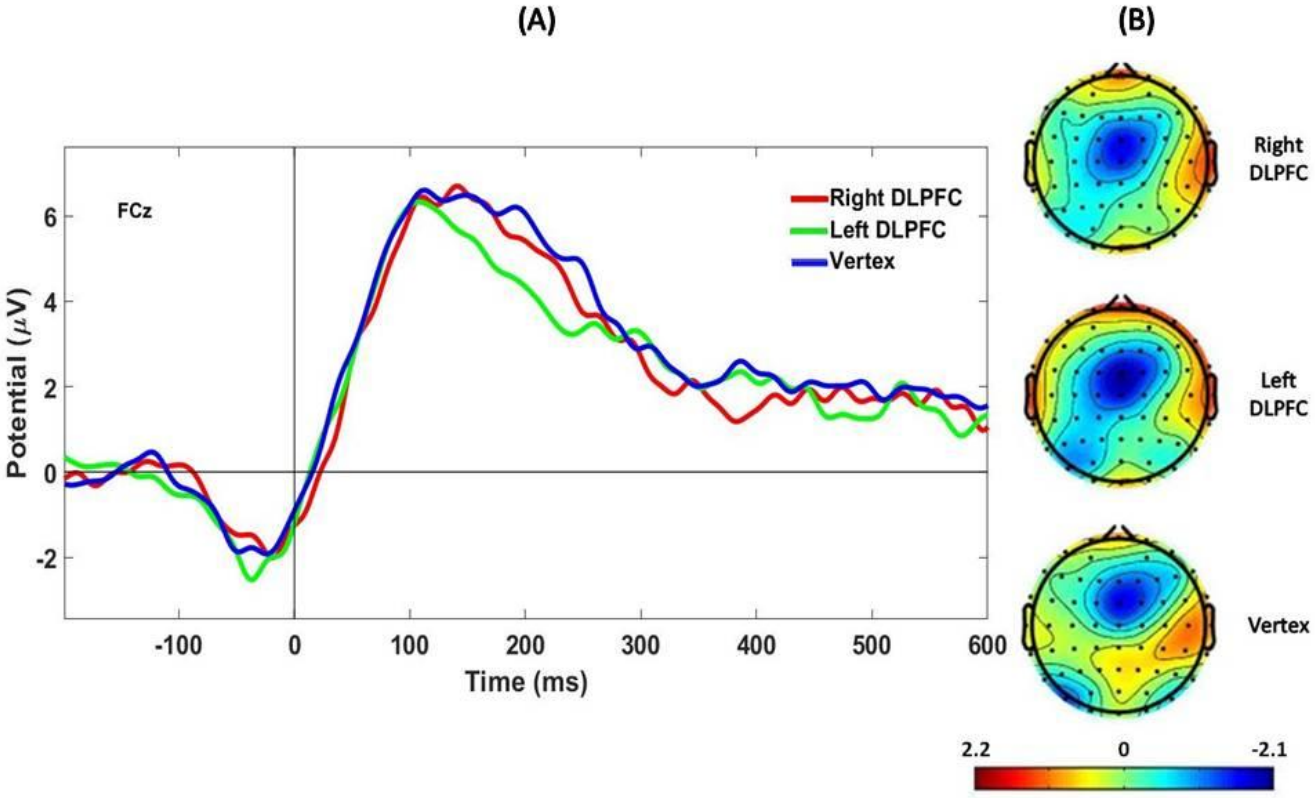

Figure 20 | (A) Response-locked ERP waveforms for aware errors as a function of stimulation site (right DLPFC/left DLPFC/Vertex) over the FCz electrode. The zero point corresponds to response time. (B) Scalp topography of aware errors in the selected time-window (from -50 ms to 0 ms). In all three conditions of stimulation (right DLPFC/left DLPFC/Vertex) the ERN was maximum over frontal sites.

The point-by-point statistical analysis over the Cz electrode revealed that from 142 to 254 ms the mean amplitude of the Pe was more reduced in the left DLPFC condition (figure 21A) compared to the other two conditions, namely the right DLPFC and the Vertex. The Pe mean amplitude in this time-window was extracted and a repeated-measures ANOVA with *stimulation*

site (right DLPFC, left DLPFC, and Vertex) as within-subject factor was performed [$F(2,17.6) = 7$, $p < 0.05$, $\eta^2_p = 0.3$]. Post-hoc comparisons confirmed the presence of a reduced amplitude in the left DLPFC condition compared the right DLPFC condition (4.8 µV vs. 6.4 µV*; p* < 0.05), without evidence of a difference between the right DLPFC and the Vertex (6.4 µV vs. 6.5 µV*; p* = 1) and the left DLPFC and the Vertex (4.8 µV vs. 6.5 µV*; p* = 0.07).

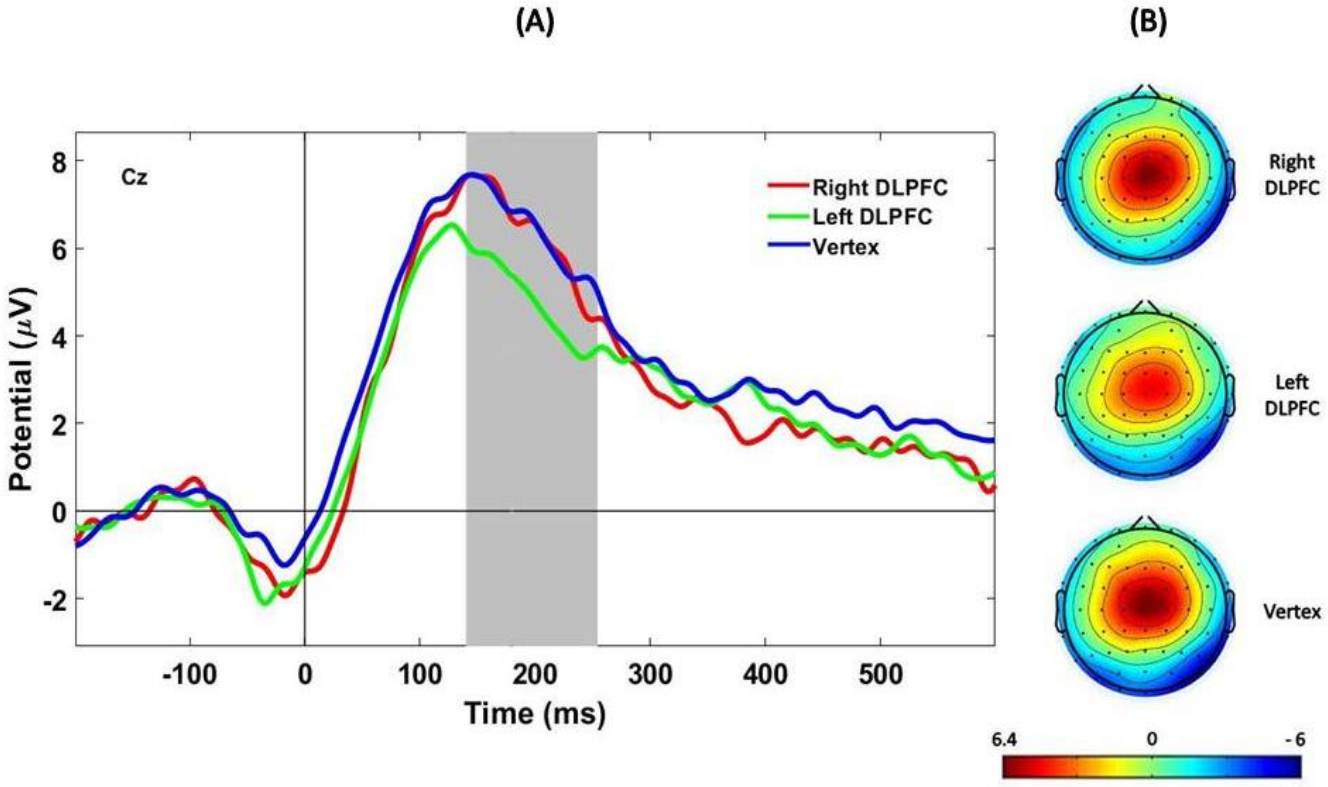

Figure 21 | (A) Response-locked ERP data at electrode Cz. The gray bar shows the time-window (142-254 ms) in which the statistical analysis indicated a significant difference between the left DLPFC and the right DLPFC. The zero point corresponds to response time. (B) Scalp topography of aware errors in the selected time-window (from 142 ms to 254 ms). In all three conditions of stimulation (right DLPFC/left DLPFC/Vertex) the positivity was maximum over central sites.

Discussion

The aim of study 3 was the modulation of error-related processes through a 1 Hz rTMS paradigm. In the present study, an off-line rTMS paradigm was employed in order to cope the limitations raised in a previous study (Masina et al., 2018b). First of all, on-line paradigms appeared

insufficient to induce a strong behavioral modulation. Although sporadic TMS pulses delivered after particular events can generally induce a modulation of brain activity, they could be not so significant to produce a strong behavioral modification. Secondly, authors found that on-line TMS non-specifically interfered with performance (Experiment 1). Thus, on-line paradigms could not represent the most appropriate solution to investigate error awareness.

An additional improvement was the introduction of EEG, a more fine-grained technique to detect brain modifications, along with behavioral changes. This solution is in line with new trends in the use of TMS, which have pointed out the fact that the neurophysiological measures can be proficient to properly evaluate TMS-induced modulation (Sokhadze et al., 2012).

Regarding **behavioral results**, in the present study, we did evidence an interesting effect of rTMS on reaction times. In fact, the left DLPFC condition was associated with a general reduction of reaction times compared to the right DLPFC condition. We think this effect would not depend on an increase of arousal as we observed in Experiment 1 of study 2. In fact, as previously explained, on that occasion TMS induced nonspecific effects (regardless of the stimulation site) due to a pervasive on-line stimulation paradigm. In study 3, we are quite confident in excluding this confound since in the present study TMS was off-line, therefore delivered before the execution of the EAT. Thus, the effect may encounter an explanation relying on a specific and area-dependent TMS effect.

An unequivocal explanation of this result is not easy because we found only a difference between the left and right DLPFC, without to evidence a difference with the Vertex. Thus, it is tricky to claim if TMS on the right DLPFC had produced an increase of reaction times, or TMS on the left DLPFC had induced an acceleration of them. A previous important study suggests that the left DLPFC plays an important role in higher levels of attentional control (Posner & Presti, 1987). TMS may have modulated the ability of participants to inhibit their responses, therefore a reduction of reaction times, without to affect the general performance. In fact, independently from the stimulation sites, we did not find any difference in terms of accuracy. However, at the same time, the right DLPFC might be implicated in our result as well. In fact, corroborating this claim, a recent study shows a relationship between phasic alertness and the right DLPFC (Mannarelli et al., 2015). Unfortunately, although the authors used a stimulation paradigm very similar to ours, contrary to our study, they did not find a reduction of reaction times after inhibitory rTMS. Because of this ambiguous result, we think that further studies are warranted to

shed light on this finding.

Contrary to our expectations, in the present study, TMS did not produce an inhibition, or a more general modulation, of error awareness. This result contrasts with previous findings in which the DLPFC appeared involved in error awareness (Harty et al., 2014; Masina et al., 2018b). Although in previous studies error awareness was modulated through a different stimulation paradigm (Masina et al., 2018b) or a different NIBS, namely tDCS (Harty et al.,2014), we expected that rTMS could induce a modulation of the process. Actually, we hypothesized rTMS would have produced stronger modulation than spTMS (study 2). Null finding we found in study 3 about a modulation of error awareness may rely on a reduction of the TMS effects after the end of the stimulation. Even if rTMS paradigms are highly employed because they induce long-lasting effects (Hallett, 2007; Ridding & Rothwell, 2007; Rossi & Rossini, 2004), it is possible that in our study the adopted paradigm could not be sufficient to modulate the process after the stimulation duration. Future studies should clarify if changing the stimulation parameters (e.g. the duration of stimulation), rTMS can modulate error awareness. Perhaps, the use of trains of pulses delivered before a target event (e.g. an error) would represent a tradeoff between paradigms of study 2 and study 3. In this way, it would be possible to selectively investigate the contingent effect of a train of pulses and a specific event. However, as study 2 showed, the risk of on-line paradigms concern possible nonspecific effects that can blur area-dependent effects produced by TMS. This confound might be controlled by, for example, a sham condition.

Finally, as regarding PES, although we confirm the PES effect, we did not find differences related to the stimulation site.

With regard to **ERP results**, a visual inspection of the waveforms shows a difference in terms of electrophysiological response of the brain after an aware error or a correct response or a correct inhibition. In fact, contrary to a correct response or inhibition, an aware error triggers a biphasic waveform in which after a negative deflection, the ERN, it follows a positive deflection, the Pe. In our study, the ERN appears shortly before the error, as figure 19 shows. The most part of studies shows that the ERN peaks shortly after the commission of an error (Falkenstein et al., 1991; O'Connell et al., 2007; Wessel, 2012), however, our result is not so exclusive and surprising because other authors reveal that the onset of the ERN can occur shortly before the moment of the erroneous button press (Gehring, Liu, Orr, & Carp, 2012). To the best of our knowledge, the latency of the ERN might depend on the nature of the error itself. In fact, if the error is an

incorrect withholding, representing a motor uninhibition, it is plausible the ERN can be observed before the motor response. This hypothesis could be easily verified in our study by analyzing the ERPs associated with Stroop and repeat errors. Since Stroop errors are generally inhibition errors, compared to repeat errors that are normally attentional errors, we should observe a different latency between the two ERNs. In particular, the ERN elicited by Stroop errors should appear earlier than the ERN elicited by repeat errors. Unfortunately, this analysis requires a sufficient number of errors in both the conditions but in study 3 this requirement is violated. For this reason, we analyzed together Stroop and repeat errors, in order to increase the statistical power of our analyses.

The analysis of the TMS effects on the ERN did not evidence a difference between our stimulation sites. The mean amplitude of the ERN was similar in all the conditions. In study 3, we predicted a modulation induced by rTMS if the stimulated site had crucial for the generation of the ERN. Since our results reveal that rTMS on the right DLPFC, the homologous left DLPFC, and the Vertex did not produce any modulation, a fallacious inference can induce us to state that these sites are not involved in the ERN. However, it is a potential error to infer something about a null result. Fortunately, previous research can help us to explain this null result, in fact, several studies demonstrate that the neural source of the ERN would be located elsewhere. In fact, a plausible neural source of the ERN seems the ACC. For example, a BESA modeling study has supported an ACC locus (van Veen & Carter, 2002). In addition, a fMRI study confirms that the ERN occurs in the ACC (Ito, Stuphorn, Brown, & Schall, 2003).

The second potential following the ERN is the Pe. The Pe seems associated with a multiple set of functions, such as the conscious detection of an error (Nieuwenhuis et al., 2001; Ullsperger et al., 2014), a potential in response to the motivational significance of an error (Ridderinkhof, Ramautar, & Wijnen, 2009), and a potential that reflects the accumulation of evidence that an error has occurred (Steinhauser & Yeung, 2010). However, all these studies define the functional role of Pe basing their statements on correlational evidence that mainly derives from EEG studies. The only causal evidence is provided by neuropsychological investigations (for instance, Ullsperger, von Cramon, & Muller, 2002) that, unfortunately, lack a fine-grained specificity due to the broad extent of the reported lesions. The originality of the present study consists in the employment of TMS to investigate error-related processes. As well-known, TMS is a technique extremely versatile that allows exploring possible causative brain-function relationships.

When we analyzed the mean amplitude of the Pe as a function of the stimulation site, we

found an interesting result. The mean amplitude of the Pe was more reduced in the left DLPFC condition than in the right DLPFC condition. Furthermore, a tendency seems to be present between the amplitude of the Pe in the left DLPFC condition and the Vertex condition (p = 0.07). Again, it seems that the mean amplitude of the Pe is more reduced after the stimulation of the left DLPFC. The Vertex and the right DLPFC do not present a difference. This trend is also corroborated by the grand average waveforms shown in figure 21A. This result contribute to provide new knowledge about error-related processes, in particular about the neural and functional bases of error awareness and the Pe.

First of all, this result is potentially incoherent with previous findings that revealed a relationship between error awareness and Pe. If the Pe is modulated by error awareness, we should expect that a modulation of the Pe can induce an effect on error awareness. However, although in our study we modulated the Pe, we did not find a behavioral effect on error awareness. We think that our result should be carefully considered, without to avoid summary conclusions. In fact, our result may not be in contrast with the error awareness-Pe relationship. In fact, it is also possible that our modulation could not so strong or long-lasting to affect the behavior, namely the frequency of the error signaling, but strong or long-lasting enough to modulate the Pe. Several studies assume that the emergence of error awareness can be conceptualized as a decision process, in which awareness about an error is achieved after that a sufficient evidence of initial error commission has been accumulated up to reach a decisional threshold (Steinhauser & Yeung, 2010; Steinhauser, Maier, & Hubner, 2008). Recent findings suggest that the amplitude of the Pe can reflect the strength of accumulated evidence about error commission (Murphy et al., 2012). Within this theoretical framework, in our study, perhaps the decisional threshold was reached anyway, even if the Pe was altered by rTMS. Thus, even if rTMS on the left DLPFC reduced the mean amplitude of the Pe, it could not be sufficient to disrupt error awareness.

A second important aspect of our result concerns the genesis of the Pe. Contrary to the ERN, the neural source of the Pe is not still defined. A previous intracerebral ERP recording study suggested a common origin of the ERN and Pe, specifically multiple cortical structures: the rostral ACC, the mesiotemporal and some prefrontal cortical sites seemed to represent integral components of the error-checking system (Brázdil et al., 2002). Differently, a second study pinpointed two different neural sources of the ERN and Pe: the caudal ACC of the ERN and the rostral ACC and the parietal cortex of the Pe (van Veen & Carter, 2002). Finally, another study

associated the Pe with the ACC and the posterior cingulate–precuneus (O'Connell et al., 2007). Taken together these studies depict a complex view of the neural sources of the Pe. Although these studies offer an extremely interesting point of view, as previously claimed, they only provide a probabilistic association between the Pe and its neural bases. The present study, for the first time, contributes to identifying, by a causative technique, the neural generator of the Pe. Obviously, this result does not exclude that other brain loci can be involved as generators of the Pe.

Conclusion

In conclusion, in study 3, behavioral results show a different scenario compared to ERP ones. On the one hand, from behavioral results, we observed that the only TMS effect concerned the modulation of reaction times. As regards error awareness and PES, the main behavioral variables considered in this study, we did not find any TMS effect. On the other hand, ERP results reveal an interesting implication of the left DLPFC in the Pe. A rTMS paradigm on the left DLPFC induced a modulation of the potential, specifically a reduction of it.

Thus, although the behavioral results did not seem to detect TMS effects, the ERP results showed the opposite. This discrepancy again underlines the importance of the combined use of TMS and other neuroscientific techniques. In fact, different indicators, both behavioral and neurophysiological, can be used as functional outcome measures to evaluate the effectiveness of brain modulation.

Chapter 7

General discussion

The plasticity is a property that allows a system changing in response to exogenous and endogenous stimuli. The central nervous system is one of the most fascinating organs because it can be considered a structure in which plastic mechanisms act massively. As we have broadly argued, several kinds of interventions, taking advantage of neural plasticity, can induce controlled modulation of behavior and, in general, brain functioning. These interventions can be defined as "controlled" because, according to the direction of the modification, it is potentially possible to enhance or reduce behaviors, cognitive functions, and brain processes. However, we cannot simplistically consider modulatory interventions as brain switches able to always produce effects in line with our expectations. For example, even if the application of rewards seems to generally support a better performance, this method may not be fitted to support all kinds of cognitive processes. Given that the brain is a nonlinear system and hundreds of factors may affect its functioning, investigators interested in brain modulation should consider as many as possible aspects before planning modulatory interventions.

The main purpose of this dissertation was the modulation of error-related processes. These set of processes support performance monitoring, a system that contributes to monitoring our behavior and to maintain an acceptable performance. When performance monitoring identifies a mismatch between executed and planned actions, an error has occurred and a series of reactions are triggered in order to on-line correct the action or avoid similar errors in future (Ullsperger, Danielmeier, & Jocham, 2014). The error-related processes reflect a sequence of events that occur after the commission of an error and range from motor adjustments, up to cognitive adaptations. In this dissertation, we focused our interest in behavioral correlates, (i.e. error awareness and PES) and neurophysiological correlates (i.e. the ERN and the Pe) of error-related processes.

In order to achieve the modulation of error-related processes, three studies were carried out. This chapter will review results from these studies and will argue some of the central issues in the design and interpretation of modulatory interventions. Throughout the chapter, we will summarize some significant points into a set of suggestions and strategies for designing modulatory interventions.

In study 1, the purpose was the modulation of error awareness supporting this process by using rewards. Given that previous evidence shows that error awareness is reduced in normal aging, study 1 aimed to improve error awareness in a group of elderly. In addition, a group of younger adults was tested to compare performance between groups. Results confirmed a reduction of error awareness in older adults, even if they were more accurate than younger adults. However, with regards to the modulation of error awareness, we found an unexpected result. Both younger and older adults were less aware of their errors when error awareness was incentivized. Thus, contrary to previous studies, instead of improving performance, rewards had produced a detrimental effect. Thus:

The same modulatory intervention can lead to different effects if applied in two different contexts.

In Chapter 2, we have described the effect of motivation on cognition. On the one hand, in a number of studies, a rewarded performance is associated with an improvement of cognitive functions (Locke & Braver, 2010; Maddox & Markman, 2010; Pessoa, 2009, 2010; Shohamy & Adcock, 2010). On the other hand, some authors point out that the use of rewards sometimes can produce a reduction in performance (Yu, 2015), as in our study. This phenomenon is defined as "choking under pressure" and concerns the performance reduction under stressful conditions. A trial-by-trial reward, as in study 1, can induce psychological pressure and impair performance. Psychological pressure may capture attentional resources and, in turn, reduce error awareness.

Similarly, we can observe that the same intervention can produce different results also in other situations. For example, several tDCS studies employ anodic stimulation with the aim to facilitate a particular process and cathodal stimulation to inhibit it. This *modus operandi* relies on previous evidence that showed a bijective correspondence between these tDCS paradigms and the effects on the motor areas, namely facilitation for anodic stimulation and inhibition for cathodal stimulation (Nitsche et al., 2008). Unfortunately, if applied on non-motor areas, these tDCS paradigms induce unexpected behavioral outcomes, with anodal tDCS usually inducing facilitation and cathodal tDCS inducing a range of effects (Jacobson et al., 2012).

Study 2 aimed to confirm the involvement of the right DLPFC in error awareness, as well as to investigate the timing of error awareness. In this study, we expected to modulate error

awareness by using on-line TMS paradigms. Three experiments were conducted: a paired-pulse and a single-pulse on-line stimulation paradigms were employed respectively in Experiments 1 and 3, whereas a control test was conducted without stimulation in Experiment 2.

Results from Experiment 1 showed no significant effect of paired-pulse TMS over either left or right DLPFC on error awareness. To the best of our knowledge, a plausible cause may derive from the stimulation paradigm we used in this experiment. By inducing nonspecific effects this stimulation paradigm would have submerged specific effects of TMS. This consideration points out an important issue:

Any modulatory intervention cannot induce only modulation of a target behavior or brain process. Unavoidably, any intervention affects multiple behaviors and brain processes.

Investigators should consider that any form of intervention they decide to adopt will not only induce modulation of a specific behavior or brain process. This principle is particularly important in rehabilitative contexts when an intervention is employed to selectively treat a symptom or a deficit. It is not surprising that in some situations the effects of an intervention on a behavior or brain process (e.g. working memory) can spread to another one (e.g. attention). Actually, the generalization of treatment effects is an ambitious goal of many clinical interventions, for example, with the aim of improving the functioning of a patient in ecological situations through selective rehabilitation of memory functions. The capability of a modulatory intervention to spread over the target behavior or brain process can depend on several factors, such as the relationship between the target behavior or brain process and the collateral behavior or brain process. Obviously, when this nonspecificity of interventions produces only positive effects, it does not represent a problem. The problem arises when the modulation of a behavior or process occurs at the expense of another behavior or process, as in Experiment 1.

An emblematic example of maladaptive nonspecificity of interventions derives from a recent study. Iuculano & Cohen Kadosh (2013) showed that cognitive enhancement induces by tES can occur at the expense of other cognitive functions. For the first time, these authors point out possible cognitive side effects of NIBS (Poreisz, Boros, Antal, & Paulus, 2007).

We think that, although the modulation of cognitive function is an promising tool in neuroscience, at the same time it is simplistic to theorize that modulation can only induce positive effects without, for example, to trigger forms of maladaptive plasticity.

In order to overcome the limitation of Experiment 1, in study 2 we carried out a second on-line TMS experiment. Experiment 3 was identical of the previous one, except from the stimulation paradigm. In Experiment 3, we adopted a single-pulse paradigm because we conceptualized it was less pervasive than a paired-pulse paradigm. In line with our hypotheses, results showed a causal relationship between the DLPFC and error awareness, without evidence for lateralization. Unfortunately, as we previously discussed, the generated modulation was weak, with a small effect size. This finding raises another important aspect that should be considered in brain modulation studies:

A modulatory effect is appreciable and reliable only if supported by a good effect size.

The effect size argument is a common and eternal problem not only in studies in which modulatory interventions are employed but in general in all fields of research. A study should demonstrate a clear biological rationale for the hypotheses tested and the effect sizes should be sufficiently good to ensure that effects are reliable and, importantly, replicable. This assumption should be always taken into account, in particular when a modulatory intervention is applied in clinical settings.

For example, in TMS studies there are no standard protocols that allow a systematic use of this method in the clinical field. Every study is characterized by multiple methodological differences ranging from the type of stimulation paradigm adopted, the duration of the intervention, up to the outcomes taken into consideration to evaluate the modulatory effects of TMS. This methodological heterogeneity inevitably leads to produce different results that cannot be easily compared to each other. In order to face this issue, the comparisons between effect sizes may represent an efficacious strategy to disambiguate reliable modulatory effects from unreliable ones. A significant goal has been achieved in the treatment of major depressive disorder through TMS. By means of meta-analyses, as well as a number of systematic reviews (Perera et al., 2016), nowadays TMS has been approved by the FDA for the treatment of major depressive disorder. Future studies should follow this example in order to assess the effectiveness of the technique and to develop standardized modulatory interventions that

can maximize the adaptive plasticity mechanisms in clinical settings. In general, regardless of the modulatory methods, the robustness of effects should be an essential must.

Finally, study 3 aimed to investigate TMS-induced brain modulation of error-related processes. The originality of this study concerned the fact that, besides the classical behavioral measures, we considered neurophysiological measures as well. Study 3 was designed taking the limitations of previous studies into account. First of all, in order to avoid nonspecific effects and confounds, instead of an on-line stimulation paradigm we employed an off-line paradigm. Secondly, we combined TMS with EEG technique, in order to deeper investigate the modulatory effects of a low-frequency rTMS paradigm. Although the behavioral results did not reveal TMS effects, the ERP results showed an opposite scenario, namely a modulation of the Pe induced by rTMS when the left DLPFC was stimulated. The discrepancy between behavioral and neurophysiological effects suggests that:

Different indicators, both behavioral and neurophysiological, should be considered as functional outcome measures to evaluate the effectiveness of brain modulation.

We think this simple solution may contribute to provide significant improvements in studies focused on neural modulation for several reasons. The combined use of behavioral and neurophysiological measures may allow:

- evaluating modulation from different points of view. The impact of an intervention can be better characterized if modulatory effects are measured in terms of behavioral and neurophysiological effects. In the past, especially in Psychology, constructs were mainly tested by measuring behavioral correlates (reaction times, accuracy, questionnaire responses, etc.). With the growing development of neuroscientific methods, more and more investigators have decided to combine several techniques in the same experiment. Of particular interest, the combined use of two methods makes it possible to compensate for some reciprocal limitations of methods.
- revealing discrepancies between effects. In study 3, our results showed that rTMS on the left DLPFC did not induce a behavioral effect on error awareness but, interestingly, produced a reduction of the Pe, an ERP strictly related to error awareness. This evidence

highlights that the exclusive use of behavioral measures might neglect other forms of modulation and reaffirm the importance of a combined use of methods to evaluate neural modulation.

- controlling for nonspecific effects of modulatory interventions. As previously argued, modulatory interventions can induce nonspecific effects. Even if prior hypotheses are correct and a selective modulation of a target behavior of process are found, we cannot exclude that the modulatory effects does not spread beyond the measured variable. Especially, it is extremely important to verify if the modulation of a behavior or a process has not occurred at the expense of another behavior or process. By combining behavioral and neurophysiological measures investigators are able to maximize the probability to evaluate nonspecific effect of interventions.
- revealing modulatory effects that extend beyond behavioral outcomes. Sometimes, modulation cannot reach a sufficient threshold to produce a significant effect on behavior. In these cases, if the gathered measure is only a behavioral variable, investigators will not able to infer anything from the manipulation and the result will be considered only a null effect. For example, in study 3, a combined use of TMS and EEG allowed us to evidence a significant effect of TMS on the Pe, even if the behavioral results did not show a modulation in terms of variation of error awareness.

To conclude, we think that this dissertation can significantly provide insights into a relatively unexplored research field: the modulation of error-related processes. In fact, a careful revision of our results can contribute to guide future investigators in designing modulatory interventions.

References

Adrian, E. D., & Moruzzi, G. (1939). Impulses in the pyramidal tract. *The Journal of Physiology*, *97*(2), 153–199. https://doi.org/10.1113/jphysiol.1939.sp003798

Altman, J. (1962). Are new neurons formed in the brains of adult mammals? *Science*, *135*(3509), 1127–1128. https://doi.org/10.1126/science.135.3509.1127

Amengual, J. L., Vernet, M., Adam, C., & Valero-Cabré, A. (2017). Local entrainment of oscillatory activity induced by direct brain stimulation in humans. *Scientific Reports*, *7*. https://doi.org/10.1038/srep41908

Anderson, V. (2005). Functional Plasticity or Vulnerability After Early Brain Injury? *PEDIATRICS*, *116*(6), 1374–1382. https://doi.org/10.1542/peds.2004-1728

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. https://doi.org/10.1093/brain/awr103

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., & Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimulation*, *1*(2), 97–105. https://doi.org/10.1016/j.brs.2007.10.001

Antal, A., & Herrmann, C. S. (2016). Transcranial Alternating Current and Random Noise Stimulation: Possible Mechanisms. *Neural Plasticity*. https://doi.org/10.1155/2016/3616807

Ariely, D., Gneezy, U., Loewenstein, G., & Mazar, N. (2009). Large stakes and big mistakes. *Review of Economic Studies*, *76*(2), 451–469. https://doi.org/10.1111/j.1467-937X.2009.00534.x

Balogh, L., & Czobor, P. (2016). Post-Error Slowing in Patients With ADHD: A Meta-Analysis. *Journal of Attention Disorders*, *20*(12), 1004–1016. https://doi.org/10.1177/1087054714528043

Banasr, M., & Duman, R. S. (2008). Keeping "Trk" of Antidepressant Actions. *Neuron*. https://doi.org/10.1016/j.neuron.2008.07.028

Bardi, L., Kanai, R., Mapelli, D., & Walsh, V. (2012). TMS of the FEF interferes with spatial conflict. *Journal of Cognitive Neuroscience*, *24*(6), 1305–1313. https://doi.org/10.1162/jocn_a_00223

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *The Lancet*. https://doi.org/10.1016/S0140-6736(85)92413-4

Bateson, P. (1979). How do sensitive periods arise and what are they for? *Animal Behaviour*, *27*(PART 2), 470–486. https://doi.org/10.1016/0003-3472(79)90184-2

Bateson, P. (2017). Robustness and plasticity in development. *Wiley Interdisciplinary Reviews: Cognitive*

Science. https://doi.org/10.1002/wcs.1386

Bateson, P., & Gluckman, P. (2011). *Plasticity, robustness, development and evolution*. Cambridge University Press.

Baumeister, R. F. (1984). Choking under pressure: Self-consciousness and paradoxical effects of incentives on skillful performance. *Journal of Personality and Social Psychology*, *46*(3), 610–620. https://doi.org/10.1037/0022-3514.46.3.610

Bengoetxea, H., Ortuzar, N., Bulnes, S., Rico-Barrio, I., Lafuente, J. V., & Argandoña, E. G. (2012). Enriched and deprived sensory experience induces structural changes and rewires connectivity during the postnatal Development of the brain. *Neural Plasticity*. https://doi.org/10.1155/2012/305693

Berlucchi, G., & Buchtel, H. A. (2009). Neuronal plasticity: Historical roots and evolution of meaning. In *Experimental Brain Research* (Vol. 192, pp. 307–319). https://doi.org/10.1007/s00221-008-1611-6

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*. https://doi.org/10.1016/S0165-0173(03)00143-7

Bikson, M., Datta, A., Rahman, A., & Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: Role of " return" electrode's position and size. *Clinical Neurophysiology*, *121*(12), 1976–1978. https://doi.org/10.1016/j.clinph.2010.05.020

Billig, N. (1986). Agitated Behaviors in the Elderly: I. A Conceptual Review. *Journal of the American Geriatrics Society*, *34*(10), 711–721. https://doi.org/10.1111/j.1532-5415.1986.tb04302.x

Bindman, L. J., Lippold, O. C. J., & Redfearn, J. W. T. (1962). Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature*, *196*(4854), 584–585. https://doi.org/10.1038/196584a0

Bliss, T. V. P., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273

Bolognini, N., & Ro, T. (2010). Transcranial Magnetic Stimulation: Disrupting Neural Activity to Alter and Assess Brain Function. *Journal of Neuroscience*, *30*(29), 9647–9650. https://doi.org/10.1523/JNEUROSCI.1990-10.2010

Bonner, S. E., Hastie, R., Sprinkle, G. B., & Young, S. M. (2000). A Review of the Effects of Financial Incentives on Performance in Laboratory Tasks: Implications for. *Journal of Management Accounting Research*, *12*(1), 19–64. https://doi.org/10.2308/jmar.2000.12.1.19

Bonner, S. E., & Sprinkle, G. B. (2002). The effects of monetary incentives on effort and task performance: theories, evidence, and a framework for research. *Accounting, Organizations and Society*, *27*(4–5), 303–345. https://doi.org/Pii S0361-3682(01)00052-6Doi 10.1016/S0361-3682(01)00052-6

Bostrom, N., & Sandberg, A. (2009). Cognitive enhancement: Methods, ethics, regulatory challenges.

Science and Engineering Ethics, *15*(3), 311–341. https://doi.org/10.1007/s11948-009-9142-5

Bothwell, M. (2014). NGF, BDNF, NT3, and NT4. *Handbook of Experimental Pharmacology*, *220*, 3–15. https://doi.org/10.1007/978-3-642-45106-5_1

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, *108*(3), 624–652. https://doi.org/10.1037/0033-295X.108.3.624

Braver, T. S., Krug, M. K., Chiew, K. S., Kool, W., Andrew Westbrook, J., Clement, N. J., … Somerville, L. H. (2014). Mechanisms of motivation-cognition interaction: Challenges and opportunities. *Cognitive, Affective and Behavioral Neuroscience*. https://doi.org/10.3758/s13415-014-0300-0

Brázdil, M., Roman, R., Falkenstein, M., Daniel, P., Jurák, P., & Rektor, I. (2002). Error processing - Evidence from intracerebral ERP recordings. *Experimental Brain Research*, *146*(4), 460–466. https://doi.org/10.1007/s00221-002-1201-y

Brown, C. E., Li, P., Boyd, J. D., Delaney, K. R., & Murphy, T. H. (2007). Extensive Turnover of Dendritic Spines and Vascular Remodeling in Cortical Tissues Recovering from Stroke. *Journal of Neuroscience*, *27*(15), 4101–4109. https://doi.org/10.1523/JNEUROSCI.4295-06.2007

Burke, S. N., & Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1809

Cabeza, R., Nyberg, L., & Park, D. C. (2009). *Cognitive Neuroscience of Aging: Linking cognitive and cerebral aging*. *Cognitive Neuroscience of Aging: Linking cognitive and cerebral aging*. https://doi.org/10.1093/acprof:oso/9780195156744.001.0001

Camerer, C. F., & Hogarth, R. M. (1999). The effects of financial incentives in experiments: A review and capital labor production framework. *Journal of Risk and Uncertainty*, *19*, 7–42. https://doi.org/10.1023/A:1007850605129

Campen, A. D. van, Keuken, M. C., Wildenberg, W. P. M. van den, & Ridderinkhof, K. R. (2013). TMS over M1 Reveals Expression and Selective Suppression of Conflicting Action Impulses. *Journal of Cognitive Neuroscience*, *26*(1), 1–15. https://doi.org/10.1162/jocn

Carstensen, L. L., & Mikels, J. A. (2005). At the Intersection of Emotion and Cognition. *Current Directions in Psychological Science*, *14*(3), 117–121. https://doi.org/10.1111/j.0963-7214.2005.00348.x

Carver, C. S., & Scheier, M. F. (1981). *Attention and Self-Regulation: A Control-Theory Approach to Human Behavior*. *Springer Series in Social Psychology* (Vol. 1). https://doi.org/10.1007/978-1-4612-5887-2

Charles, L., Van Opstal, F., Marti, S., & Dehaene, S. (2013). Distinct brain mechanisms for conscious versus subliminal error detection. *NeuroImage*, *73*, 80–94. https://doi.org/10.1016/j.neuroimage.2013.01.054

Chaumon, M., Bishop, D. V. M., & Busch, N. A. (2015). A practical guide to the selection of independent components of the electroencephalogram for artifact correction. *Journal of Neuroscience Methods*,

250, 47–63. https://doi.org/10.1016/j.jneumeth.2015.02.025

Chen, C.-C., Lu, J., & Zuo, Y. (2014). Spatiotemporal dynamics of dendritic spines in the living brain. *Frontiers in Neuroanatomy*, *8*. https://doi.org/10.3389/fnana.2014.00028

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, *48*(5), 1398–1403. https://doi.org/10.1212/WNL.48.5.1398

Cieslik, E. C., Zilles, K., Caspers, S., Roski, C., Kellermann, T. S., Jakobs, O., … Eickhoff, S. B. (2013). Is there one DLPFC in cognitive action control? Evidence for heterogeneity from Co-activation-based parcellation. *Cerebral Cortex*, *23*(11), 2677–2689. https://doi.org/10.1093/cercor/bhs256

Coelho, L. F., Barbosa, D. L. F., Rizzutti, S., Muszkat, M., Amodeo Bueno, O. F., & Miranda, M. C. (2015). Use of cognitive behavioral therapy and token economy to alleviate dysfunctional behavior in children with attention-deficit hyperactivity disorder. *Frontiers in Psychiatry*, *6*(NOV). https://doi.org/10.3389/fpsyt.2015.00167

Cohen-Cory, S., Dreyfus, C. F., & Black, I. B. (1991a). NGF and excitatory neurotransmitters regulate survival and morphogenesis of cultured cerebellar Purkinje cells. *J Neurosci*, *11*(2), 462–471. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1671407

Cohen-Cory, S., Dreyfus, C. F., & Black, I. B. (1991b). NGF and excitatory neurotransmitters regulate survival and morphogenesis of cultured cerebellar Purkinje cells. *J Neurosci*, *11*(2), 462–471.

Cohen, M. X., Van Gaal, S., Ridderinkhof, K. R., & Lamme, V. (2009). Unconscious errors enhance prefrontal-occipital oscillatory synchrony. *Frontiers in human neuroscience*, *3*, 54.

Colino, F. L., Howse, H., Norton, A., Trska, R., Pluta, A., Luehr, S. J. C., … Krigolson, O. E. (2017). Older adults display diminished error processing and response in a continuous tracking task. *Psychophysiology*, *54*(11), 1706–1713. https://doi.org/10.1111/psyp.12907

Collins, A. G. E., & Frank, M. J. (2015). Surprise! Dopamine signals mix action, value and error. *Nature Neuroscience*, *19*(1), 3–5. https://doi.org/10.1038/nn.4207

Conti, S., Bonazzi, S., Laiacona, M., Masina, M., & Coralli, M. V. (2015). Montreal Cognitive Assessment (MoCA)-Italian version: regression based norms and equivalent scores. *Neurological Sciences*, *36*(2), 209–214. https://doi.org/10.1007/s10072-014-1921-3

Corrigan, P. W., Yudofsky, S. C., & Silver, J. M. (1993). Pharmacological and behavioral treatments for aggressive psychiatric inpatients. *Hospital & Community Psychiatry*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8432495

Couillard-Després, S. (2012). Hippocampal neurogenesis and ageing. *Current Topics in Behavioral Neurosciences*, *15*, 343–355. https://doi.org/10.1007/7854_2012_232

Cramer, S. C. (2004). Functional imaging in stroke recovery. In *Stroke* (Vol. 35, pp. 2695–2698). https://doi.org/10.1161/01.STR.0000143326.36847.b0

Critchley, H. D., Tang, J., Glaser, D., Butterworth, B., & Dolan, R. J. (2005). Anterior cingulate activity during error and autonomic response. *NeuroImage*, *27*(4), 885–895. https://doi.org/10.1016/j.neuroimage.2005.05.047

Danielmeier, C., Eichele, T., Forstmann, B. U., Tittgemeyer, M., & Ullsperger, M. (2011). Posterior Medial Frontal Cortex Activity Predicts Post-Error Adaptations in Task-Related Visual and Motor Areas. *J Neurosci*, *31*(5), 1780–1789. https://doi.org/31/5/1780 [pii]\n10.1523/JNEUROSCI.4299-10.2011

Danielmeier, C., & Ullsperger, M. (2011). Post-error adjustments. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2011.00233

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., & Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation*, *2*(4). https://doi.org/10.1016/j.brs.2009.03.005

David, A. S. (1992). Illness and insight. *British Journal of Hospital Medicine*, *48*(10), 652–654. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1458274

De Graaf, T. A., & Sack, A. T. (2011). Null results in TMS: From absence of evidence to evidence of absence. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2010.10.006

Dehaene, S., Posner, M. I., Tucker, D. M., Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a Neural System for Error Detection and Compensation LOCALIZATION OF A NEURAL SYSTEM FOR ERROR. *Psychological Science*, *5*(5), 303–305. https://doi.org/10.1111/j.1467-9280.1994.tb00630.x

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Deng, Z. De, Lisanby, S. H., & Peterchev, A. V. (2013). Electric field depth-focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs. *Brain Stimulation*, *6*(1), 1–13. https://doi.org/10.1016/j.brs.2012.02.005

Di Gregorio, F., Maier, M. E., & Steinhauser, M. (2018). Errors can elicit an error positivity in the absence of an error negativity: Evidence for independent systems of human error monitoring. *NeuroImage*, *172*, 427–436. https://doi.org/10.1016/j.neuroimage.2018.01.081

Dockree, P. M., Tarleton, Y. M., Carton, S., & FitzGerald, M. C. C. (2015). Connecting Self-Awareness and Error-Awareness in Patients with Traumatic Brain Injury. *Journal of the International Neuropsychological Society*, *21*(7), 473–482. https://doi.org/10.1017/S1355617715000594

Dräger, B., Breitenstein, C., Helmke, U., Kamping, S., & Knecht, S. (2004). Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification. *The European Journal of Neuroscience*, *20*(6), 1681–1687. https://doi.org/10.1111/j.1460-9568.2004.03623.x

Durstewitz, D., & Seamans, J. K. (2008). The Dual-State Theory of Prefrontal Cortex Dopamine Function with Relevance to Catechol-O-Methyltransferase Genotypes and Schizophrenia. *Biological Psychiatry*.

https://doi.org/10.1016/j.biopsych.2008.05.015

Dutilh, G., Forstmann, B. U., Vandekerckhove, J., & Wagenmakers, E.-J. (2013). A diffusion model account of age differences in posterror slowing. *Psychology and Aging*, *28*(1), 64–76. https://doi.org/10.1037/a0029875

Dutilh, G., Van Ravenzwaaij, D., Nieuwenhuis, S., Van der Maas, H. L. J., Forstmann, B. U., & Wagenmakers, E. J. (2012). How to measure post-error slowing: A confound and a simple solution. *Journal of Mathematical Psychology*, *56*(3), 208–216. https://doi.org/10.1016/j.jmp.2012.04.001

Eder, M., Zieglgänsberger, W., & Dodt, H.-U. (2002). Neocortical long-term potentiation and long-term depression: site of expression investigated by infrared-guided laser stimulation. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *22*(17), 7558–7568. https://doi.org/22/17/7558 [pii]

Elliott, R., Sahakian, B. J., Michael, A., Paykel, E. S., & Dolan, R. J. (1998). Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. *Psychological Medicine*, *28*(3), 559–571. https://doi.org/10.1017/S0033291798006709

Endrass, T., Franke, C., & Kathmann, N. (2005). Error awareness in a saccade countermanding task. *Journal of Psychophysiology*, *19*(4), 275–280. https://doi.org/10.1027/0269-8803.19.4.275

Endrass, T., Reuter, B., & Kathmann, N. (2007). ERP correlates of conscious error recognition: Aware and unaware errors in an antisaccade task. *European Journal of Neuroscience*, *26*(6), 1714–1720. https://doi.org/10.1111/j.1460-9568.2007.05785.x

Endrass, T., Schuermann, B., Kaufmann, C., Spielberg, R., Kniesche, R., & Kathmann, N. (2010). Performance monitoring and error significance in patients with obsessive-compulsive disorder. *Biological Psychology*, *84*(2), 257–263. https://doi.org/10.1016/j.biopsycho.2010.02.002

Eriksson, P. S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A., & Gage, F. H. (1998). Neurogenesis in the adult human hippocampus. *Nat Med*, *4*(11), 1313–1317. https://doi.org/10.1038/3305

Esser, S. K., Huber, R., Massimini, M., Peterson, M. J., Ferrarelli, F., & Tononi, G. (2006). A direct demonstration of cortical LTP in humans: A combined TMS/EEG study. *Brain Research Bulletin*, *69*(1), 86–94. https://doi.org/10.1016/j.brainresbull.2005.11.003

Falkenstein, M. (2004). ERP correlates of erroneous performance. *Errors, conflicts, and the brain. Current opinions on performance monitoring*, *1*, 5-14.

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology*, *78*(6), 447–455. https://doi.org/10.1016/0013-4694(91)90062-9

Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology*, *51*(2–3), 87–107.

https://doi.org/10.1016/S0301-0511(99)00031-9

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2001). Changes of error-related ERPs with age. *Experimental Brain Research*, *138*(2), 258–262. https://doi.org/10.1007/s002210100712

Farah, M. J., Illes, J., Cook-Deegan, R., Gardner, H., Kandel, E., King, P., … Wolpe, P. R. (2004). Neurocognitive enhancement: What can we do and what should we do? *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1390

Fauth, M., & Tetzlaff, C. (2016). Opposing Effects of Neuronal Activity on Structural Plasticity. *Frontiers in Neuroanatomy*, *10*. https://doi.org/10.3389/fnana.2016.00075

Fertonani, A., Pirulli, C., & Miniussi, C. (2011). Random Noise Stimulation Improves Neuroplasticity in Perceptual Learning. *Journal of Neuroscience*, *31*(43), 15416–15423. https://doi.org/10.1523/JNEUROSCI.2002-11.2011

Fleming, J. M., Strong, J., & Ashton, R. (1996). Self-awareness of deficits in adults with traumatic brain injury: How best to measure? *Brain Injury*, *10*(1), 1–15. https://doi.org/10.1080/026990596124674

Fleming, S. M., Huijgen, J., & Dolan, R. J. (2012). Prefrontal contributions to metacognition in perceptual decision making. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *32*(18), 6117–6125. https://doi.org/10.1523/JNEUROSCI.6489-11.2012

Floel, A., & Cohen, L. G. (2010). Recovery of function in humans: Cortical stimulation and pharmacological treatments after stroke. *Neurobiology of Disease*, *37*(2), 243–251. https://doi.org/http://dx.doi.org/10.1016/j.nbd.2009.05.027

Fox, S. E., Levitt, P., & Nelson, C. A. (2010). How the timing and quality of early experiences influence the development of brain architecture. *Child Development*. https://doi.org/10.1111/j.1467-8624.2009.01380.x

Foy, M. R., Stanton, M. E., Levine, S., & Thompson, R. F. (1987). Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behavioral and Neural Biology*, *48*(1), 138–149. https://doi.org/10.1016/S0163-1047(87)90664-9

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *The Journal of Neuroscience*, *23*(27), 9240–9245. https://doi.org/23/27/9240 [pii]

Gazzaniga, M. S. [Ed]. (2004). *The cognitive neurosciences (3rd ed.). The cognitive neurosciences (3rd ed.).* https://doi.org/10.1136/bmj.312.7024.193

Gehring, W. J., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1990a). The error-related negativity: an event-related brain potential accompanying errors. *Psychophysiology*, *27*(4A), 34. https://doi.org/10.1111/j.1469-8986.1990.tb02374.x

Gehring, W. J., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1990b). The error-related negativity: an event-related brain potential accompanying errors. *Psychophysiology*, *27*(4A), 34. https://doi.org/10.1111/j.1469-8986.1990.tb02374.x

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A Neural System for Error Detection and Compensation. *Psychological Science*, *4*(6), 385–390. https://doi.org/10.1111/j.1467-9280.1993.tb00586.x

Gehring, W. J., Himle, J., & Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, *11*(1), 1–6. https://doi.org/10.1111/1467-9280.00206

Gehring, W. J., Liu, Y., Orr, J. M., & Carp, J. (2012). The Error-Related Negativity (ERN/Ne). In *The Oxford Handbook of Event-Related Potential Components*. https://doi.org/10.1093/oxfordhb/9780195374148.013.0120

Gheusi, G., Lepousez, G., & Lledo, P. M. (2012). Adult-born neurons in the olfactory bulb: Integration and functional consequences. *Current Topics in Behavioral Neurosciences*, *15*, 49–72. https://doi.org/10.1007/7854_2012_228

Gholipour, A., Abolghasemi, S. H., Gholinia, K., & Taheri, S. (2012). Token reinforcement therapeutic approach is more effective than exercise for controlling negative symptoms of schizophrenic patients: A randomized controlled trial. *International Journal of Preventive Medicine*, *3*(7), 466–470.

Gómez-Palacio-Schjetnan, A., & Escobar, M. L. (2013). Neurotrophins and synaptic plasticity. *Current Topics in Behavioral Neurosciences*, *15*, 117–136. https://doi.org/10.1007/7854_2012_231

Grady, C. (2012). Brain Ageing: The Cognitive Neuroscience of Ageing. *Nature Reviews Neuroscience*, *13*(7), 491–505. https://doi.org/Doi 10.1038/Nrn3256

Greenwood, P. M. (2007). Functional Plasticity in Cognitive Aging: Review and Hypothesis. *Neuropsychology*, *21*(6), 657–673. https://doi.org/10.1037/0894-4105.21.6.657

Hajcak, G., McDonald, N., & Simons, R. F. (2003). To err is autonomic: Error-related brain potentials, ANS activity, and post-error compensatory behavior. In *Psychophysiology* (Vol. 40, pp. 895–903). https://doi.org/10.1111/1469-8986.00107

Hallett, M. (2007). Transcranial Magnetic Stimulation: A Primer. *Neuron*. https://doi.org/10.1016/j.neuron.2007.06.026

Han, L., Liu, Y., Zhang, D., Jin, Y., & Luo, Y. (2013). Low-Arousal Speech Noise Improves Performance in N-Back Task: An ERP Study. *PLoS ONE*, *8*(10). https://doi.org/10.1371/journal.pone.0076261

Harsay, H. A., Spaan, M., Wijnen, J. G., & Ridderinkhof, K. R. (2012). Error Awareness and Salience Processing in the Oddball Task: Shared Neural Mechanisms. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00246

Harty, S., Murphy, P. R., Robertson, I. H., & O'Connell, R. G. (2017). Parsing the neural signatures of reduced error detection in older age. *NeuroImage*, *161*, 43–55. https://doi.org/10.1016/j.neuroimage.2017.08.032

Harty, S., O'Connell, R. G., Hester, R., & Robertson, I. H. (2013). Older adults have diminished awareness of errors in the laboratory and daily life. *Psychology and Aging*, *28*(4), 1032–1041.

https://doi.org/10.1037/a0033567

Harty, S., Robertson, I. H., Miniussi, C., Sheehy, O. C., Devine, C. a, McCreery, S., & O'Connell, R. G. (2014). Transcranial direct current stimulation over right dorsolateral prefrontal cortex enhances error awareness in older age. *Journal of Neuroscience*, *34*(10), 3646–3652. https://doi.org/10.1523/JNEUROSCI.5308-13.2014

Hebb, D. O. (1949). The Organization of Behavior. *New York: JohnWiley & Sons*. https://doi.org/10.1016/S0361-9230(99)00182-3

Henze, D. A., Gonzalez-Burgos, G. R., Urban, N. N., Lewis, D. A., & Barrionuevo, G. (2000). Dopamine increases excitability of pyramidal neurons in primate prefrontal cortex. *Journal of Neurophysiology*, *84*(6), 2799–2809. https://doi.org/10.1152/jn.2000.84.6.2799

Herwig, U., Abler, B., Schönfeldt-Lecuona, C., Wunderlich, A., Grothe, J., Spitzer, M., & Walter, H. (2003). Verbal storage in a premotor-parietal network: Evidence from fMRI-guided magnetic stimulation. *NeuroImage*, *20*(2), 1032–1041. https://doi.org/10.1016/S1053-8119(03)00368-9

Hester, R., Foxe, J. J., Molholm, S., Shpaner, M., & Garavan, H. (2005). Neural mechanisms involved in error processing: A comparison of errors made with and without awareness. *NeuroImage*, *27*(3), 602–608. https://doi.org/10.1016/j.neuroimage.2005.04.035

Hester, R., Nestor, L., & Garavan, H. (2009). Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *34*(11), 2450–2458. https://doi.org/10.1038/npp.2009.67

Hester, R., Simões-Franklin, C., & Garavan, H. (2007). Post-error behavior in active cocaine users: Poor awareness of errors in the presence of intact performance adjustments. *Neuropsychopharmacology*, *32*(9), 1974–1984. https://doi.org/10.1038/sj.npp.1301326

Hodgkin, A. L., & Huxley, A. F. (1990). A quantitative description of membrane current and its application to conduction and excitation in nerve. *Bulletin of Mathematical Biology*, *52*(1–2), 25–71. https://doi.org/10.1007/BF02459568

Hoerold, D., Pender, N. P., & Robertson, I. H. (2013). Metacognitive and online error awareness deficits after prefrontal cortex lesions. *Neuropsychologia*, *51*(3), 385–391. https://doi.org/10.1016/j.neuropsychologia.2012.11.019

Hof, P. R., & Morrison, J. H. (2004). The aging brain: Morphomolecular senescence of cortical circuits. *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2004.07.013

Hoffmann, S., & Falkenstein, M. (2011). Aging and error processing: Age related increase in the variability of the error-negativity is not accompanied by increase in response variability. *PLoS ONE*, *6*(2). https://doi.org/10.1371/journal.pone.0017482

Holmes, A. J., & Pizzagalli, D. A. (2008). Spatiotemporal dynamics of error processing dysfunctions in major

depressive disorder. *Archives of General Psychiatry*, *65*(2), 179–188. https://doi.org/10.1001/archgenpsychiatry.2007.19

Holtmaat, A., & Svoboda, K. (2009). Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn2699

Hoogendam, J. M., Ramakers, G. M. J., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation*, *3*(2), 95–118. https://doi.org/10.1016/j.brs.2009.10.005

Hughes, B. L., & Zaki, J. (2015). The neuroscience of motivated cognition. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2014.12.006

Hummel, F. C., & Cohen, L. G. (2005). Drivers of brain plasticity. *Current Opinion in Neurology*. https://doi.org/10.1097/01.wco.0000189876.37475.42

Iannaccone, R., Hauser, T. U., Staempfli, P., Walitza, S., Brandeis, D., & Brem, S. (2015). Conflict monitoring and error processing: New insights from simultaneous EEG-fMRI. *NeuroImage*, *105*, 395–407. https://doi.org/10.1016/j.neuroimage.2014.10.028

Ismail, F. Y., Fatemi, A., & Johnston, M. V. (2017). Cerebral plasticity: Windows of opportunity in the developing brain. *European Journal of Paediatric Neurology*. https://doi.org/10.1016/j.ejpn.2016.07.007

Ito, M. (1982). Experimental verification of Marr-Albus' plasticity assumption for the cerebellum. *Acta Biol Acad Sci Hung*, *33*(2–3), 189–199. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6129762

Ito, S., Stuphorn, V., Brown, J. W., & Schall, J. D. (2003). Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science*, *302*(5642), 120–122. https://doi.org/10.1126/science.1087847

Iuculano, T., & Cohen Kadosh, R. (2013). The Mental Cost of Cognitive Enhancement. *Journal of Neuroscience*, *33*(10), 4482–4486. https://doi.org/10.1523/JNEUROSCI.4927-12.2013

Iyer, M. B., Schleper, N., & Wassermann, E. M. (2003). Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *23*(34), 10867–10872. https://doi.org/23/34/10867 [pii]

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). TDCS polarity effects in motor and cognitive domains: A meta-analytical review. *Experimental Brain Research*. https://doi.org/10.1007/s00221-011-2891-9

James, W. (1890). *The Principles of Psychology*. *The Principles of Psychology* (Vol. 21). https://doi.org/10.1353/hph.1983.0040

Jentzsch, I., & Dudschig, C. (2009). Why do we slow down after an error? Mechanisms underlying the effects of posterror slowing. *Quarterly Journal of Experimental Psychology*, *62*(2), 209–218. https://doi.org/10.1080/17470210802240655

Kaas, J. H. (2015). Neural Plasticity. In *International Encyclopedia of the Social & Behavioral Sciences: Second Edition* (pp. 619–622). https://doi.org/10.1016/B978-0-08-097086-8.55036-3

Kanai, R., Chaieb, L., Antal, A., Walsh, V., & Paulus, W. (2008). Frequency-Dependent Electrical Stimulation of the Visual Cortex. *Current Biology*, *18*(23), 1839–1843. https://doi.org/10.1016/j.cub.2008.10.027

Kappenman, E. S., & Luck, S. J. (2012). *The Oxford Handbook of Event-Related Potential Components*. *The Oxford Handbook of Event-Related Potential Components*. https://doi.org/10.1093/oxfordhb/9780195374148.001.0001

Keenan, H. T., Hooper, S. R., Wetherington, C. E., Nocera, M., & Runyan, D. K. (2007). Neurodevelopmental consequences of early traumatic brain injury in 3-year-old children. *Pediatrics*, *119*(3), e616-23. https://doi.org/10.1542/peds.2006-2313

Kemp, A., & Manahan-Vaughan, D. (2007). Hippocampal long-term depression: master or minion in declarative memory processes? *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2007.01.002

Kerns, J. G., Cohen, J. D., MacDonald, A. W., Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior Cingulate Conflict Monitoring and Adjustments in Control. *Science*, *303*(5660), 1023–1026. https://doi.org/10.1126/science.1089910

Kim, E. J., Kim, W. R., Chi, S. E., Lee, K. H., Park, E. H., Chae, J. H., … Choi, J. S. (2006). Repetitive transcranial magnetic stimulation protects hippocampal plasticity in an animal model of depression. *Neuroscience Letters*, *405*(1–2), 79–83. https://doi.org/10.1016/j.neulet.2006.06.023

King, J. A., Korb, F. M., von Cramon, D. Y., & Ullsperger, M. (2010). Post-Error Behavioral Adjustments Are Facilitated by Activation and Suppression of Task-Relevant and Task-Irrelevant Information Processing. *Journal of Neuroscience*, *30*(38), 12759–12769. https://doi.org/10.1523/JNEUROSCI.3274-10.2010

Kinnison, J., Padmala, S., Choi, J.-M., & Pessoa, L. (2012). Network Analysis Reveals Increased Integration during Emotional and Motivational Processing. *Journal of Neuroscience*, *32*(24), 8361–8372. https://doi.org/10.1523/JNEUROSCI.0821-12.2012

Klein, T. A., Endrass, T., Kathmann, N., Neumann, J., von Cramon, D. Y., & Ullsperger, M. (2007). Neural correlates of error awareness. *NeuroImage*, *34*(4), 1774–1781. https://doi.org/10.1016/j.neuroimage.2006.11.014

Klein, T. a, Ullsperger, M., & Danielmeier, C. (2013). Error awareness and the insula: links to neurological and psychiatric diseases. *Frontiers in Human Neuroscience*, *7*(February), 14. https://doi.org/10.3389/fnhum.2013.00014

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine*, *58*(4), 208–213. https://doi.org/10.1016/j.rehab.2015.05.005

Korchounov, A., & Ziemann, U. (2011). Neuromodulatory neurotransmitters influence LTP-Like plasticity in human cortex: A pharmaco-TMS study. *Neuropsychopharmacology*, *36*(9), 1894–1902.

https://doi.org/10.1038/npp.2011.75

Kou, Z., & Iraji, A. (2014). Imaging brain plasticity after trauma. *Neural Regeneration Research*, *9*(7), 693–700. https://doi.org/10.4103/1673-5374.131568

Kouneiher, F., Charron, S., & Koechlin, E. (2009). Motivation and cognitive control in the human prefrontal cortex. *Nature Neuroscience*, *12*(7), 939–945. https://doi.org/10.1038/nn.2321

Krames, E. S., Hunter Peckham, P., Rezai, A., & Aboelsaad, F. (2009). What Is Neuromodulation? In *Neuromodulation* (pp. 3–8). https://doi.org/10.1016/B978-0-12-374248-3.00002-1

Kujirai, K., Kujirai, T., Sinkjaer, T., & Rothwell, J. C. (2006). Associative plasticity in human motor cortex during voluntary muscle contraction. *Journal of Neurophysiology*, *96*(3), 1337–1346. https://doi.org/10.1152/jn.01140.2005

Kuo, M. F., Paulus, W., & Nitsche, M. A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.05.117

Lambourne, K., & Tomporowski, P. (2010). The effect of exercise-induced arousal on cognitive task performance: A meta-regression analysis. *Brain Research*. https://doi.org/10.1016/j.brainres.2010.03.091

Laming, D. R. J. (1968). Information theory of choice-reaction times. *Information Theory of Choicereaction Times*, *14*, 172. https://doi.org/10.1002/bs.3830140408

Laming, D. R. J. (1968). Information theory of choice-reaction times. *Information Theory of Choice-Reaction Times*, *14*, 172. https://doi.org/10.1080/1461670X.2011.557559

Lang, N., Siebner, H. R., Ward, N. S., Lee, L., Nitsche, M. A., Paulus, W., … Frackowiak, R. S. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *European Journal of Neuroscience*, *22*(2), 495–504. https://doi.org/10.1111/j.1460-9568.2005.04233.x

Larson, M. J., & Perlstein, W. M. (2009). Awareness of deficits and error processing after traumatic brain injury. *NeuroReport*, *20*(16), 1486–1490. https://doi.org/10.1097/WNR.0b013e32833283fe

Larson, M. J., Perlstein, W. M., Demery, J. A., & Stigge-Kaufman, D. A. (2006). Cognitive Control Impairments in Traumatic Brain Injury. *Journal of Clinical and Experimental Neuropsychology*, *28*(6), 968–986. https://doi.org/10.1080/13803390600646860

Lazarov, O., & Hollands, C. (2016). Hippocampal neurogenesis: Learning to remember. *Progress in Neurobiology*. https://doi.org/10.1016/j.pneurobio.2015.12.006

Lim, D. A., & Alvarez-Buylla, A. (2016). The adult ventricular–subventricular zone (V-SVZ) and olfactory bulb (OB) neurogenesis. *Cold Spring Harbor Perspectives in Biology*, *8*(5). https://doi.org/10.1101/cshperspect.a018820

Lisman, J. E. (2001). Three Ca2+ levels affect plasticity differently: The LTP zone, the LTD zone and no man's

land. *Journal of Physiology*, *532*(2), 285. https://doi.org/10.1111/j.1469-7793.2001.0285f.x

Lisman, J., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2011.07.006

Locke, H. S., & Braver, T. S. (2010). Motivational Influences on Cognitive Control: A Cognitive Neuroscience Perspective. In *Self Control in Society, Mind, and Brain*. https://doi.org/10.1093/acprof:oso/9780195391381.003.0007

Lois, C., & Alvarez-Buylla, A. (1994). Long-distance neuronal migration in the adult mammalian brain. *Science*, *264*(5162), 1145–1148. https://doi.org/10.1126/science.8178174

Longo, F. M., & Massa, S. M. (2013). Small-molecule modulation of neurotrophin receptors: a strategy for the treatment of neurological disease. *Nat Rev Drug Discov*, *12*(7), 507–525. https://doi.org/10.1038/nrd4024

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., … Lindenberger, U. (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*, *48*(13), 3878–3883. https://doi.org/10.1016/j.neuropsychologia.2010.08.026

Lövdén, M., Wenger, E., Mårtensson, J., Lindenberger, U., & Bäckman, L. (2013). Structural brain plasticity in adult learning and development. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2013.02.014

Lu, B., Nagappan, G., & Lu, Y. (2015). BDNF and synaptic plasticity, cognitive function, and dysfunction. *Handbook of Experimental Pharmacology*, *220*, 223–250. https://doi.org/10.1007/978-3-642-45106-5_9

Luck, S. (2005). *An introduction to the event related potential technique*. *An introduction to the event related potential technique*. https://doi.org/10.1111/mono.12122

Łukowska, M., Sznajder, M., & Wierzchoń, M. (2018). Error-related cardiac response as information for visibility judgements. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-19144-0

Lüscher, C., & Malenka, R. C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harbor Perspectives in Biology*, *4*(6), 1–15. https://doi.org/10.1101/cshperspect.a005710

Maddox, W. T., & Markman, A. B. (2010). The motivation-cognition interface in learning and decision making. *Current Directions in Psychological Science*, *19*(2), 106–110. https://doi.org/10.1177/0963721410364008

Maeda, F., Keenan, J. P., Tormos, J. M., Topka, H., & Pascual-Leone, A. (2000). Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiology*, *111*, 800–805. https://doi.org/10.1016/s1388-2457(99)00323-5

Magno, E. (2006). The Anterior Cingulate and Error Avoidance. *Journal of Neuroscience*, *26*(18), 4769–4773. https://doi.org/10.1523/JNEUROSCI.0369-06.2006

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences*, *97*(8), 4398–4403. https://doi.org/10.1073/pnas.070039597

Maier, M. E., Di Gregorio, F., Muricchio, T., & Di Pellegrino, G. (2015). Impaired rapid error monitoring but intact error signaling following rostral anterior cingulate cortex lesions in humans. *Frontiers in Human Neuroscience*, *9*(June), 339. https://doi.org/10.3389/fnhum.2015.00339

Malec, J. F., & Moessner, A. M. (2000). Self-awareness, distress, and postacute rehabilitation outcome. *Rehabilitation Psychology*, *45*(3), 227–241. https://doi.org/10.1037/0090-5550.45.3.227

Mandolesi, L., Gelfo, F., Serra, L., Montuori, S., Polverino, A., Curcio, G., & Sorrentino, G. (2017). Environmental factors promoting neural plasticity: Insights from animal and human studies. *Neural Plasticity*. https://doi.org/10.1155/2017/7219461

Mannarelli, D., Pauletti, C., Grippo, A., Amantini, A., Augugliaro, V., Currà, A., … Fattapposta, F. (2015). The role of the right dorsolateral prefrontal cortex in phasic alertness: Evidence from a contingent negative variation and repetitive transcranial magnetic stimulation study. *Neural Plasticity*, *2015*. https://doi.org/10.1155/2015/410785

Mansouri, F. A., Fehring, D. J., Feizpour, A., Gaillard, A., Rosa, M. G. P., Rajan, R., & Jaberzadeh, S. (2016). Direct current stimulation of prefrontal cortex modulates error-induced behavioral adjustments. *European Journal of Neuroscience*, *44*(2), 1856–1869. https://doi.org/10.1111/ejn.13281

Masina, F., Di Rosa, E., & Mapelli, D. (2018a). Intra-Individual Variability of Error Awareness and Post-error Slowing in Three Different Age-Groups. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.00902

Masina, F., Vallesi, A., Di Rosa, E., Semenzato, L., & Mapelli, D. (2018b). Possible role of dorsolateral prefrontal cortex in error awareness: Single-pulse TMS evidence. *Frontiers in Neuroscience*, *12*(MAR). https://doi.org/10.3389/fnins.2018.00179

Mattson, M. P., Maudsley, S., & Martin, B. (2004). BDNF and 5-HT: A dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2004.08.001

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*. https://doi.org/10.1007/s00429-010-0262-0

Merton, P. A., & Morton, H. B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature*, *285*(5762), 227. https://doi.org/10.1038/285227a0

Milshtein-Parush, H., Frere, S., Regev, L., Lahav, C., Benbenishty, A., Ben-Eliyahu, S., … Slutsky, I. (2017). Sensory Deprivation Triggers Synaptic and Intrinsic Plasticity in the Hippocampus. *Cerebral Cortex*, *27*(6), 3457–3470. https://doi.org/10.1093/cercor/bhx084

Ming, G. L., & Song, H. (2005). Adult neurogenesis in the mammalian central nervous system. *Annual*

Review of Neuroscience, *28*, 223–250. https://doi.org/10.1146/annurev.neuro.28.051804.101459

Ming, G. li, & Song, H. (2011). Adult Neurogenesis in the Mammalian Brain: Significant Answers and Significant Questions. *Neuron*. https://doi.org/10.1016/j.neuron.2011.05.001

Miniussi, C., Brignani, D., & Pellicciari, M. C. (2012). Combining transcranial electrical stimulation with electroencephalography: A multimodal approach. *Clinical EEG and Neuroscience*, *43*(3), 184–191. https://doi.org/10.1177/1550059412444976

Miniussi, C., Harris, J. A., & Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2013.06.014

Misonou, H., Mohapatra, D. P., Park, E. W., Leung, V., Zhen, D., Misonou, K., … Trimmer, J. S. (2004). Regulation of ion channel localization and phosphorylation by neuronal activity. *Nature Neuroscience*, *7*(7), 711–718. https://doi.org/10.1038/nn1260

Montanelli, I. (1992). *Il testimone (Vol. 232)*. (C. degli Editori, Ed.).

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimulation*, *6*(3), 424–432. https://doi.org/10.1016/j.brs.2012.04.011

Monte-Silva, K., Liebetanz, D., Grundey, J., Paulus, W., & Nitsche, M. a. (2010). Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. *The Journal of Physiology*, *588*, 3415–3424. https://doi.org/10.1113/jphysiol.2010.190181

Mora, F., Segovia, G., & del Arco, A. (2007). Aging, plasticity and environmental enrichment: Structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Research Reviews*. https://doi.org/10.1016/j.brainresrev.2007.03.011

Moran, T. P. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychological Bulletin*, *142*(8), 831–864. https://doi.org/10.1037/bul0000051

Munafò, M., & Neill, J. (2016). Null is beautiful: On the importance of publishing null results. *Journal of Psychopharmacology*, *30*(7), 585–585. https://doi.org/10.1177/0269881116638813

Murphy, P. R., Robertson, I. H., Allen, D., Hester, R., & O'Connell, R. G. (2012). An electrophysiological signal that precisely tracks the emergence of error awareness. *Frontiers in Human Neuroscience*, *6*(March), 1–16. https://doi.org/10.3389/fnhum.2012.00065

Nabavi, S., Fox, R., Proulx, C. D., Lin, J. Y., Tsien, R. Y., & Malinow, R. (2014). Engineering a memory with LTD and LTP. *Nature*, *511*(7509), 348–352. https://doi.org/10.1038/nature13294

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.

Nicoll, R. A. (2017). A Brief History of Long-Term Potentiation. *Neuron*.

https://doi.org/10.1016/j.neuron.2016.12.015

Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P. H., & Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, *38*(5), 752–760. https://doi.org/10.1111/1469-8986.3850752

Niimi, M., Hashimoto, K., Kakuda, W., Miyano, S., Momosaki, R., Ishima, T., & Abo, M. (2016). Role of brain-derived neurotrophic factor in beneficial effects of repetitive transcranial magnetic stimulation for upper limb hemiparesis after stroke. *PLoS ONE*, *11*(3). https://doi.org/10.1371/journal.pone.0152241

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., … Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. https://doi.org/10.1016/j.brs.2008.06.004

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., … Paulus, W. (2003). Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans. *The Journal of Physiology*, *553*(1), 293–301. https://doi.org/10.1113/jphysiol.2003.049916

Nitsche, M. A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004). Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology*, *29*(8), 1573–1578. https://doi.org/10.1038/sj.npp.1300517

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(3), 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Notebaert, W., Houtman, F., Opstal, F. Van, Gevers, W., Fias, W., & Verguts, T. (2009). Post-error slowing: An orienting account. *Cognition*, *111*(2), 275–279. https://doi.org/10.1016/j.cognition.2009.02.002

O'Connell, R. G., Bellgrove, M. A., Dockree, P. M., Lau, A., Hester, R., Garavan, H., … Robertson, I. H. (2009). The neural correlates of deficient error awareness in attention-deficit hyperactivity disorder (ADHD). *Neuropsychologia*, *47*(4), 1149–1159. https://doi.org/10.1016/j.neuropsychologia.2009.01.011

O'Connell, R. G., Dockree, P. M., Bellgrove, M. A., Kelly, S. P., Hester, R., Garavan, H., … Foxe, J. J. (2007). The role of cingulate cortex in the detection of errors with and without awareness: A high-density electrical mapping study. *European Journal of Neuroscience*, *25*(8), 2571–2579. https://doi.org/10.1111/j.1460-9568.2007.05477.x

O'Keefe, J., & Nadel, L. (1978). Hippocampus Physiology. *The Hippocampus as a Cognitive Map*, (1), 141–230.

O'Reilly, R. C., & Frank, M. J. (2006). Making working memory work: A computational model of learning in the prefrontal cortex and basal ganglia. *Neural Computation*, *18*(2), 283–328. https://doi.org/10.1162/089976606775093909

O'Shea, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2004). Timing of target discrimination in human

frontal eye fields. *Journal of Cognitive Neuroscience*, *16*(6), 1060–1067. https://doi.org/10.1162/0898929041502634

Oberman, L. (2014). Repetitive Transcranial Magnetic Stimulation (rTMS) Protocols. In *Transcranial Magnetic Stimulation* (pp. 129–139). https://doi.org/10.1007/978-1-4939-0879-0

Obeso, I., Oliviero, A., & Jahanshahi, M. (2016). Editorial: Non-invasive brain stimulation in neurology and psychiatry. *Frontiers in Neuroscience*, *10*(DEC). https://doi.org/10.3389/fnins.2016.00574

Olvet, D. M., & Hajcak, G. (2008). The error-related negativity (ERN) and psychopathology: Toward an endophenotype. *Clinical Psychology Review*. https://doi.org/10.1016/j.cpr.2008.07.003

Orr, C., & Hester, R. (2012). Error-related anterior cingulate cortex activity and the prediction of conscious error awareness. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00177

Overbeek, T. J. M., Nieuwenhuis, S., & Ridderinkhof, K. R. (2005). Dissociable Components of Error Processing. *Journal of Psychophysiology*, *19*(4), 319–329. https://doi.org/10.1027/0269-8803.19.4.319

Palmer, E. C., David, A. S., & Fleming, S. M. (2014). Effects of age on metacognitive efficiency. *Consciousness and Cognition*, *28*(1), 151–160. https://doi.org/10.1016/j.concog.2014.06.007

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). THE PLASTIC HUMAN BRAIN CORTEX. *Annual Review of Neuroscience*, *28*(1), 377–401. https://doi.org/10.1146/annurev.neuro.27.070203.144216

Pascual-Leone, A., Dang, N., Cohen, L. G., & Brasil-Neto, J. P. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *Journal of Neurophysiology*, *74*(3), 1037–1045.

Patton, H. D., & Amassian, V. E. (1954). Single- and Multiple-Unit Analysis of Cortical Stage of Pyramidal Tract Activation. *Journal of Neurophysiology*, *17*(4), 345–363.

Paulus, W. (2011). Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychological Rehabilitation*, *21*(5), 602–617. https://doi.org/10.1080/09602011.2011.557292

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. (2016). The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. *Brain Stimulation*, *9*(3), 336–346. https://doi.org/10.1016/j.brs.2016.03.010

Pessoa, L. (2009). How do emotion and motivation direct executive control? *Trends in Cognitive Sciences*, *13*(4), 160–166. https://doi.org/10.1016/j.tics.2009.01.006

Pessoa, L. (2010). Embedding reward signals into perception and cognition. *Frontiers in Neuroscience*, *4*. https://doi.org/10.3389/fnins.2010.00017

Petruska, J. C., & Mendell, L. M. (2009). Nerve Growth Factor. In *Encyclopedia of Neuroscience* (pp. 71–78). https://doi.org/10.1016/B978-008045046-9.00672-0

Pogosyan, A., Gaynor, L. D., Eusebio, A., & Brown, P. (2009). Boosting Cortical Activity at Beta-Band Frequencies Slows Movement in Humans. *Current Biology*, *19*(19), 1637–1641.

https://doi.org/10.1016/j.cub.2009.07.074

Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nature Neuroscience*. https://doi.org/10.1038/s41593-017-0054-4

Pontifex, M. B., Scudder, M. R., Brown, M. L., O'Leary, K. C., Wu, C. T., Themanson, J. R., & Hillman, C. H. (2010). On the number of trials necessary for stabilization of error-related brain activity across the life span. *Psychophysiology*, *47*(4), 767–773. https://doi.org/10.1111/j.1469-8986.2010.00974.x

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects. *Brain Research Bulletin*, *72*(May), (208-14.

Posner, M. I., & Presti, D. E. (1987). Selective attention and cognitive control. *Trends in Neurosciences*, *10*(1), 13–17. https://doi.org/10.1016/0166-2236(87)90116-0

Pridmore, S., Fernandes Filho, J. a, Nahas, Z., Liberatos, C., & George, M. S. (1998). Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *The Journal of ECT*.

Priori, A., Hallett, M., & Rothwell, J. C. (2009). Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? *Brain Stimulation*, *2*(4), 241–245. https://doi.org/10.1016/j.brs.2009.02.004

Purpura, D. P., & McMurtry, J. G. (1965). Intracellular Activities and Evoked Potential Changes During of motor cortex. *Neurophysiol*, *28*(1), 166–185. https://doi.org/10.1152/jn.1965.28.1.166

Rabbitt, P. (1967). Time to detect errors as a function of factors affecting choice-response time. *Acta Psychologica*, *27*, 131–142. https://doi.org/10.1016/0001-6918(67)90053-4

Rabbitt, P. (1990). Age, IQ and awareness, and recall of errors. *Ergonomics*, *33*(10–11), 1291–1305. https://doi.org/10.1080/00140139008925333

Rabbitt, P. M. (1966). Errors and error correction in choice-response tasks. *Journal of Experimental Psychology*, *71*(2), 264–272. https://doi.org/10.1037/h0022853

Rabbitt, P. M. (1968). Three kinds of error-signalling responses in a serial choice task. *The Quarterly Journal of Experimental Psychology*, *20*(2), 179–188. https://doi.org/10.1080/14640746808400146

Raz, N. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*, *7*(3), 268–282. https://doi.org/10.1093/cercor/7.3.268

Reason, J. (1990). Human error. *Human Error.*, 1056–1057. https://doi.org/10.1017/CBO9781139062367

Reed, A. E., & Carstensen, L. L. (2012). The theory behind the age-related positivity effect. *Frontiers in Psychology*, *3*(SEP). https://doi.org/10.3389/fpsyg.2012.00339

Ridderinkhof, K. R. (2002). Micro- and macro-adjustments of task set: Activation and suppression in conflict tasks. *Psychological Research*, *66*(4), 312–323. https://doi.org/10.1007/s00426-002-0104-7

Ridderinkhof, K. R., Ramautar, J. R., & Wijnen, J. G. (2009). To PEor not to PE: A P3-like ERP component reflecting the processing of response errors. *Psychophysiology*, *46*(3), 531–538.

https://doi.org/10.1111/j.1469-8986.2009.00790.x

Ridding, M. C., & Rothwell, J. C. (2007). Is there a future for therapeutic use of transcranial magnetic stimulation? *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn2169

Robertson, E. M., Théoret, H., & Pascual-Leone, a. (2003). Studies in cognition: the problems solved and created by transcranial magnetic stimulation. *Journal of Cognitive Neuroscience*, *15*, 948–960. https://doi.org/10.1162/089892903770007344

Robertson, I. H. (2014). A right hemisphere role in cognitive reserve. *Neurobiology of Aging*. https://doi.org/10.1016/j.neurobiolaging.2013.11.028

Rollnik, J. D., Schröder, C., Rodríguez-Fornells, A., Kurzbuch, A. R., Däuper, J., Möller, J., & Münte, T. F. (2004). Functional lesions and human action monitoring: Combining repetitive transcranial magnetic stimulation and event-related brain potentials. *Clinical Neurophysiology*, *115*(1), 145–153. https://doi.org/10.1016/j.clinph.2003.05.001

Rosenberg, T., Gal-Ben-Ari, S., Dieterich, D. C., Kreutz, M. R., Ziv, N. E., Gundelfinger, E. D., & Rosenblum, K. (2014). The roles of protein expression in synaptic plasticity and memory consolidation. *Frontiers in Molecular Neuroscience*, *7*. https://doi.org/10.3389/fnmol.2014.00086

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: An update. *Clinical Neurophysiology*, *122*(8), 1686. https://doi.org/10.1016/j.clinph.2010.12.037

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Avanzini, G., Bestmann, S., … Ziemann, U. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2009.08.016

Rossi, S., & Rossini, P. M. (2004). TMS in cognitive plasticity and the potential for rehabilitation. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2004.04.012

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., … Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application: An updated report from an I.F.C.N. Committee. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2015.02.001

Rotenberg, A., Horvath, J. C., & Pascual-Leone, A. (2014). The Transcranial Magnetic Stimulation (TMS) device and foundational techniques. *Neuromethods*, *89*, 3–13. https://doi.org/10.1007/978-1-4939-0879-0_1

Roth, Y., Amir, A., Levkovitz, Y., & Zangen, A. (2007). Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society*, *24*(1), 31–38. https://doi.org/10.1097/WNP.0b013e31802fa393

Sala, C., & Segal, M. (2014). Dendritic Spines: The Locus of Structural and Functional Plasticity. *Physiological*

Reviews, *94*(1), 141–188. https://doi.org/10.1152/physrev.00012.2013

Sale, A., Berardi, N., & Maffei, L. (2014). Environment and Brain Plasticity: Towards an Endogenous Pharmacotherapy. *Physiological Reviews*, *94*(1), 189–234. https://doi.org/10.1152/physrev.00036.2012

Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society : JINS*, *16*(5), 754–760. https://doi.org/10.1017/S1355617710000706

Sampaio-Baptista, C., & Johansen-Berg, H. (2017). White Matter Plasticity in the Adult Brain. *Neuron*. https://doi.org/10.1016/j.neuron.2017.11.026

Sandrini, M., Umiltà, C., & Rusconi, E. (2011). The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2010.06.005

Santangelo, G., Siciliano, M., Pedone, R., Vitale, C., Falco, F., Bisogno, R., … Trojano, L. (2015). Normative data for the Montreal Cognitive Assessment in an Italian population sample. *Neurological Sciences*, *36*(4), 585–591. https://doi.org/10.1007/s10072-014-1995-y

Schaefer, N., Rotermund, C., Blumrich, E. M., Lourenco, M. V., Joshi, P., Hegemann, R. U., … Turner, A. J. (2017). The malleable brain: plasticity of neural circuits and behavior – a review from students to students. *Journal of Neurochemistry*. https://doi.org/10.1111/jnc.14107

Scheffers, M. K., & Coles, M. G. H. (2000). Performance monitoring in a confusing world: Error-related brain activity, judgments of response accuracy, and types of errors. *Journal of Experimental Psychology: Human Perception and Performance*, *26*(1), 141–151. https://doi.org/10.1037/0096-1523.26.1.141

Schlaug, G., Forgeard, M., Zhu, L., Norton, A., Norton, A., & Winner, E. (2009). Training-induced neuroplasticity in young children. In *Annals of the New York Academy of Sciences* (Vol. 1169, pp. 205–208). https://doi.org/10.1111/j.1749-6632.2009.04842.x

Schreiber, M., Pietschmann, M., Kathmann, N., & Endrass, T. (2011). ERP correlates of performance monitoring in elderly. *Brain and Cognition*, *76*(1), 131–139. https://doi.org/10.1016/j.bandc.2011.02.003

Schulz, R., Gerloff, C., & Hummel, F. C. (2013). Non-invasive brain stimulation in neurological diseases. *Neuropharmacology*. https://doi.org/10.1016/j.neuropharm.2012.05.016

Seifert, S., von Cramon, D. Y., Imperati, D., Tittgemeyer, M., & Ullsperger, M. (2011). Thalamocingulate Interactions In Performance Monitoring. *Journal of Neuroscience*, *31*(9), 3375–3383. https://doi.org/10.1523/JNEUROSCI.6242-10.2011

Sellaro, R., van Leusden, J. W. R., Tona, K.-D., Verkuil, B., Nieuwenhuis, S., & Colzato, L. S. (2015). Transcutaneous Vagus Nerve Stimulation Enhances Post-error Slowing. *Journal of Cognitive Neuroscience*, *27*(11), 2126–2132. https://doi.org/10.1162/jocn_a_00851

Seri, B., García-Verdugo, J. M., Collado-Morente, L., McEwen, B. S., & Alvarez-Buylla, A. (2004). Cell types,

lineage, and architecture of the germinal zone in the adult dentate gyrus. *Journal of Comparative Neurology*, *478*(4), 359–378. https://doi.org/10.1002/cne.20288

Shalgi, S., O'Connell, R. G., Deouell, L. Y., & Robertson, I. H. (2007). Absent minded but accurate: Delaying responses increases accuracy but decreases error awareness. *Experimental Brain Research*, *182*(1), 119–124. https://doi.org/10.1007/s00221-007-1054-5

Shenhav, A., Botvinick, M. M., & Cohen, J. D. (2013). The expected value of control: An integrative theory of anterior cingulate cortex function. *Neuron*. https://doi.org/10.1016/j.neuron.2013.07.007

Shidara, M., & Richmond, B. J. (2002). Anterior cingulate: Single neuronal signals related to degree of reward expectancy. *Science*, *296*(5573), 1709–1711. https://doi.org/10.1126/science.1069504

Shohamy, D., & Adcock, R. A. (2010). Dopamine and adaptive memory. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2010.08.002

Silvanto, J. (2013). Transcranial magnetic stimulation and vision. *Handbook of Clinical Neurology*, *116*, 655–669. https://doi.org/10.1016/B978-0-444-53497-2.00052-8

Simões-Franklin, C., Hester, R., Shpaner, M., Foxe, J. J., & Garavan, H. (2010). Executive function and error detection: The effect of motivation on cingulate and ventral striatum activity. *Human Brain Mapping*, *31*(3), 458–469. https://doi.org/10.1002/hbm.20879

Singh, P., Satyarthee, G., Sharma, B., Mahapatra, A., Vaghani, G., Sinha, S., … Gupta, D. (2013). Outcome of patients with traumatic head injury in infants: An institutional experience at level 1 trauma center. *Journal of Pediatric Neurosciences*, *8*(2), 104. https://doi.org/10.4103/1817-1745.117836

Sokhadze, E. M., Baruth, J. M., Sears, L., Sokhadze, G. E., El-Baz, A. S., & Casanova, M. F. (2012). Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. *Applied Psychophysiology Biofeedback*, *37*(2), 91–102. https://doi.org/10.1007/s10484-012-9182-5

Spaniol, J., Schain, C., & Bowen, H. J. (2014). Reward-enhanced memory in younger and older adults. *Journals of Gerontology - Series B Psychological Sciences and Social Sciences*, *69*(5), 730–740. https://doi.org/10.1093/geronb/gbt044

Spaniol, J., Voss, A., Bowen, H. J., & Grady, C. L. (2011). Motivational incentives modulate age differences in visual perception. *Psychology and Aging*, *26*(4), 932–939. https://doi.org/10.1037/a0023297

Starkstein, S. E., Jorge, R., Mizrahi, R., Adrian, J., & Robinson, R. G. (2007). Insight and danger in Alzheimer's disease. *European Journal of Neurology*, *14*(4), 455–460. https://doi.org/10.1111/j.1468-1331.2007.01745.x

Starns, J. J., & Ratcliff, R. (2010). The effects of aging on the speed–accuracy compromise: Boundary optimality in the diffusion model. *Psychology and Aging*, *25*(2), 377–390. https://doi.org/10.1037/a0018022

Steffens, D. C., Wagner, H. R., Levy, R. M., Horn, K. A., & Krishnan, K. R. R. (2001). Performance feedback deficit in geriatric depression. *Biological Psychiatry*, *50*(5), 358–363. https://doi.org/10.1016/S0006-

3223(01)01165-9

Steinhauser, M., Maier, M., & Hübner, R. (2008). Modeling behavioral measures of error detection in choice tasks: response monitoring versus conflict monitoring. *Journal of Experimental Psychology: Human Perception and Performance*, *34*(1), 158.

Steinhauser, M., & Yeung, N. (2010). Decision Processes in Human Performance Monitoring. *Journal of Neuroscience*, *30*(46), 15643–15653. https://doi.org/10.1523/JNEUROSCI.1899-10.2010

Steinmetz, H., Fürst, G., & Meyer, B. U. (1989). Craniocerebral topography within the international 10-20 system. *Electroencephalography and Clinical Neurophysiology*, *72*(6), 499–506. https://doi.org/10.1016/0013-4694(89)90227-7

Stewart, L. M., Walsh, V., & Rothwell, J. C. (2001). Motor and phosphene thresholds: a transcrainal magnetic stimulation correlation study. *Neuropsychologia*, *39*, 415–419. https://doi.org/10.1002/hbm.20427

Swain, R. A., Harris, A. B., Wiener, E. C., Dutka, M. V., Morris, H. D., Theien, B. E., … Greenough, W. T. (2003). Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience*, *117*(4), 1037–1046. https://doi.org/10.1016/S0306-4522(02)00664-4

Taupin, P. (2006). *Neurogenesis and The Effect of Antidepressants*. *Drug Target Insights* (Vol. 1). Retrieved from http://www.la-press.com/copyright.htm

Tavakoli, A. V., & Yun, K. (2017). Transcranial Alternating Current Stimulation (tACS) Mechanisms and Protocols. *Frontiers in Cellular Neuroscience*, *11*. https://doi.org/10.3389/fncel.2017.00214

Taylor, H. G., & Alden, J. (1997). Age-related differences in outcomes following childhood brain insults: an introduction and overview. *Journal of the International Neuropsychological Society*, *3*, 555–567.

Taylor, S. F., Stern, E. R., & Gehring, W. J. (2007). Neural systems for error monitoring: recent findings and theoretical perspectives. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *13*(2), 160–172. https://doi.org/10.1177/1073858406298184

Terao, Y., Ugawa, Y., Suzuki, M., Sakai, K., Hanajima, R., Gemba-Shimizu, K., & Kanazawa, I. (1997). Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. *Experimental Brain Research*, *115*(3), 541–545. https://doi.org/10.1007/PL00005724

Themanson, J. R., Hillman, C. H., & Curtin, J. J. (2006). Age and physical activity influences on action monitoring during task switching. *Neurobiology of Aging*, *27*(9), 1335–1345. https://doi.org/10.1016/j.neurobiolaging.2005.07.002

Thurley, K., Senn, W., & Lüscher, H.-R. (2008). Dopamine Increases the Gain of the Input-Output Response of Rat Prefrontal Pyramidal Neurons. *Journal of Neurophysiology*, *99*(6), 2985–2997. https://doi.org/10.1152/jn.01098.2007

Thut, G., & Miniussi, C. (2009). New insights into rhythmic brain activity from TMS-EEG studies. *Trends in*

Cognitive Sciences. https://doi.org/10.1016/j.tics.2009.01.004

Tsumoto, T. (1990). Long-term potentiation and depression in the cerebral neocortex. *The Japanese Journal of Physiology*, *40*(5), 573–593. https://doi.org/10.2170/jjphysiol.40.573

Ullsperger, M., Danielmeier, C., & Jocham, G. (2014). Neurophysiology of Performance Monitoring and Adaptive Behavior. *Physiological Reviews*, *94*(1), 35–79. https://doi.org/10.1152/physrev.00041.2012

Ullsperger, M., Fischer, A. G., Nigbur, R., & Endrass, T. (2014). Neural mechanisms and temporal dynamics of performance monitoring. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2014.02.009

Ullsperger, M., & Von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage*, *14*(6), 1387–1401. https://doi.org/10.1006/nimg.2001.0935

Ullsperger, M., von Cramon, D. Y., & Muller, N. G. (2002). Interactions of focal cortical lesions with error processing: evidence from event-related brain potentials. *Neuropsychology*, *16*(4), 548–561. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12382993

Vallesi, A., Shallice, T., & Walsh, V. (2007). Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation. *Cerebral Cortex*, *17*(2), 466–474. https://doi.org/10.1093/cercor/bhj163

van Gaal, S., de Lange, F. P., & Cohen, M. X. (2012). The role of consciousness in cognitive control and decision making. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00121

Van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: FMRI and ERP studies. *Physiology and Behavior*, *77*(4–5), 477–482. https://doi.org/10.1016/S0031-9384(02)00930-7

Veen, V. van, & Carter, C. S. (2002). The Timing of Action-Monitoring Processes in the Anterior Cingulate Cortex. *Journal of Cognitive Neuroscience*, *14*(4), 593–602. https://doi.org/10.1162/08989290260045837

Veniero, D., Strüber, D., Thut, G., & Herrmann, C. S. (2016). Noninvasive Brain Stimulation Techniques Can Modulate Cognitive Processing. *Organizational Research Methods*, 1–32. https://doi.org/10.1177/1094428116658960

Volkow, N. D., Wise, R. A., & Baler, R. (2017). The dopamine motive system: Implications for drug and food addiction. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn.2017.130

Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive Human Brain Stimulation. *Annual Review of Biomedical Engineering*, *9*(1), 527–565. https://doi.org/10.1146/annurev.bioeng.9.061206.133100

Wessel, J. R. (2012). Error awareness and the error-related negativity: evaluating the first decade of evidence. *Frontiers in Human Neuroscience*, *6*(April), 1–16.

https://doi.org/10.3389/fnhum.2012.00088

Wessel, J. R., & Aron, A. R. (2017). On the Globality of Motor Suppression: Unexpected Events and Their Influence on Behavior and Cognition. *Neuron*. https://doi.org/10.1016/j.neuron.2016.12.013

Wessel, J. R., Danielmeier, C., & Ullsperger, M. (2011). Error awareness revisited: Accumulation of multimodal evidence from central and autonomic nervous systems. *Journal of Cognitive Neuroscience*, *23*(10), 3021–3036. https://doi.org/10.1162/jocn.2011.21635

Wiethoff, S., Hamada, M., & Rothwell, J. C. (2014). Variability in Response to Transcranial Direct Current Stimulation of the Motor Cortex. *Brain Stimulation*, *7*(3), 468–475. https://doi.org/10.1016/j.brs.2014.02.003.

Wine, J. (1971). Test anxiety and direction of attention. *Psychological Bulletin*, *76*(2), 92–104. https://doi.org/10.1037/h0031332

Woods, B. T., & Carey, S. (1979). Language deficits after apparent clinical recovery from childhood aphasia. *Annals of Neurology*, *6*(5), 405–409. https://doi.org/10.1002/ana.410060505

Yavari, F., Jamil, A., Mosayebi Samani, M., Vidor, L. P., & Nitsche, M. A. (2017). Basic and functional effects of transcranial Electrical Stimulation (tES)—An introduction. *Neuroscience & Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2017.06.015

Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of comparative neurology and psychology*, *18*(5), 459-482.

Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: Conflict monitoring and the error-related negativity. *Psychological Review*. https://doi.org/10.1037/0033-295X.111.4.931

Yeung, N., & Summerfield, C. (2012). Metacognition in human decision-making: confidence and error monitoring. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1594), 1310–1321. https://doi.org/10.1098/rstb.2011.0416

Yu, R. (2015). Choking under pressure: the neuropsychological mechanisms of incentive-induced performance decrements. *Frontiers in Behavioral Neuroscience*, *9*. https://doi.org/10.3389/fnbeh.2015.00019

Ziemann, U. (2004). TMS and drugs. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2004.03.006

Appendix

Per cortesia, prima di sottoporsi a Stimolazione Magnetica Transcranica (TMS) risponda alle seguenti domande. Le informazioni che fornirà sono strettamente confidenziali.

Soffre o ha mai sofferto di crisi epilettiche, convulsioni febbrili o ricorrenti svenimenti? SI NO

Ci sono in famiglia casi di epilessia? SI NO

Se SI, indichi il grado di parentela del/dei familiare/i _____

Ha mai subito un trauma cranico? SI NO

Se SI, fornisca di seguito i dettagli _____

Ha inserti metallici o clip chirurgiche in testa (eccetto per i denti)? SI NO

Ha problemi di cuore? SI NO

È portatore di pacemaker cardiaco? SI NO

È portatore di protesi acustiche? SI NO

Ha problemi di udito o acufeni? SI NO

Prende antidepressivi triciclici? SI NO

Prende farmaci neurolettici? SI NO

Soffre di severi e frequenti mal di testa? 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

Ha già partecipato ad altri esperimenti con la TMS? SI NO

Solo per le donne:

Potrebbe essere incinta? SI NO

È destrimane o mancino? destrimane mancino