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SEEING EMOTIONS IN OTHERS: IMPROVING COGNITIVE AND NEURONAL MECHANISMS OF FACIAL EXPRESSION PROCESSING

Presentata da: Antonio Peta

Coordinatore Dottorato

Prof.re Maurizio Codispoti

Supervisore

Prof.re Giuseppe di Pellegrino

Co-supervisore

Prof.re Vincenzo Romei

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ABSTRACT

In the conceptual framework of affective neuroscience, this thesis intends to advance the understanding of the plasticity mechanisms of other's emotional facial expression representations. Chapter 1 outlines a description of the neurophysiological bases of Hebbian plasticity, reviews influential studies that adopted paired associative stimulation procedures, and introduces new lines of research where the impact of cortico-cortical paired associative stimulation protocols on higher order cognitive functions is investigated. The experiments in Chapter 2 aimed to test the modulatory influence of a perceptual-motor training, based on the execution of emotional expressions, on the subsequent emotion intensity judgements of others' high (i.e., full visible) and low-intensity (i.e., masked) emotional expressions. As a result of the training-induced learning, participants showed a significant congruence effect, as indicated by relatively higher expression intensity ratings for the same emotion as the one that was previously trained. Interestingly, although judged as overall less emotionally intense, surgical facemasks did not prevent the emotion-specific effects of the training to occur, suggesting that covering the lower part of other's face do not interact with the training-induced congruence effect. In Chapter 3 it was implemented a transcranial magnetic stimulation study targeting neural pathways involving re-entrant input from higher order brain regions into lower levels of the visual processing hierarchy. We focused on cortical visual networks within the temporo-occipital stream underpinning the processing of emotional faces and susceptible to plastic adaptations. Importantly, we tested the plasticity-induced effects in a state dependent manner, by administering ccPAS while presenting different facial expressions yet afferent to a specific emotion. Results indicated that the discrimination accuracy of emotion-specific expressions is enhanced following the ccPAS treatment, suggesting that a multi-coil TMS intervention might represent a suitable tool to drive brain remodeling at a neural network level, and consequently influence a specific behavior.

1 CHAPTER I

Associative neuroplasticity: A literature review

1.1 Introduction

The term neuroplasticity indicates the ability of the nervous system to adapt to intrinsic or extrinsic stimuli through the dynamic regulation of its connections, structures, and functions (Cramer et al., 2011). Therefore, neuroplasticity represents a hot topic for cognitive neuroscientists, attempting to better characterize clinical phenotypes, and to identify both new diagnostic tools and cognitive rehabilitation protocols (fig 1). Mechanisms of neural plasticity are at their maximum in the developing brain, where earlier interactions with the surrounding environment normally result in adaptive learning of functional cognitive abilities. However, plasticity might sometimes have a negative effect on clinical status. For instance, the loss of cognitive functions following brain injury have occasionally been indicated as a consequence of maladaptive neuroplasticity outcomes (Nudo, 2006). These detrimental effects might be caused by traumatic events (e.g., stroke) that interfere with local synaptic functionality, which would eventually impact higher order neuronal activation patterns (Cramer et al., 2011). In a related vein, lack of early typical auditory experiences, due to congenital hearing loss, causally determine dysfunctional neural adaptations in the auditory system, leading to weakened neural communication between primary and secondary areas within the auditory cortex (Sharma et al., 2009). As for the visual domain, hereditary optical problems (e.g., cataracts), which inhibit visual input, limit the typical development of the sensory fibers within the visual cortex, such unsuccessful neuronal maturation would ultimately result in persistent visual deficits (Awaya & Miyake, 1988).

There is a contrast between two alternative views regarding neurodegeneration and ageing processes. According to a more classical view, the cognitive decline associated with ageing would be caused by an inexorable decline in the efficiency of the structures (and therefore the functions) of the brain. Alternatively, others postulate that such cognitive decline might be partly due to reduced involvement in cognitively stimulating and challenging activities (Hertzog et al., 2008). The latter assertion drives interesting lines of research, investigating the effectiveness of both preventive and rehabilitative interventions able to induce brain plasticity even in the adults. For instance, a mouse study has proven the beneficial effects on brain functions induced by an “enriched environment”, as compared to a “standard housing” condition (Lazarov et al, 2005), opening possibilities for the development of behavioral programs triggering adaptive neuroplasticity and delaying neurodegenerative processes also in humans. Consistently, it was found that neuroplastic adaptations mediate behavioral improvements induced by rehabilitation protocols administered in psychiatric patients. For instance, Eack et al. (2010) implemented a relatively long-term remediation treatment centered on the social-cognitive domain in schizophrenic participants. Their follow up monitoring revealed meaningful and progressive increase in the grey matter of both the left hippocampus and amygdala. Remarkably, such volume modifications were correlated with the improvement recorded by cognitive assessments (Eack et a., 2010). These conclusions indicate that effective remediation protocols of psychiatric disorders possibly involve significant neuroplastic modifications in the underlying neural structures.

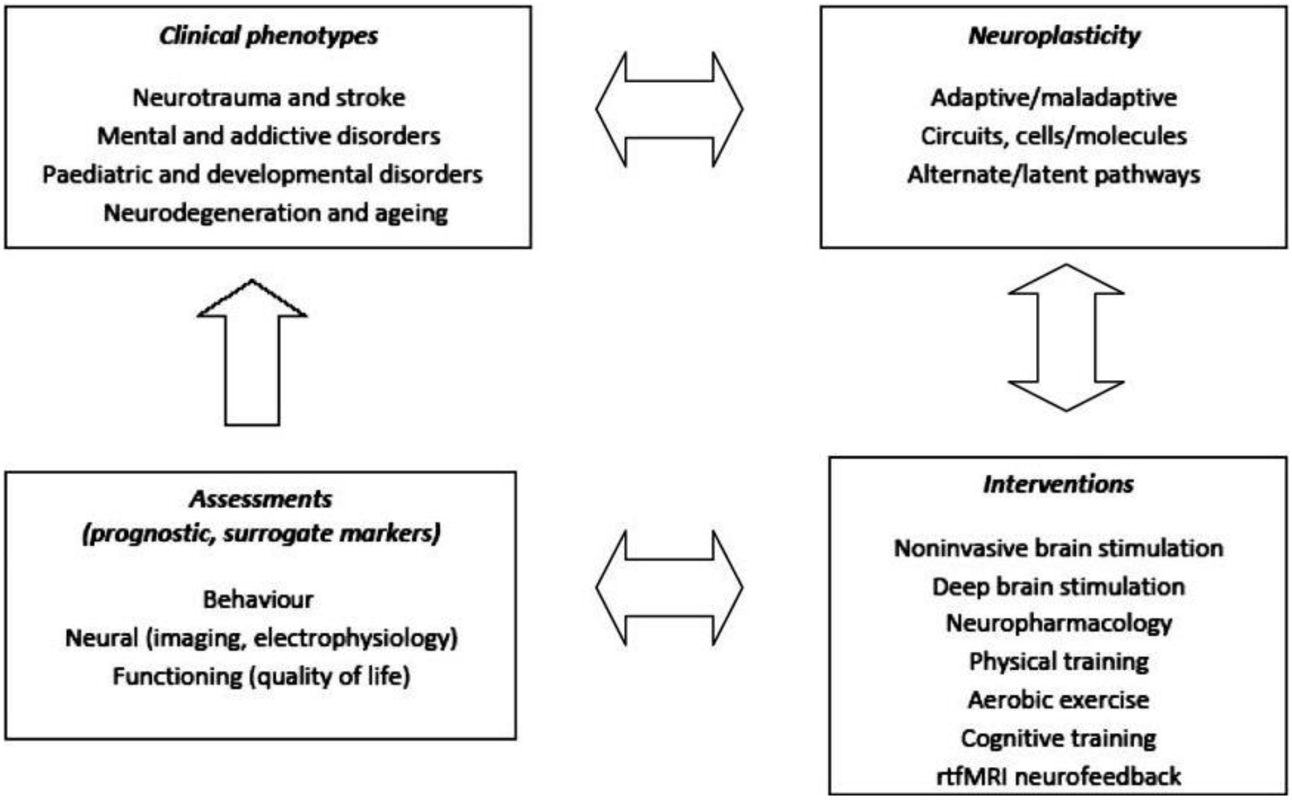


Fig. 1. Image taken from Cramer et al. (2011). Conceptual association between neuroplasticity mechanisms, clinical evidence, assessment procedures, and rehabilitative interventions.

Like deep brain stimulation, transcranial magnetic stimulation (TMS) is based on electrical inputs aiming at influencing the physiological brain activity and shaping the corresponding cognitive functions. In the following paragraphs are presented several TMS procedures designed to test neuroplasticity mechanisms in healthy and clinical populations.

1.2 Transcranial magnetic stimulation and its use

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) technique by which the magnetic fields conveyed by the coils (stimulators) transiently intrude into the brain neurophysiological activity. Decades of research in cognitive neuroscience have indicated TMS as an effective experimental device since it offers the possibility to study the functional relevance of distinct cortical regions. Concerning this, studies have demonstrated TMS-induced inhibitive effects, and boosting consequences on the efficiency of distinct cortical areas (Walsh et al., 1998; Jahanshahi and Rothwell, 2000; Cappa et al., 2002; Harris et al., 2008). Traditionally, TMS has been used as a tool to induce virtual lesions by temporarily disrupting neural firing in order to study the corresponding impairments of the cognitive functions (Pascual-Leone et al., 2000). This approach made it possible to define a causal relationship between the targeted anatomical area and the cognitive processes affected. However, performance-facilitating effects have also been reported following TMS, and such pro-cognitive effects may result from the fact that TMS facilitates task-relevant processing of the neural bases involved in the task (Kamke et al., 2012). Intensity, frequency, and duration of stimulation are the parameters of the TMS that the experimenter can control. For example, Lang et al. (2006) manipulated stimulus intensity and demonstrated that suprathreshold and subthreshold (of the resting motor threshold) repetitive TMS (rTMS) differentially influences the corticospinal excitability as measured by motor evoked potentials (MEPs) amplitude. Huang and colleagues (2005) were among the first to introduce a rTMS protocol to induce plastic changes in the human cortex. They sought to define the frequency properties that could lead to an increase or decrease in the cortical excitability of the motor cortex. Their results report that a continuous TBS (cTBS) protocol is associated with inhibitory effects on performance, whereas intermittent TBS (iTBS) determines facilitatory effects (Huang et al., 2005) on the motor function. Their pioneering study offered a more sustainable alternative to transcranial direct-current stimulation (tDCS) protocols that typically required longer stimulation durations and could sometimes be uncomfortable to the participants. However, the effects of the stimulation intervention can sometimes produce conflicting results, so trying to define rigid causal effects between the stimulation protocol adopted and the effects on cognitive function may represent an oversimplification (Gangitano et al., 2002). For example, it has been seen that the effects of TBS on cortical excitability and resting-state functional connectivity of the motor cortex are not absolute, but dose-dependent (Nettekoven et al., 2014). Gamboa and colleagues (2010) targeted the primary motor cortex with cTBS (40 vs. 80s) or iTBS (190 vs. 380s), their results revealed that both protocols can have both excitatory and inhibitory effects depending on the duration of stimulation.

However, TMS also has limitations, since its spatial resolution goes from approximately 1 to 2 cm from the coil (Kammer, 1999), making impossible to directly target subcortical areas. Nevertheless, TMS application has been extended over the direct application on superficial brain regions, indeed it might also indirectly influence deeper neural structures. In fact, recent literature suggests that this stimulation protocol can be used for the study of cognitive functions whose neural substrate is more attributable to a neural network than to a single area (Nicolo et al., 2015; Romei et al., 2016a; Chiappini et al., 2018). A growing literature is recently giving space to the hypothesis that TMS can modulate not only the excitability of specific target areas, but also that of distant but functionally connected regions (Noh et al., 2012). For example, combined TMS / functional magnetic resonance imaging (fMRI) studies allow to investigate how the reversible inhibition of a target region can impact the neural activity of other regions, thus allowing to highlight the existence of a functional connection between them (Handwerker et al., 2019). Theta Burst Stimulation (TBS) is a repetitive TMS protocol in which the pulses are given at high frequency allowing to reduce the duration of the stimulation session, this represents an advantage since TBS induces long-lasting effects on cortical excitability with relatively short stimulation times. In some studies, the neural activity of the face network was recorded before and after the TMS intervention on cortical areas such as occipital face area (OFA) and the posterior section of the superior temporal sulcus (pSTS). They have shown how these stimulation protocols can induce effects also in subcortical regions such as FFA (Pitcher, 2014) and the amygdala (Pitcher et al., 2017). It was found that inhibitory stimulation on right pSTS caused a decrease in functional connectivity not only in the areas of the dorsal pathway but also between the rFFA and the amygdala. This shows that disrupting a face network node reduces connectivity between the areas interconnected to it, even if these have not been directly targeted. Accordingly, it has been demonstrated that single-site TMS over left parietal lobe enhances cortico-subcortical coupling by determining consequent activity in medial temporal lobe regions such as the hippocampus (Eldaief et al., 2011; Wang et al., 2014).

1.3 Associative plasticity: From slice preparation to neural networks

Hebb (1949) was the first to assert that synaptic plasticity occurs when a brain cell “A” systematically supports the activity of another cell “B” functionally related to it, such interaction would result in strengthened “AB” connectivity. Seminal studies in slice preparations demonstrated that when the associative stimulation was applied following a pre- to post-synaptic sequence it determined a boost in the postsynaptic axon, whereas when the direction of the coupled inputs was reversed (post- to pre-synaptic stimulation) the synapses were weakened (Levy & Steward 1983; Markram et al. 1997; Magee & Johnston, 1997; Bi & Poo 1998; Markram et al., 2011). This kind of plasticity is referred to as spike-timing-dependent plasticity (STDP), it indicates the mechanisms according to which repeated coupled activation of pre/post-synaptic neurons modulates their synaptic efficacy (Sejnowski, 1999). Levy and Steward (1983) demonstrated the crucial concept of STDP: the stimuli delivered to hippocampal tissue could causally determine synaptic strengthening (long-term potentiation, LTP) or weaking (long-term depression, LTD) depending on the direction of the exogenous stimulation. Pairing presynaptic input with coincident postsynaptic depolarization in hippocampal rat cells induced associative plasticity which reflected long term potentiation (LTP) effects (Brown, 1986; Robinson, 1986; Sastry et al. 1986). Similar results were obtained from cats as well, where concurrent stimulation of the motor cortex and its cortical afferents determined LPT (Baranyi & Szente, 1987; Baranyi & Feher, 1981), indicating STDP modifications consistent with the Hebbian rule (Hebb, 1949).

Understanding associative plasticity and the neurophysiological mechanisms leading to activity-dependent modelling of the synaptic interactions (Friston, 2002) is relevant since it has the potential of influencing cognition (Feldman, 2009). Accordingly, such phenomena of associative plasticity might be considered as a cellular basis providing the brain the flexibility needed to allow learning processes both in developmental years and adulthood (Kamke et al., 2012). Indeed, it has been suggested that lower order cognitive functions such as memory creation can be possible through long-lasting changes in synaptic properties (Katz & Shatz, 1996). Therefore, combined neurostimulation and imaging techniques might represent an experimental approach not only to investigate the functional connectivity between interrelated neural nodes, but also to study how cortical plasticity in humans has a role in shaping behavioral outcomes.

LTP/LTD changes in humans have been operationalized by the recording of neurophysiological measures such as the motor evoked potentials (MEPs), which represents the effect of stimulation on motor function. The literature on associative plasticity has mainly focused on the motor system since it is relatively easy to have an objective measure of the cortical excitability by considering MEPs amplitude. For visual areas, this kind of investigation might be hampered by the fact that the measure of plasticity is based on the subjective report of phosphenes (Cowey & Walsh, 2000; Pascual-Leone & Walsh, 2001). However, researchers have demonstrated changes in phosphene threshold after rTMS was applied to the occipital cortex (Ray et al., 1998). In the original PAS protocol, non-painful coupled stimulation is applied over the somatosensory afferents and the primary motor cortex (M1) (Stefan et al., 2000). The peripheral nerve stimulation is given before the M1 TMS, with precise inter stimulus interval (ISI), so that the moment in which M1 is targeted by the stimulating coil likely corresponds with the arrival of the ascending neural signal. Repeatedly activating this neural route with such a timing of PAS would result in enhanced motor evoked potentials (MEPs) amplitude, resembling LTP-like effects (Ziemann et al., 2004; Kamke et al., 2012). Classical PAS studies in humans showed that the ISI between the coupled inputs can sometimes reverse the aftereffects from a LTP to LTD-like effects (Wolters et al. 2003; 2005), proving that associative plasticity has a bidirectional dimension depending on the direction of the exogenous stimulation (pre- to -

postsynaptic *vs*. post- to - presynaptic coupled stimulation of the targeted pathway). Thus, it remarks the crucial timing feature of the sequential paired inputs to effectively produce associative plasticity instead of inhibiting the mono/polysynaptic communication (Bi & Poo, 1998; Wolters et al. 2003, 2005).

Therefore, evidence demonstrated that PAS-induced plastic changes in supraspinal structures are caused by changes in synaptic efficiency provided by LTP- and LTD-like processes (Stefan et al., 2002; Wolters et al., 2003; Ziemann, et al., 2004). Furthermore, these traditional PAS protocols produced plastic modifications in humans lasting on average 30-60 min after the stimulation, mirroring significant, yet labile and short-term, changes compatible with an early stage of the observed activity-dependent changes.

Studies indicated that the ISI crucially drives the aftereffects of the stimulation protocol, as the timing of the spikes causally influences the efficacy of the LTP (Hess et al. 1996; Hess & Donoghue, 1996; Bell et al. 1997; Bi & Poo, 1998; Holmgren & Zilberter, 2001). Indeed, STDP modifications share fundamental characteristics of classic Hebbian synaptic LTP and LTD (Bliss & Collingridge 1993): (i) the direction and temporal interval of the stimulation applied over the pre-postsynaptic target, (ii) relatively long-term duration of the aftereffects, (iii) topographical specificity, (iv) metaplasticity mechanisms (influence of previous neural activity; see discussion below; Stefan et al. 2000; Stefan et al. 2002; Wolters et al. 2003; Ziemann et al. 2004). However, it seems necessary to specify LTP/LTD "-like" because plastic changes in cortical excitability, induced by non-invasive brain stimulation (NIBS) protocols, involve neural mechanisms that only indirectly suggest STDP mechanisms, that could otherwise be described at a deeper level only in animal studies (Bliss & Gardner-Medwin, 1973; Dudek & Bear, 1993).

Although the literature involves a certain degree of variability regarding the outcome of plasticity inducing stimulation protocols (Do et al., 2018; Ridding & Ziemann, 2010; Goldsworthy et al., 2014), some studies claim that PAS protocols induce activity-dependent plastic modulations more reliably than other stimulation techniques (Rosenkranz & Rothwell, 2006; Ilić et al., 2009; Player et al., 2012). Accordingly, in recent years it has been developed a novel TMS methodology of dual-coil intervention termed cortico-cortical paired associative stimulation (ccPAS).

This type of associative stimulation consists of the application of two consequent TMS pulses (i.e., a first conditioning input followed by the activation of the target area), applied on two distinct cortical regions by means of two separate coils, such a protocol would probe direction-specific functional dynamics occurring between two brain regions. Besides intensity, frequency, and duration, ccPAS protocols rely on the interval between paired pulses mimicking the direction and time of communication between two brain areas (Rolston et al., 2007; Masquelier et al., 2008; Gilson et al., 2011). Indeed, non-invasive human brain stimulation is recently moving beyond the notion of simply enhancing or impairing single brain regions, which would be less appropriate to characterize the network-based physiological functioning of cognitive processes (Park & Friston, 2013; Haber & Behrens, 2014; Fornito, et al., 2015; Edwards et al., 2019; Zibman et al., 2019). For instance, some authors claim that, besides the degenerative processes targeting the hippocampus, the cognitive disfunctions observed in Alzheimer's disease patients might be caused by abnormal long-range connectivity emerging from the posterior parietal cortex (PPC) and projecting to distal structures of the associative cerebral cortices (Delbeuck et al., 2003; Buckner et al., 2005; Wang et al., 2007).

However, growing evidence claims that targeting long-range connections might lead to a flip of the traditional pre-to-postsynaptic pairing Hebbian rule (Letzkus et al., 2006; Sjöström & Häusser, 2006). This suggests that STDP changes, as the dendritic distance increases, might determine a complete reversion of traditional spike-timing requirements. This evidence has been termed anti-Hebbian STDP and indicates that the direction of stimulation observed to induce LTP/LTD is opposite with respect of the classical Hebbian STDP: LTP is induced when postsynaptic input preceded presynaptic activity, whereas LTD is provoked when postsynaptic input follows presynaptic activity (Froemke et al., 2010). Therefore, it has recently become evident that the temporal Hebbian rule might not be inflexible. Indeed, when studying neural system more complex than those investigated in animal brain slices it must be considered the interacting ongoing spontaneous neural activity in the human brain (Feldman, 2012). Indeed, higher order cognitive functions involve large-scale dynamic neural interaction (Varela et al., 2001). Thus, it is a present challenge trying to increase the knowledge on plastic adaptation of functional networks, focusing on the connectivity between brain areas.

1.4 Inter-regional offline neuromodulation of motor functions

Rizzo et al. (2009) for the first time implemented a ccPAS protocol aimed at promoting plasticity by pairing bi-hemispherical TMS over left and right primary motor cortex (M1). During the brain stimulation, the pulses were delivered at an inter stimulus interval (ISI) of 8ms, resembling the physiological timing of communication among the two cortical areas. The protocol adopted consisted in a left-to-right direction of stimulation. By adopting a 8ms ISI it was reasonable to hypothesize that the neural volley evoked by the first TMS pulse reached the contralateral M1 at about the same time in which the second pulse was applied. Long term modifications in the inter-hemispheric connectivity were induced, interpreted as a reduction of the inhibitory influence of the left motor cortex over the homologous contralateral M1 that lasted up to one hour after the stimulation (Rizzo et al., 2009). These effects were measured through MEPs, that represent an index of the corticospinal excitability, and by looking at the reaction times recorded during a simple task where responses with the left index finger were required. The authors ruled out the possibility that the effects of the ccPAS were due to a “cooperative” rather than “associative” stimulation by showing that the effects were obtained only when the two associated motor cortices were stimulated at the optimal ISI of 8ms. Such a very short latency ccPAS protocol would engage a neural transmission occurring via direct corticocortical routes (Buch et al., 2010; Neubert et al., 2010). Thus, the results are in line with those of PAS protocols in which was applied a stimulation of a peripheral nerve before the TMS pulse to the corresponding sensorimotor cortex in order to shape the amplitude of the MEPs (Stefan et al. 2000; Wolters et al. 2003). It should be noted that if the plastic modifications were simply due to the isolated stimulation of each individual region, then stimulating the same regions at different ISIs should have led to the same modulating effects on MEPs as observed in the condition in which an optimal ISI of 8ms between pulses was chosen. Rather, the influences derived from the distinct experimental conditions indicated that enhanced pathway efficiency, due to changes in functional connectivity, can be found only when the ISI was set at 8ms, suggesting that precise interpulse timing is essential to induce STDP-like changes. Indeed, it was not observed any changes in hemispheric corticospinal excitability when ccPAS was applied at an ISI of 1ms, thus demonstrating that the aftereffects of the intervention critically depended on an interpulse interval compatible with the Hebbian learning rule (Egger et al., 1999; Holmgren & Zilberter, 2001; Sjöström et al., 2001; Froemke & Dan, 2002; Markram et al., 2012; Feldman, 2012). Interestingly, the inter-hemispherical inhibition was not observed when ccPAS was given at multiple ISIs randomly delivered, suggesting that the induction of plasticity causally depended on a fixed temporal association of the pulse pairs during the stimulation protocol. Koganemaru and colleagues (2009) extended the research field by comparing the effects of a paired bi-hemispheric stimulation (PBS) of the motor cortices (i.e., interconnected cortical areas in the two hemispheres) with the inter-hemispheric parieto-M1 (not interconnected cortical areas in the two hemispheres) stimulation. To evaluate the aftereffects of the protocols, it was measured the performance at the Nine-Hole Peg Test (9-HPT; Mathiowetz et al., 1985; Grice et al., 2003), in which complex fine motor control of digits is required. In the experimental condition the first pulse was given to right motor cortex (conditioned side) followed by a second one over left M1 (targeted side) with a time interval of 15ms. To demonstrate that the effects were timing dependent, the study also included control conditions in which both the order of stimulation and the duration of the inter pulses interval varied. Increased motor performances and motor cortical excitability were shown following TMS over both motor areas. Specifically, a significant improvement was observed during the 9HPT only when the conditioning pulse was given 15ms before to the target pulse over M1. Notably, the behavioral improvement was observed for the contralateral hand independently of which motor cortex (i.e., left or right) was stimulated by the target TMS pulse. Therefore, contrary to Rizzo et al., (2009), Koganemaru and colleagues (2009) observed specular LTP-like effects in both left and right M1. The behavioral consequences had a trend such that an improvement was shown for 40 minutes after stimulation, after which a return to baseline levels was observed. As for Rizzo et al., (2009), these authors failed to show LTD-like effects when the order of the pulses delivered was reversed. They speculated that ccPAS detrimental effects could be observed if, along with inverting the order of stimulation, also the interpulse stimulus was made longer. Besides this, the kind of synapses that are being targeted may play a crucial role when trying to induce symmetric LTP/LTD-like aftereffects. Relevantly, LTP-like effects were not showed when the TMS over the contralateral parietal area preceded that over the left M1. Thus, demonstrating that PBS successfully induces plastic changes in one cortical area only when the conditioned pulse is applied over another cortical area directly associated to it (Koganemaru et al., 2009).

In another study, Mars et al. (2009) looked at the influence that left pre supplementary motor area (pre-SMA) exerts over the left M1 by employing a ccPAS protocol to investigate how it affects the selection of a predicted *vs*. an unpredicted (i.e., alternative) response. They looked at the aftereffects by comparing the performance on stay (predicted response) and switch (alternative response) trials. The results showed that Pre-SMA-to-M1 ccPAS facilitated the selection of the hand contralateral to M1 side in which the target pulse was delivered selectively in switch (but not in stay) trials. This indicates that pre-SMA conditioning effect over M1 is expressed through a direct influence on the action reprogramming function (i.e., action selection under conflict), which is evident only when the pre-SMA-M1 neural network is engaged with an ISI of 6 ms between the TMS pulses, not shorter (i.e., 3ms) nor longer (i.e., 9,12,18ms) ones. A control experiment was run in order to prove the anatomical specificity of left pre-SMA-to-M1 ccPAS. It was implemented a stimulation protocol engaging left pre-SMA and right dorsal PM, maintaining the same ISI proved to successfully induce associative plasticity in the main experiment. It failed to show any behavioral aftereffects, suggesting that only preSMA-M1 functional connectivity is relevant for action reprogramming.

In an interesting methodological evolution, Arai et al. (2011) employed an innovative multicoil associative stimulation protocol in which the modulatory effect of the supplementary motor area (SMA) on the inter-hemispheric M1 functional connectivity was investigated. Besides the right and left motor cortices near-simultaneous (i.e., 0.8ms ISI) stimulation, a third coil over SMA delivered a conditioning pulse at variable ISIs. Thus, the SMA pulse could be delivered before or after the bi-hemispheric M1 stimulation, allowing authors to observe the changes in the MEPs magnitude corresponding to the directionality and timing of stimulation. As a result, LTP-like effects were observed when SMA was stimulated selectively 6ms before bilateral M1 TMS, whereas LTD-like effects occurred when the SMA pulse followed the M1s stimulation by 15ms. Therefore, the cortical spinal excitability, reflected in increasing or decreasing of MEPs amplitude, was causally dependent on both the ISI between SMA-M1s and the direction of stimulation. Therefore, differently from Rizzo et al (2009) and Koganemaru et al (2009), Arai et al. (2011) were the first to show bidirectional associative plasticity over a cortico-cortical system. Namely, by varying the directionality of the stimulating pulses over SMA and M1s, those authors alternatively showed LTP (SMA-to-M1s ccPAS) and LTD (M1s-to-SMA ccPAS) -like aftereffect on MEPs amplitude. Furthermore, when ISIs of 3.2 or 10ms were adopted, the ccPAS-induced behavioral aftereffects did not emerge, highlighting that adopting an optimal stimulation timing (i.e., 6 ms in this case) is crucial, consistently with preliminary peripheral-cortical PAS protocols (Wolters et al., 2003, 2005). Moreover, Arai et al. (2011) tested the topographical specificity of the ccPAS effects on MEPs amplitude by comparing two stimulating protocols: SMA-M1s *vs*. a control condition targeting pre-SMA-M1s. Although the two stimulation protocols had identical parameters (i.e., ISI, stimulation intensity and directionality), targeting pre-SMA did not determine ccPAS-induced behavioral effects, in keeping with studies claiming no direct anatomical connections between pre-SMA and M1 (Bestmann et al., 2003;

Johansen-Berg et al., 2004; Kim et al., 2010). Such assertion would stand in stark contrast with Mars et al.'s (2009) findings, which however measured the impact of the ccPAS protocol on an action reprogramming task rather than MEPs amplitude (Arai et al., 2011). Interestingly, the bilateral M1s stimulation alone failed to determine any modulation in MEPs amplitudes, further corroborating the notion that the timing of transcallosal communication between the targeted nodes is a crucial variable in determining associative plasticity (Rizzo et al., 2009).

In another study, Chao et al. (2015) targeted PPC-to-M1 (8ms ISI) and found increased MEP amplitude relative to baseline, suggesting the occurrence of ccPAS-induced cortical plasticity. Such effects peaked 60 min after the stimulation phase and lasted up to 2 hours, in keeping with previous results showing that associative plasticity does not reach its maximal expression immediately after the PAS or ccPAS protocol (Stefan et al., 2000; Rizzo et al., 2009). Relevantly, no significant ccPAS-induced aftereffects were determined when, as the dependent variable, it was measured the performance (i.e., accuracy and RTs) on a task involving participants' fine finger control (i.e., Purdue pegboard task; Tiffin & Asher, 1948). These null findings indicate that ccPAS protocols are task-dependent, and might need different parameters (e.g., higher intensity pulses, longer ISIs, longer ccPAS duration) in order to shape the performance on complex motor tasks as well. Again, it was demonstrated that the interval between pulses plays a critical role in shaping cortical plasticity: when the ISI was set at 100ms, the ccPAS protocol did not cause modulation of MEP amplitudes. Indeed, with such a long interval it is unlikely that the conditioning volley would have coincided with the second TMS pulse applied to M1, thereby indicating that under such circumstances the conditional stimulation fails to determine plasticity. In a follow-up experiment, Chao et al., (2015) compared MEP amplitude after a single pulse over M1 and a double pulse engaging the PPC-to-M1 pathway, showing that MEP levels only change when M1 stimulation is preceded by the PPC conditioning pulse. Thus, this offers an important demonstration that in order to induce cortical plasticity, when a low frequency stimulation protocol is adopted (as for ccPAS), repeatedly activating a single area by applying focal TMS stimulation might be insufficient. Differently, Thickbroom et al. (2006) found that repeated paired TMS pulses over a single target induced STDP aftereffects. Therefore, an important question would be whether giving a conditioning TMS pulse directly over M1 could induce plasticity such that it would not be necessary to engage a cortical network by pre-stimulating an afferent cortical node. In this scenario, M1 would be given double pulses for each trial. Anyway, previous study demonstrated that repeatedly activating M1 by delivering coupled pulses does not determine the same behavioral and physiological consequences as does the almost-concurrent stimulation of ventral premotor cortex (PMv) or pre-SMA (Davare et al., 2008, Mars et al., 2009, Buch et al., 2010, Catmur et al., 2011).

Rather, when aiming to induce plastic changes by singularly stimulating M1, it should be first probed the timing of recurrent neural communication occurring within the targeted area, and it could be derived by combining to PAS techniques neuroimaging investigations (Johnen et al., 2015; Santarnecchi et al., 2018; Zibman et al., 2019; Momi et al., 2020). Accordingly, the ISI between the TMS pulses over two linked cortical areas has revealed to be a fundamental variable in successfully inducing LTP-like effects, then probing the timing of communication of functionally connected neural nodes (Davare et al., 2008, 2009; Buch et al., 2010; Neubert et al., 2010).

Fiori et al., (2018) tested whether targeting the left PMv-M1 pathway with a ccPAS protocol would boost its efficacy leading to significant meliorative effects on motor actions. In a between-subject design, participants were assigned either to a PMv-to-M1 or M1-to-PMv ccPAS condition, keeping a constant ISI of 8ms, but manipulating the direction of the coupled stimuli delivered (i.e., premotor-to-motor *vs*. motor-to-premotor neural stream engaging). The behavioral task consisted in performing a Nine-Hole Peg Test as fast as possible (9-HPT; Mathiowetz et al., 1985; Grice et al., 2003), where grasping and handling small objects is required to complete the participants’ assignment. As a preliminary result, it was found that PMv→M1 coupled stimulation induced a significant enhancement of MEP magnitude, conversely the M1→PMv paired activation did not produce any aftereffects on corticospinal excitability. Relevant to the purpose of the study, it was found an enhanced motor efficiency only after the PMv→M1 ccPAS, as revealed by a reduction on the average time needed to complete the 9-HPT. Interestingly, such ccPAS protocol failed to modulate participants' performance on a control visuomotor task in which fine hand shaping, and objects manipulation were not task requirements. Therefore, results proved the functional specificity and susceptibility to behavioral changes of the dorsolateral stream circuit, when engaged by a ccPAS protocol that respected the hierarchical, top-down and inter-area timing properties of the targeted neural network (Buch et al., 2011; Johnen et al., 2015).

1.5 Endogenous neural activity interacts with ccPAS-induced STDP

1.5.1 Metaplasticity

Besides comparing the impact of stimulating specific cortical regions prior to task administering, NIBS paradigms allow to test how TMS-induced plastic modifications and cognition interact with each other. Accordingly, there are studies suggesting that cortical plasticity is influenced by the activity endogenously elicited by manipulating the brain state (i.e., asking participants to concurrently perform a cognitive task) in other cortical areas, not strictly related to those targeted by the PAS protocol (Kamke et al., 2012). For instance, participants undergoing PAS expressed weakened motor cortical plasticity when they were contemporary busy solving an arithmetic task (Stefan et al., 2004). In a similar vein, Antal et al.'s (2007) subjects showed reduced susceptibility to M1 cortical plasticity when, conjointly to brain stimulation, they were tested on a cognitively demanding intelligence test. In another study, it was shown that successfully inducing plasticity by PAS depended on the simultaneous participants' attentional load: reduced plastic changes were found in participants exerting higher attentional efforts as compared to low attentional effort group (Kamke et al., 2012).

Apart from the contingent, state-dependent factors reported above, other variables might contribute to modulate LTP/LTD-like after-effects. For instance, Sale et al., (2007) reported that intrinsic circadian fluctuations interact with PAS-induced plasticity, making PAS aftereffects more reliable and evident when the stimulation protocol is administered in the afternoon instead of the morning. Other factors that cannot be controlled by the experimenter have been reported to shape plastic modifications, for instance younger people have demonstrated to be more respondent to PAS protocols than elderly people (Müller-Dahlhaus et al., 2008).

The term metaplasticity refers to the fact that plastic changes in the brain depend on the history of previous activity within the related neural networks (Murakami et al., 2012). For instance, studies suggest that the susceptibility of motor areas to respond to external stimulation depends both on the baseline neural activity at the stimulation site and on its functional connectivity with remote areas (Grefkes et al., 2010; Cardenas-Morales et al., 2014). In other words, metaplasticity concerns the mechanisms by which the previous synaptic activity can alter the sensitivity to subsequent activity-dependent or PAS-induced neural plasticity (Artola et al., 1990; Abraham & Bear, 1996; Abraham, 2008; Karabanov et al., 2015). In particular, homeostatic metaplasticity predicts that neural capacity for dynamic modulations resembles a regression toward a mean value of plastic changes: the higher the preceding postsynaptic activity the smaller the space for subsequent plastic changes, whereas lower previous postsynaptic activity would favor the following induction of LTP (Bienestock et al., 1982). This neurophysiological principle would allow to maintain plastic modifications within a certain range relevant for the functional properties of the neural networks, thus preventing uncontrolled plasticity (Suppa et al., 2017). Pioneering animal studies demonstrated that homeostatic adjustments influence plasticity mechanisms operating in several brain regions (Artola et al., 1990; Abraham & Bear, 1996; Cohen et al., 1998). For instance, rats previously engaged in motor skill performance subsequently manifested less LTP but more LTD as compared with rats that did not undergo preliminary motor training (Rioult-Pedotti et al., 1998, 2000).

Regarding human cortex, several studies supported the notion that metaplastic processes regulate cortical plasticity induced by NIBS techniques (Müller et al., 2007; Bliem et al., 2008; Pötter-Nerger et al., 2009). For instance, Ziemann et al., (2004) found that antecedent voluntary contraction of the thumb abductor (i.e., leading to motor learning) inhibited the following increase of MEPs amplitude as induced by a facilitating PAS protocol, but it made MEPs decrement more consistent after an inhibiting PAS protocol. In a following study, Jung and Ziemann (2009) demonstrated the inverted causal relationship between those variables: the PAS-induced plastic changes had an influence on the subsequent motor learning, according to a homeostatic metaplastic principle. Specifically, LTP-like plasticity induced by a PAS protocol prevented successive motor learning, whereas LTD-like aftereffects facilitated the following acquisition of motor skill. Similarly, Gentner et al., (2008) demonstrated that Theta Burst Stimulation (TBS)-induced neuroplasticity depended on the previously manipulated muscular contraction of the targeted effector: priming the motor system with voluntary activity decreased cortical excitability as compared to the group who did not perform muscular action before undergoing TBS. In relation to the priming effects of two subsequent PAS protocols, Müller et al. (2007) demonstrated that participants who first underwent a PAS protocol boosting M1 excitability subsequently showed reduced LTP induction after a similar facilitating PAS protocol was applied. Conversely, priming participants with a LTD-inducing PAS made them more respondent to a following LTP PAS-induced protocol as measured by the effects on MEP amplitude.
In summary, these studies indicated that neurophysiological aftereffects induced by both motor action and PAS protocols are susceptible to the previous brain state. When implementing NIBS protocols, expected behavioral and physiological outcomes critically depend on the past neural activity and plasticity (Peineau et al., 2007; Vallence & Ridding, 2014; Müller-Dalhaus et al., 2015; Suppa et al., 2017), and it concerns both the brain state within the same area (or network) and other functionally connected regions, consistently with a “heterosynaptic” homeostatic metaplasticity (Bienestock et al., 1982; Pötter-Nerger et al., 2009; Popa et al., 2013).

However, considering that knowledge is accumulated through education and experiences throughout life, if synaptic plasticity mechanisms underlie learning processes and memory storing (Hebb, 1949; Morris et al., 1990; Bliss & Collingridge, 1993; Katz & Shatz, 1996; Zhou & Poo, 2004; Kalia, 2008; Feldman, 2009; Xerri, 2012), then it would be quite unlikely that cognitive abilities evolve uniquely via homeostatic metaplastic principles. Therefore, non-homeostatic metaplastic rules should as well characterize physiological processes subordinated to cognitive functions where (almost) unlimited possibilities for neural modifications are plausible. Thus, under certain circumstances it could be even possible to observe further plastic changes following LTP-like modifications. Müller-Dahlhaus et al., (2015) tested this hypothesis and found that delivering two facilitating PAS protocols at 10 to 30 minutes apart resulted in a summation of LTP-like aftereffects, i.e., the second stimulation protocol enhanced the amplitude and the duration of the first PAS-induced LTP-like effects on MEPs.

1.5.2 State-dependency

The influence of cognitive processes on associative plasticity was also noted. For example, Conte et al. (2007) found that the effect of a 5 Hz-rTMS on the amplitude of MEPs depended on attentional processes: the amplitude of MEPs was greater when participants looked at the hand whose motor representation was stimulated than under "relaxed" and "non-target hand" control conditions. Therefore, we are progressively moving from an offline TMS approach towards a greater consideration of the state and activity of the neural substrate to begin to define the circumstances under which specific aftereffects are observed. Indeed, online TMS refers to the brain stimulation applied while a cognitive process is ongoing (Walsh & Pascual-Leone, 2003), in contrast, offline TMS involves a stimulation protocol applied before the subject is tested on a cognitive task. For instance, it might be hypothesized that the endogenous activity of a neural network at the time of ccPAS intervention would interact with the induced aftereffects. Accordingly, Buch et al. (2011)

investigated whether offline and online ccPAS might differentially alter the physiological connectivity of the PMv-M1 network as indexed by MEPs modulation. To do so, they compared the amplitude of the MEPs after a single pulse over left M1 with trials in which the M1 pulse was preceded by PMv stimulation. They examined (i) the MEPs modulation at different time points after the stimulation protocol, (ii) whether it depended on the order of stimulation (i.e., PMv-to-M1 *vs*. M1-to-PMv), and (iii) how the aftereffects were influenced by the ongoing cognitive activity (i.e., state-dependent stimulation). They also targeted the functional connectivity between pre-SMA and M1, by applying the same stimulation protocol, in order to control for the cortical specificity of the aftereffects. Indeed, pre-SMA-M1 and PMv-M1 are connected and interact with each other with a similar timing (Davare et al., 2008, 2009; Mars et al., 2009; Buch et al., 2010; Neubert et al., 2010). Thus, each one of these networks would represent a good control for the other since both would be efficaciously engaged by identical stimulation parameters while allowing to isolate their different functional contribution. Relevantly, it was studied the interaction between the exogenous stimulation over PMv and the physiological activity of this area during manual grasping, by applying TMS shortly after movement instruction and immediately before movement onset. Buch et al. (2011) also wanted to see if reversing the direction of stimulation (i.e., PMv pulse before M1 pulse) could either facilitate or have a detrimental effect at rest and during the grasping task. Authors found that when a conditioning pulse was given to PMv the following M1 pulse produced a modulation in MEPs amplitude that depended on the activation state of the motor system: when at rest, ccPAS inhibited MEPs with respect to single pulse over M1; whereas, when involved in a behavioral task a M1 pulse following PMv determined an enhancement in MEP levels. Interestingly, the behavioral consequences following the boosting of the PMv-M1 network were not replicated when the preSMA-M1 pathway was targeted. This leads to the conclusion that although the signal from both pre-SMA and PMv reaches M1 they do not modulate the same behavioral outcome. This important finding shed light on the functional value of the area in which the conditioning pulse is applied, playing a crucial role in shaping the plastic changes while performing on a specific motor task. Importantly, reversing the direction of the stimulating pulses inhibited the pathway efficacy, consistent with LTD-like aftereffects. Regarding the crucial STDP rule of directional specific effects, Groppa et al. (2012) implemented a ccPAS paradigm targeting dorsal premotor cortex (PMd)-M1 pathway. Remarkably, experimenters reversed the typical pre-to-postsynaptic direction of stimulation in favor of a feedback hierarchical system. Indeed, the test stimulus over M1 preceded the conditioning stimulus over PMd, and a small range of very brief ISIs from 0.8ms to 2.0ms between pulses was used. Data showed that when at rest, the ccPAS at an ISI of 1.2ms resulted in a significant increase of MEPs amplitude as compared to the condition in which it was delivered a single pulse over M1. Differently, during tonic contraction of the hand muscle the (online) ccPAS failed to produce a significant enhancement of MEPs (Groppa et al., 2012). Interestingly, such pattern of results appears somehow related to Buch et al.'s (2011) findings. Indeed, the detrimental effects of offline PMv-to-M1 ccPAS observed by Buch et al. (2011) might somehow be complementary to the Groppa et al.'s (2012) induced LTP-like aftereffects when the direction of stimulation was reversed, following a M1-to-PMd direction of stimulation. However, when participants were contemporary undergoing ccPAS and motor action (i.e., online ccPAS), Buch et al.'s (2011) results indicated LTP-like effects whereas Groppa et al.'s (2012) data indicated no modulatory effects on MEPs. In spite of that, both studies converge on reporting the powerful contribute of the conditioning stimulus of ccPAS protocols as compared with conditions in which an isolated pulse is applied over the target area. Indeed, both the facilitatory (Buch et al., 2011) and inhibitory (Groppa et al., 2012) ccPAS-induced aftereffects demonstrated to elicit stronger MEPs modulation than a single node stimulation protocol, remarking on the value of ccPAS paradigms.

Johnen et al., (2015) provided a novel paradigm to probe the modulation of a network efficacy following ccPAS, they adopted a TMS-fMRI approach to shed light on the functional connectivity within and outside the PMv-M1 pathway. It was performed a ccPAS with the aim of influencing the synaptic efficacy of PMv-M1 pathway (8ms ISI) while participants were asked to either rest or to make a grasping movement inside the fMRI scanner. The prehension task was particularly relevant because it has been proven to elicit activity within the same motor neural pathway (Grol et al., 2007), thus offering the possibility to study the interaction between the externally and internally induced activity. The prolonged pairing of TMS pulses induced an amplified PMv-M1 BOLD coupling but only while participants were concurrently performing a prehension task. Further analysis confirmed that ccPAS modulates the responsiveness of M1 following the PMv input depending on the state of the participant at the time of stimulation: at rest, the TMS intervention on PMv-M1 pathway failed to induce any significant changes in the PMv-M1 BOLD association. Thus, by inducing pre- and post-synaptic activity it was causally demonstrated a shift in functional connectivity in interaction with the ongoing endogenous cognitive state as measured by fMRI. As a control experiment, it was targeted the same PMv-to-M1 network but the ISI was set at 500ms, which should rule out the possibility of inducing spike timing-dependent plasticity. Accordingly, such a stimulation condition revealed to be ineffective in influencing network functional connectivity. Interestingly, were conducted further analyses on other areas which might be functionally related to the PMv-M1 pathway, therefore affected by a certain degree of reorganization following the plasticity induction protocol. Indeed, it cannot be excluded a contribution of the dual-areas TMS intervention to remote neural nodes with which they share the same cognitive function, as a part of a wider motor network. It was found that prolonged coupling TMS of the PMv-M1 network enhanced dorsolateral (AIP-PMv-M1) circuit coupling but inhibited dorsomedial (pSPL-PMd-M1) circuit coupling.

1.5.3 Anti-Hebbian mechanisms

As described before, STDP rules might demonstrate a certain degree of flexibility when considering cortical circuits involved in complex neural dynamics. Accordingly, it has been shown that not only parameters such as intensity, frequency, and duration of TMS are important in modulating the cortical plasticity in M1. Indeed, a prominent role is played by the direction of the current induced in the brain which is responsible for the specific neural involvement engaged by the stimulating coils (Day et al., 1989; Di Lazzaro et al., 2006). Specifically, the rotation of the TMS coil makes it possible to orient the current delivered from a posterior-anterior (PA) to an anterior-posterior (AP) direction (see. fig. 2). Consistently, distinct set of neurons are perturbed depending on the coil orientation (Ni et al., 2011). Starting from these premises, Koch et al., 2013 targeted the left short-latency posterior parietal cortex (PPC)-M1 pathway (5ms ISI) aiming to explore whether the stimulation protocol could induce both Hebbian and anti-Hebbian STD-like plasticity. Relevantly, the authors assessed whether the neuroplastic changes depended on the orientation of the stimulating TMS coil, thus manipulating the direction of the current delivered to M1. The PPC pulse could be applied before or after the M1 TMS, the ISI was set at 5ms. In the first experiment it was adopted a posterior-anterior current direction, with such an orientation M1-to-PPC stimulation inhibited the excitability of M1, meaning LTD-like effects. Conversely, when the M1 pulse precedes PPC stimulation occurred enhanced excitability of M1, suggesting a LTP effect. This pattern of results met the anti-Hebbian conceptualization of associative plasticity for the PPC-M1 pathway: LTP is obtained when the presynaptic input follows the postsynaptic activity, whereas LTD is induced in the reverse condition. Similar results were obtained when the ISI of the PPC-to-M1 ccPAS was set at 20ms but not when it was 50ms. In a follow up experiment, the ccPAS was applied after changing the coil orientation over M1 in order to invert the current direction from PA to AP. As expected, authors found a different pattern of results: LTP-like effects were obtained when PPC preceded M1 stimulation; conversely, when M1 was stimulated before the PPC the protocol inhibited the corticospinal excitability (LTD-like effects). Thus, these experiments unequivocally proved that changes in MEPs after the engagement of the PPC-M1 neural network critically depended on the preferential activation of distinct neural groups (Koch et al., 2013). Veniero et al. (2013) replicated Koch et al.’s (2013) by showing that PPC-to-M1 ccPAS (5ms ISI) weakened MEPs amplitude whereas the opposite results were found when was adopted M1-to-PPC directionality of stimulation, resembling anti-Hebbian STDP rules. Anyway, by turning the direction of the current applied over M1 to antero-posterior orientation, it was demonstrated the classical Hebbian STDP according to which meliorative plastic changes only occur when the presynaptic cell spikes before the postsynaptic target neuron. These findings for the first time prove transition from anti-Hebbian to Hebbian plasticity in humans, probably involving local dynamics of interaction with distinct groups of postsynaptic neurons. In a separate experiment, Koch et al. (2013) asked participants to maintain a mild muscular contraction concurrently to PPC-M1 (with posterior-anterior current direction) ccPAS (with 5ms ISI), thus in this case a state-dependent ccPAS protocol could be tested. Interestingly, results showed that differently from the resting state results, stimulating the PPC-to-M1 pathway during contraction determined a facilitation of MEP amplitude suggesting LTP-like effects. Conversely, when the pulses followed a M1-to-PPC order it occurred a decrease of MEP magnitude, in contrast with the LTP-like effects observed by administering the same stimulation protocol at rest. Thus, Koch et al. (2013) gave an important contribution by characterizing another variable that might influence the neuromodulating effects of inter-regional TMS protocols. Likewise, animal studies showed that anti-Hebbian STDP might be induced when there is a relatively long distance between the synaptic contact and the cell body of the neuron (Froemke et al., 2005; Sjöström & Häusser, 2006). Thus, in future studies scholars should be careful discussing their results in light of the possibility that anti-Hebbian plastic changes could take place in cortical long-distance neural interactions.

In sum, besides varying the ISI depending on the proximity of the synapses, leading to distinct patterns of LTP/LTD-like effects (Kampa et al., 2007), the nature of the induced plasticity might depend on the direction of the current flow delivered over M1. Indeed, Sommer et al., (2013) proposed that an antero-posterior orientation of the stimulating coil would determine activity in more superficial neuronal groups. Furthermore, an antero-posterior gradient could favor stronger backpropagating action potentials than posterior-anterior current direction, which would instead perturb neural populations at deeper layers. So PA orientation would offer an explanation to the anti-

Hebbian STDP mechanisms because it likely induced a weakened depolarization of distal neurons resulting in LTD, which would instead reverse to LTP when muscular contraction was kept during the online ccPAS, probably because of the summative effects of endogenous and the exogenously-induced neural activity.

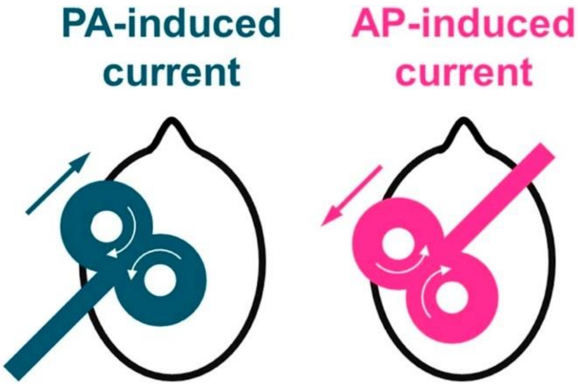


Fig. 2. Image taken from Hannah & Rothwell (2017). Straight arrows represent the direction of the current delivered over the brain; whereas curved arrows indicate the direction of the current flow in the TMS coil.

1.6 Probing cortical networks efficiency in neurological patients

Cortico-cortical pathways have recently started to be targeted by PAS-like protocols which have been proven to effectively induce modulations in synaptic strength of interconnected cortical areas (Arai et al., 2011; Buch, et al., 2011; Groppa et al., 2012). An interesting advancement in the application of NIBS techniques would be using them as a diagnostic tool for neurological disorders. Indeed, if a disruption of inter-areas functional connectivity had occurred in a neurological condition, then implementing a stimulation protocol aiming at strengthening or inhibiting a neural pathway should fail to produce any physiological or behavioral after-effects. This is relevant when considering that STDP modifications observed in behavioral outcomes mirror neurophysiological changes that took place at a neural level. For instance, schizophrenic patients reported abnormalities of LTP/LTD-like effects when tested with transcranial direct current stimulation (tDCS), suggesting impaired intra-M1 activity and inter-areas unresponsiveness to TMS intervention (Hasan et al., 2011; 2012; 2013). Growing literature is emphasizing the importance of combined TMS/neuroimaging studies. For instance, Santarnecchi et al. (2018) studied whether ccPAS over left dorsolateral prefrontal (DLPFC) and inferior parietal lobule (IPL) regions induced LTP-like effects. Importantly, the ccPAS aftereffects were assessed on the fronto-parietal functional connectivity, as measured by fMRI analysis in both resting-state and attention task performance. Specifically, the parietal target (exerting influence on the default mode network, DMN) and prefrontal target (perturbing the task positivity network, TPN) were addressed by manipulating the direction of stimulation (i.e., prefronto-parietal *vs*. parieto-prefrontal stream). Furthermore, the occurrence of simple cooperative rather than associative ccPAS effects were controlled by varying the ISI from contemporary parieto-prefrontal stimulation to 10ms ISI between pulses. It was found that ccPAS influenced the reciprocation between the default mode and test positivity networks. Specifically, bidirectional prefronto-parietal ccPAS accelerated the inhibition of attention-related areas and the activation of the DMN contextually to the switch from resting to attentional demanding blocks. Relevantly, these effects were observed only when the temporal STDP requirement was met, namely in the ccPAS conditions with 10ms ISI.

TMS-evoked potentials (TEPs) are another important source of information which provides the possibility to observe the *in vivo* neural activity occurring within the brain after an exogenous trigger. Specifically, it consists of the application of a single TMS pulse and the concurrent electroencephalographic (EEG) recordings, such method would allow to measure the spread of neural activity starting from the site of stimulation to more distant regions (Miniussi & Thut, 2010; Rogasch & Fitzgerald, 2013). Accordingly, Casula et al., (2016) gave an important contribution to the understanding of STDP at a physiological level. Specifically, they investigated how a ccPAS protocol could influence the neurophysiological state of the fronto-parietal pathway. To this aim, TMS-evoked potentials (TEPs) were recorded in order to assess the connectivity properties in the targeted neural network, known to be particularly involved in attention and memory processes (Olesen et al., 2003; 2004; Sauseng et al., 2005). Indeed, the combined use of ccPAS and EEG allows to examine whether ccPAS outcomes (e.g., MEPs for motor studies), could be associated to changes in the actual neural communication among the targeted cortical nodes. In a within-subjects design, participants were first tested on both orders of stimulation (i.e., DLPF-to-PPC *vs*. PPC-to-DLPFC), then it was administered a block of single-pulse TMS to DLPFC, PPC, and M1 while recording EEG to assess ccPAS physiological effects on cortical activity. It was found that DLPF-to-PPC ccPAS increased the TMS-evoked activity following a single pulse delivered over DLPFC, whereas when the sequence of pulses was reversed (i.e., PPC-to-DLPFC ccPAS) stimulating DLPFC elicited a weaker spread of signal. Thus, demonstrating that bi-directional STDP plasticity can be induced in the DLPFC of healthy participants. Relevantly, these results suggested an anti-Hebbian STDP pattern (Letzkus etal.,2006; Sjöström & Häusser, 2006), consistent with studies in which MEP amplitude modulations indicated LTP-like effects when the postsynaptic activity preceded the presynaptic input, and LTD-like changes when the presynaptic cells fire before the postsynaptic spike (Koch et al., 2013). A possible explanation for the scheme of results in Casula et al.'s (2016) study can be individuated in the distance among the fronto-parietal synaptic inputs. Indeed, such a long range polysynaptic cortical connection could have produced a conversion of the timing prerequisite to induce LTP/LTD-like effects, as a consequence it occurred a reversion of the traditional Hebbian rules (Froemke et al., 2010) Interestingly, when M1 or PPC were targeted, no differences were observed in the TMS-evoked activity before *vs*. after the ccPAS protocol. The absence of physiological changes following the single pulse over the control area M1 (not addressed by the double stimulation protocol) confirmed the relevance of the topographical specificity for STDP mechanisms to take place. However, repeatedly stimulating PPC failed to show any influence in the subsequent single pulse-evoked activity as well. This unexpected result can be explained by considering two ccPAS parameters: (i) the intensity might differently elicit a response among distinct neural populations depending on factors such as the distance from the stimulating coil or their anatomical structures (Kähkönen et al.,2004; Rosanova et al., 2009); (ii) the ISI selected between the TMS pulses (10ms) might not have been optimal to elicit bidirectional STDP modifications within PPC, suggesting that feedback fronto-parietal neural flow might have a different timing than a feedforward parieto-frontal neural volley.

Thus, TEPs brought an objective measure of inter-areas neural interaction, allowing researchers to observe the cortical plasticity aftereffects within non-motor regions that might be deficient in clinical samples (Ilmoniemi et al., 1997; Komssi et al., 2002; 2004; Kähkönen et al., 2005). Parkinson's neurodegenerative disorder can result from abnormal cortical plasticity deriving from dysfunctional subcortical-cortical projections (Morgante et al., 2006). Accordingly, Kim et al. (2015) tested whether targeting basal ganglia with deep brain stimulation (DBS) modulated cortical plasticity in Parkinson's disease (PD) patients. Interestingly, it was found that the conjoint contribution of deep brain stimulation and dopaminergic treatment reactivated plasticity processes in PD as indexed by PAS-induced changes (Kim et al., 2015). Other studies implementing PAS protocols in Huntington's disease (HD) patients have demonstrated altered plasticity in primary motor cortex (Mazarakis et al., 2005; Milnerwood et al., 2006). For instance, Crupi et al. (2008) reported that HD patients were not respondent to PAS as indicated by unaltered MEPs amplitude after the stimulation phase. These findings demonstrated occluded susceptibility to LTP-like plastic modifications, indicating impaired plasticity processes that might be associated with the motor symptoms afflicting people with HD.

To further investigate this field, Ribolsi et al., (2017) tested the validity of a ccPAS intervention to discriminate between schizophrenic and healthy subjects. Specifically, authors hypothesized that in schizophrenic patients the induced cortical plasticity would be altered and not symmetric in the left and right hemisphere, whereas it should be specular in healthy controls. The M1-to-PPC pathway was repeatedly stimulated (5ms ISI) aiming to induce LTP-like short-term plasticity as previously demonstrated by Koch et al. (2013). As a dependent measure of associative plasticity, MEPs were recorded before and at different moments after the stimulation phase so to track the changes over time in M1 excitability. Schizophrenic patients demonstrated to not be susceptible of plasticity-induction in the left hemisphere following the ccPAS protocol, such impairment was not evident in healthy subjects who expressed equal MEPs modulation irrespective of which side of the brain (i.e., left *vs.* right hemisphere) received ccPAS. Furthermore, besides local cortical plasticity of M1, these authors investigated whether ccPAS influenced the activity of M1-related neural nodes. To do so, they focused on the modifications occurred in connectivity between PPC and M1 by combining TMS and EEG techniques. Indeed, TMS-evoked potentials (TEPs) allowed to compare the oscillations and connectivity changes induced by the stimulating coil. The experimental manipulation consisted in changing the direction of stimulation by having a condition in which left PPC TMS precede left M1 pulse, and another condition in which the order was reversed by keeping a constant ISI of 5ms while continuously recording EEG (Ribolsi et al., 2017). They found that irrespective of the STDP mechanisms elicited (Hebbian *vs.* anti-Hebbian) the stimulation of the PPC-M1 pathway increased the inter-area connectivity as shown by the significant modifications of cortico-cortical rhythms in the alpha and beta bands. Specifically, analysis on the interregional connectivity showed that PPC-M1 PAS produced an increase on functional pairing between P3 and C3 electrodes in alpha and beta bands. In addition, when MEP amplitude signaled a LTP-like effect it was found an increase in the alpha band in M1, whereas LTD-like effects where associated to an increment in beta band activity. These results underline the importance of a coherent communication between distal neural populations as a mechanism that modulates associative plasticity, in keeping with the literature claiming that only groups of neurons showing coherent oscillation interact effectively (Fries, 2005; Miltner et al., 1999; Knoblauch et al., 2012). Interestingly, when considering PPC or M1 alone, it was not recorded any difference in the alpha or beta power before and after PAS protocols. Thus, the increase in phase coupling among these cortical areas can be the only factor able to explain the enhanced parietomotor coherence observed.

Di Lorenzo et al., (2018) tested whether the efficiency of the PPC-M1 network is compromised in Alzheimer's disease (AD) patients, aiming to investigate how the cognitive disfunctions are characterized at a synaptic plasticity level. Specifically, left PPC-M1 pathway was targeted by a ccPAS intervention varying the order in which the coupled pulses were delivered (PPC→M1 *vs*. M1→PPC, separated by 5ms ISI), in a within-subjects design. As a dependent measure, MEPs were recorded before and after the stimulation phase to assess and compare plastic changes in both patients and healthy controls. Importantly, the TMS coil orientation over M1 induced a posterior–anterior current direction, this coil orientation was expected to induce anti-Hebbian plastic changes (Ni et al., 2011; Koch et al., 2013; Veniero et al., 2013). Regarding healthy participants, data analyses showed that PPC→M1 ccPAS occluded MEP magnitude, whereas M1→PPC augmented the MEP amplitude, thus the stimulation protocol caused the predicted bidirectional STDP as indexed by the corticospinal excitability measure. Differently, MEP amplitude was not modulated in the clinical sample by any condition of the ccPAS protocols. Therefore, repeated exogenous engagement of the PPC-M1/M1-PPC network in AD patients failed to prompt cortical plasticity, indicating impaired connectivity between those two brain regions. In another study, Tübing et al., (2018) investigated whether a ccPAS protocol targeting SMA-M1 pathway would successfully induce associative plasticity in Gilles de la Tourette syndrome (GTS) patients, known to have deficient functional connectivity in movement related cortical areas (Hampson et al., 2009; Franzkowiak et al., 2012). To this aim, plasticity in SMA-M1 circuits was probed by delivering a pulse over SMA 6ms before the stimulation of M1, MEPs were subsequently recorded as elicited by a single TMS pulse over left M1 (Arai et al., 2011). It was found that the degree of associative plasticity induced in GTS patients was not different from that observed in healthy subjects. Thus, the susceptibility of the SMA-M1 pathway to ccPAS induced plasticity did not seem to be significantly impaired in this clinical sample. Notably, it was found a positive correlation between the motor tic severity and the LTP-like changes. However, the amplitude of LTP-like aftereffects in GTS patients was not higher than the LTP-like modulations in healthy controls, thus making this association unlikely to be considered as a cause (GTS symptoms severity)-effect (LTP-like amplitude) relationship.

In sum, growing evidence is converging on the claim that neurological disorders might be associated with altered plasticity processes (Mazarakis et al., 2005; Milnerwood et al., 2006; Crupi et al., 2008; Hampson et al., 2009; Franzkowiak et al., 2012; Kim et al. 2015; Ribolsi et al., 2017; Di Lorenzo et al., 2018). However, in some cases induced plasticity changes could not be considered as an effective predictor of neurological disorder. For instance, Gilles de la Tourette neuropsychiatric disfunction is not related to altered plasticity associated to sensorimotor streams (Tübing et al., 2018). Moreover, it is difficult to disentangle whether abnormal plasticity is a primary or a secondary effect of the neurological insult. Indeed, confounding factors of compensatory neural plasticity mechanisms could lead to neurophysiological modifications in the post-accident time (Robertson & Murre, 1999; Suppa et al., 2017). Is altered plasticity directly caused by the neurodegenerative disorder? Impaired plastic changes and neurological symptoms are associated by a reciprocal cause-effect relationship? future research is needed to shed light on these issues.

1.7 ccPAS and higher order cognitive functions

Several studies have shown that the first brain responses to visual stimuli consist of a flow of neural activity that proceeds from the primary visual cortex to higher-level areas, for an increasingly detailed processing of visual information (Lamme, 2006). Causal evidence of this comes from chronometric TMS studies, in which the neural activity of a given brain area is perturbed at variable post-presentation timing of the stimulus. For example, Pitcher (2014) gave participants a match-to-sample expression recognition task of emotional faces in which a match face was followed by a target face. Relevantly, during the presentation of the target face, a pair of TMS pulses separated by 40 ms were applied on right OFA (rOFA) and rpSTS with the intention of inhibiting the recognition task. Performance was found to be significantly impaired when rOFA was stimulated 60 and 100ms after the onset of the target stimulus. Instead, as regards rpSTS, the inhibitory effect of the double pulse TMS (dpTMS) was observed in a time window ranging from 60 to 140ms post onset of the probe stimulus. These results demonstrated that the processing of emotional faces begins with a first flow of neural activity that goes from low-level areas (rOFA) to higher-level areas (rpSTS), reflecting a first passage of feedforward information into the system visual (Pitcher et al., 2012). The final stage of a perceptual activity would be in the awareness of the visual information processed. According to the first theories, awareness would be acquired through the so-called recurrent or re-entering neural activity, in which cortico-cortical feedback activity proceeds from higher level areas to the primary visual cortex (Lamme & Roelfsema, 2000; Pascual-Leone & Walsh, 2001; Lamme, 2006).

Romei et al., (2016a) were among the first to prove the ccPAS application over the visual system. These authors targeted the feedback flow of neural information in the V5-V1 pathway demonstrated to be crucial for visual motion processing (Lamme et al., 1998; Pascual Leone & Walsh, 2001; Silvanto et al., 2005). To test the behavioral effects of the ccPAS intervention, a motion coherence task was administered before and at different time points after the ccPAS. Repeatedly activating the V5-to-V1 stream succeeded to induce plasticity only when the Hebbian requirement of adequate interpulse interval was met, according to previous studies in which has been indicated that 20ms corresponds to the optimal timing for V5 to influence the neural activity in V1 (Pascual Leone & Walsh, 2001; Silvanto et al., 2005). Interestingly, when the sequence of pulses engaged feedforward V1-to-V5 stream, no meliorative nor inhibiting effects were observed on the following visual task. Therefore, Romei et al.’s (2016a) study indicates that Hebbian and anti-Hebbian plasticity mechanisms can vary depending on the functional properties of both the bottom-up (V1-to-V5) and top-down (V5-to-V1) modulatory influences of the neural network considered. Indeed, re-entrant V5-to-V1 neural projections have more functional relevance on the motion perception task administered

(Koivisto et al., 2010; Silvanto 2015; Vetter et al., 2015; Gilbert & Li, 2013). Therefore, participants' performance in the experimental group demonstrated to be susceptible of changes (i.e., increased motion sensitivity) contrary to those who received V1-to-V5 ccPAS that supposedly boosted the feedforward neural stream. In a similar vein, Borgomaneri et al (in prep) compared the contribution of feedforward *vs*. feedback neural projections on the processing of emotional faces through a ccPAS protocol. The ccPAS session involved paired and repeated offline stimulation of right posterior STS (rpSTS) and right V1 (rV1), targeting for the first time simultaneously 2 nodes of the neural network involved in emotional faces processing (Pitcher, 2014). Crucially, the ISI interval between the TMS pulses and the directionality of stimulation was manipulated, so to define the optimal conditions for the induction of cortical plasticity. An increase of the performance in the task (in terms of emotion discrimination accuracy) was found only when the stimulation occurred in the temporal-occipital direction, demonstrating that visual back projections have a critical role on emotional perception.

In a following study, Chiappini et al (2018) extended the field of associative plasticity to new considerations about the functional specificity that might characterize the targeted cortico-cortical pathway. Specifically, Chiappini et al., (2018) implemented an online stimulation protocol in which ccPAS of V5-to-V1 (20ms ISI) neural stream was conjointly coupled with the visual presentation of dots moving either leftward or rightward. The rationale behind this was to elicit the activity of neurons preferentially coding for a direction (i.e., left *vs*. right motion coherence) while the stimulation phase was going on, thus applying the ccPAS intervention in a state-dependent manner. In a following session, participants were asked to indicate if the dots patterns were perceived as prevalently moving to left or right. Results indicated that participants' performance significantly improved for trials congruent with the direction primed during ccPAS. Specifically, participants became more accurate in perceiving the motion flow congruent with the direction to which subjects paid attention during ccPAS. Such improvements were not recorded for incongruent motion stimuli (i.e., trials in which the motion direction was the opposite of that presented during ccPAS). Notably, no effects were found when the order of pulses was inverted (i.e., V1-to-V5 ccPAS), consistently with previous results underling the importance of feedback V5-to-V1 neural stream for visual motion processing (Pascual-Leone & Walsh, 2001).

In another study, Zibman et al. (2019) implemented a combined ccPAS/EEG study in which targeted bi-hemispherical lateral prefrontal cortex (LPFC) to evaluate the involvement of this pathway on the attentional bias induced by a pictorial emotional Stroop task (d'Alfonso et al., 2000; van Honk et al., 2002). The attentional bias was measured by subtracting the mean reaction time to emotional faces (i.e., the colour associated to angry faces) from the average response time to non-emotional face (i.e., the colour associated to neutral faces), the higher the index the higher the conflict between coding the colors and the emotional value of the faces. In particular, the direction of ccPAS was varied such that a group of subjects received left to right LPFC ccPAS, while in another group the pair of pulses followed the opposite direction (i.e., right to left bilateral PAS), the ISI between TMS pulses was fixed at 8 ms regardless of the direction of stimulation. Results indicated that ccPAS interacted with the attentional bias measured in a following behavioral task: right-to-left ccPAS inhibited attentional bias, whereas left-to-right ccPAS enhanced it. Interestingly, the ccPAS conditions interacted with bi-hemispherical frontal asymmetry in the alpha band. Specifically, left→right LPFC ccPAS enhanced alpha asymmetry in frontal regions, whereas right→left LPFC ccPAS led to apha asymmetry reduction, no modulation of frontal alpha asymmetry was shown following sham stimulation. Furthermore, inter-hemispherical signal propagation (ISP) analyses indicated enhanced interhemispheric connectivity consistent with ccPAS direction. Specifically, rightward ccPAS induced an increase in left-to-right activation flow as triggered by single pulse TMS over the left LPFC, whereas leftward ccPAS facilitated the right-to-left stream of activity as induced by spTMS over the right LPFC. Thus, these findings provide a neurophysiological demonstration that ccPAS successfully mimics the flow of neural information and accordingly modulates the network connectivity depending on the ccPAS sequence (Zibman et al. 2019). Thus, this study showed that inter-hemispherical ccPAS is a suitable tool for higher order cognitive functions modulation. Indeed, active bidirectional ccPAS sessions significantly interacted with attentional bias and bi-lateral frontal alpha activity, as shown by EEG recordings that gave the possibility to correlate electrophysiological markers to behavioral effects (Zibman et al., 2019).

Momi et al. (2020) implemented a study aiming at assessing the aftereffects on fluid intelligence abilities caused by a ccPAS protocol. Importantly, TMS targets were identified by individualized data collection corresponding to prefrontal (i.e., left middle frontal gyrus) and parietal (i.e., left inferior parietal lobule) regions, that showed higher positive correlation when looking at MRI measures of the fluid intelligence network. By manipulating the order of pulses (i.e., fronto→parietal *vs*. parieto→frontal associative direction), authors examined the specific modulating effects of both antero-posterior and posterior-anterior engagement of the fronto-parietal network. Importantly, two control conditions were included in which (i) ccPAS was delivered at 0ms ISI (differently from the experimental conditions in which the ISI was set at 10ms), and (ii) stimulation was fake (sham condition). Moreover, the potential aftereffects of ccPAS were compared with a condition in which only prefrontal region was targeted by means of a spTMS. Indeed, it was previously demonstrated that prefrontal-TMS alone can determine meliorative effects on cognition (Boroojerdi et al. 2001; Santarnecchi et al. 2013), therefore including this condition would allow a direct comparison of the cognitive effects following a single area vs. dual-site TMS intervention. Results showed that boosting the parieto-to-frontal projections increased the accuracy ratings and shortened the RTs on items tapping into logical reasoning competence as compared to both the simultaneous ccPAS (i.e., 0ms ISI), and the single-site prefrontal TMS. Relevantly, flipping the ccPAS direction to fronto→parietal sequence determined a poorer performance on the same tests with respect to the control conditions. However, the feedback fronto-parietal ccPAS sequence demonstrated to significantly enhance the performance on the relational thinking items, representing a distinct sub-dimension of the fluid intelligence domain. Thus, these findings demonstrated bidirectional STDP-like changes consistent with the functional importance of the receiving end of the two regions targeted with ccPAS: frontal regions on logical thinking, and parietal structures for relational reasoning processing (Houdé et al. 2000; Prado et al. 2010).

Nord et al., (2019) conducted a ccPAS study targeting the connectivity between right LPFC and IPS (intraparietal sulcus) in healthy participants aiming at influencing the strategy adopted on a following decision-making task. These authors manipulated the directionality of stimulation in order to explore any differential behavioral outcome following LPFC→iPS *vs*. iPS→LPFC (10ms ISI) ccPAS sequence. To control for nonspecific effects, it was included a control ccPAS condition with a 100 ms ISI that would presumably violate STDP rules since it improbably would reflect inter-areas communication (i.e., which instead would likely be faster). Results indicated that iPS→LPFC (but not LPFC→iPS) ccPAS facilitated participants' choice of a goal-directed decision plan as compared with the control ccPAS condition. Interestingly, analyses indicated that bidirectional ccPAS at a 100ms ISI did not produce any significant change in decision-making strategy, proving evidence that even when complex cognitive functions are considered the inter-regional timing of communication did not take longer latencies. Conversely, although both targeted regions are involved in working memory and decision-making processes (Chafee & Goldman-Rakic, 2000; Mars et al., 2011), visuospatial working memory abilities were not impacted by any of the ccPAS conditions. This suggests that the effects of ccPAS in the cognitive sphere still needs further investigations, indeed only few studies to date have addressed this issue (Zibman et al., 2018; Kohl et al., 2019; Nord et al., 2019).

1.8 Conclusion

In sum, this chapter provides a preliminary description of the neurophysiological bases concerning Hebbian associative plasticity. The core part of the review is centered on paired associative stimulation (PAS) protocols aimed at manipulating the strength of synaptic connections. A particular focus is oriented to cortico-cortical paired associative stimulation (ccPAS) procedures in which two cortical stimulators jointly target two distant cortical areas. Since the pioneering applications on motor cortex, ccPAS-induced plastic changes have largely been documented outside the motor system. Likewise, innovative activity-dependent brain stimulation protocols have started documenting the selective modulation of low-level cognitive functions (e.g., motion detection). Such preliminary evidence “stimulates” new lines of research pointing the possibility to investigate the potential of ccPAS on modulating higher order cognitive functions as well.

2 CHAPTER II

The role of facial mimicry on delayed expression intensity judgements of masked and unmasked emotional faces

2.1 Abstract

In the present study we explore the plasticity and learning mechanisms of facial expression representations in healthy subjects. We investigate the possibility that a perceptual-motor training, based on facial expressions of emotion, influences the emotion intensity judgements of both high- and low-intensity (i.e., masked) emotional faces. Participants were divided into three groups, according to the training performed: Imitation, counter-imitation, or simulation (i.e., no visual reference) of joyful and angry expressions. As a consequence of the training-induced learning, participants in the imitation group showed the strongest congruence effect, as reflected by higher expression intensity ratings for the congruent, relative to the incongruent, facial expressions. Importantly, although rated as overall less emotionally intense, masked faces did not undermine the emotion-specific aftereffects of the training. Furthermore, we demonstrated that learning effects biased the perceived emotion intensity of non-emotional facial displays as well. Overall, our findings suggest that stimulus (i.e., visual reference) – response (i.e., participants facial movements) compatibility mechanisms modulate the subsequent judgements of others' emotion intensity. These results provide evidence for training-specific perceptual learning processes in high-level vision.

2.2 Introduction

Emotion recognition plays a critical role in interpersonal relationships, it can be considered a basic social cognitive skill which pertains to everyday experiences. Indeed, the capacity to catch emotional cues such as facial expressions, decode them, and react accordingly crucially guides social interactions. Some authors have consistently shown that dysfunctional affect recognition is associated to poor social functioning (Couture et al., 2006), and lack of interpersonal skills (Pinkham & Penn, 2006). Such impairments represent a barrier to successful outcomes in community life, preventing the possibility to take part in many life activities. Accordingly, evidence from clinical psychology indicate that facial emotion recognition atypicalities are associated to depression (Jenness et al., 2014), externalizing behavior (Aspan et al., 2013), and are especially prominent and widely documented in autism spectrum disorder (ASD, Bölte et al. 2008). Indeed, dysfunctions in ASD are evident both when expressing emotions as well as when trying to interpret others' feelings from facial cues (Golan et al., 2007). Consistently, studies have shown that alterations in the ability to recognize others' emotions predispose ASD patients to adverse outcomes such as isolation, social rejection, or bullying, as well as contribute to low occupational status and facilitate the occurrence of coexistent medical conditions (Hill & Frith, 2003). Therefore, the ability to accurately produce and "read" facial expressions represent an important target for intervention in the domain of social cognition, aiming to improve one's capacity to understand social information. However, a better comprehension of the processes involved in social cognition cannot be separated from the study of the underling neural structures. Accordingly, some authors suggest that social-cognitive trainings might encourage the occurrence of related neurogenesis and neuroplastic processes (Kurtz & Richardson, 2012; Barlati et al., 2013). Consistent with this idea, rehabilitation programs including exercises with emotional faces have been associated to neurofunctional changes in the brain (Hooker et al., 2013). Importantly, such modifications occurred in regions supporting facial emotion recognition (Hooker et al., 2013), providing evidence that specific training programs might be able to boost the efficiency of the neurocognitive systems underling emotion processing. In particular, Hooker et al. (2013) found increased neural activity in bilateral amygdala and right MPFC of schizophrenia patients who had previously underwent a training designed to combine cognitive tests (i.e., working memory exercises) with emotion identification exercises. Importantly, these increased neural activity patterns were positively correlated with behavioral improvements on a standardized test measuring emotion perception. Therefore, these results suggest that stimulating experiences within the training environment offered by social-cognitive protocols might cause plasticity-driven modifications in brain activity, which possibly lead to enhanced social behavior and cognitive functioning (Dodell-Feder et al., 2015). Accordingly, human neuroimaging studies of training-induced neuroplasticity indicate that this process is evident in a multitude of cognitive domains. For instance, Draganski et al. (2004) found that intensive juggling practice led to transient grey matter expansion in mid-temporal areas and left posterior intraparietal sulcus, providing causal proof for learning-induced anatomical changes in motion perception regions. Similarly, it was found that long-term training with musical instruments cause structural enlargement of the corpus callosum, which allows interhemispheric communication particularly important during bimanual execution of complex motor sequences (Wan & Schlaug, 2010). In the social-cognitive domain as well, neuroimaging data have revealed relationships between behavioral practices and changes in the underlying neural systems. For instance, Carr et al. (2003) have reported that observing and imitating emotional faces induces greater neural activity within the superior temporal sulcus and the mirror neuron system (MNS) as compared to simply viewing emotional faces. This is of particular interest for the development of emotional training programs. Indeed, studies on children with ASD indicated reduced MNS activity during both observation and imitation of emotional faces as compared to typically developing children (Dapretto et al., 2006). These findings indicate that dysfunctions in the neural systems underling social cognition are at the core of the impaired social functioning documented in autism. Similarly, socio-emotional deficits in schizophrenic patients have been associated to dysfunctional activity patterns in the mirror neuron network (Metha et al., 2014). At a behavioral level, Schwartz et al., (2006) found that patients with schizophrenia had significantly more difficulties to produce and imitate facial expressions as compared to non-psychiatric subjects, suggesting that such dysfunctions should be addressed to improve patients' efficacious interindividual communication. Indeed, imitation is a prevalent form of social communication that favors the understanding of others' actions and affects. The pervasive connection between one's perception and behavior has been defined as "the chameleon effect" (Chartrand et al., 1999). Relevantly, this effect is sometimes manifested as a spontaneous emulation of others' facial expressions, providing behavioral evidence for social mirroring that would eventually facilitate empathic attunement and reciprocal identification (Iacoboni, 2005; Dimberg et al., 2011; Balconi & Canavesio, 2016; Prochazkova & Kret, 2017). Indeed, the predisposition to engage in facial mimicry could represent a facilitating effect when it comes to catch others' emotions. Accordingly, the "matched motor hypothesis" (Hess & Fischer, 2013) suggests that performing a certain action (e.g., a facial expression) would facilitate its recognition when enacted by someone else (Carr & Winkielman, 2014; Vitale et al., 2014; Wood et al., 2016). For instance, Borgomaneri et al. (2020) found that inhibiting the movement of facial muscles activated in smiling impaired the recognition of other's happiness, while it spared the identification of fearful and neutral facial expressions. In another study, De la Rosa et al. 2018 showed that repeatedly simulating a certain facial expression makes participants more prone to see a congruent facial expression when subsequently presented with an ambiguous test stimulus. Thus, these results are consistent with previous literature showing that targeting specific facial expressions determines selective aftereffects in the recognition of congruent emotions (Oberman et al., 2007; Ponari et al., 2012; Maringer et al., 2011; Rychlowska et al., 2014). Interestingly, converging findings come from observations over longer period of time post-training. For instance, Du et al. (2016) implemented an 8-days training program in which subjects exercised discriminating either happy or sad facial expressions. Their results indicated not only emotion-specific before/after improvements in the discrimination abilities for the trained facial expression (e.g., either happy or sad faces), but that such ameliorative effects were still evident after a month post-training. Interestingly, the training-induced learning effects were even extended to congruent but low-intensity emotional faces, providing insights into the generalizability of training programs effects when specific facial features (i.e., expression intensity) vary (Du et al., 2016).

Relatedly, it is currently of particular interest the study of the emotion intensity conveyed by facial expressions. Indeed, the ongoing COVID-19 emergency makes necessary the use of facemasks covering the mouth and nose. On the one hand, facemasks certainly reduce the spread of the infection (Coclite et al., 2020); on the other hand, face covering determines important consequences on inter-individual communication, bringing challenges in catching others' emotional facial cues (Boucher & Ekman, 1975; Nestor et al., 2020; Carbon, 2020). However, the recognition of distinct emotions (e.g., anger, happiness) is differentially impacted by wearing facemasks. Accordingly, studies demonstrated that the eyes provide stronger visual information for the detection of anger as compared to happiness (Fischer et al., 2012; Kret & de Gelder, 2012; Kret & Fischer, 2018), which in turn is better revealed when the mouth is visible (Blais et al., 2012; Calvo & Nummenmaa, 2008; Eisenbarth & Alpers, 2011; Nusseck et al., 2008; Schurgin et al., 2014; Smith et al., 2005; Wegrzyn et al., 2017). For instance, Marini et al. 2021 measured the explicit emotion recognition abilities of participants who attended to facial expressions in the presence of either standard sanitary masks or transparent masks (i.e., restoring the visibility of the mouth region). Results showed that standard facemasks reduced the correct interpretation of the emotional faces, suggesting that when the mouth is not fully visible the recognition of other's facial expression is significantly impaired. In particular, it was found that lower face covering reduced the ability to detect happiness from 94% to 83% rate of accuracy (Marini et al., 2021). Differently, Calbi et al., (2021) found that the correct recognition of happy and angry expressions, and the explicit categorization of the emotions conveyed, was not affected by wearing surgical facemasks.

2.2.1 Aim of the study

It has consistently been suggested that training programs implemented in behavioral experiments represent a viable tool for inducing transient improvements in cognitive processes (Mothersill & Donohoe, 2019). Starting from these premises, in the present study we aimed to behaviorally investigate the plasticity and learning mechanisms of facial expression representations in healthy subjects. To this purpose, we designed a perceptual-motor training in which subjects were instructed to execute either congruent or incongruent facial expressions with respect to faces presented on a screen. Therefore, we implemented a training resembling the principles of "drill and practice" learning (Wykes et al., 2011), based on the assumption that practicing a certain activity eventually leads to learning outcomes. Specifically, we tested the hypothesis that the repeated imitation of emotional faces determines training-induced aftereffects on the processing of congruent expressions. Relevantly, our stimuli included both fully visible faces and faces covered by a surgical mask, aiming to compensate for limitations in the ecological validity of studies using only full-face stimuli showing stereotypical expressions (for instance, Matsumoto & Hwang, 2011). Furthermore, an additional control group was included in which participants were engaged in a different training based on the mere self-generation of facial expressions (i.e., without a model to imitate). Comparisons between the different groups of subjects allowed us to distinguish the behavioral aftereffects between the two training programs designed.

To measure such effects, we implemented a dependent variable focusing on a rather specific feature of the emotional faces, that is the intensity of the facial expressions. We reasoned that our training would not have been so long or intense to elicit a significant shift in participants' accuracy rates. Furthermore, although the test phase included facial stimuli with the mouth covered by a sanitary mask, other facial cues such as the frowns for anger or the wrinkles around the eyes for joy are generally considered to provide sufficient information for emotional recognition (Baron-Cohen et al., 1997, Schmidtmann et al., 2020).

The present study would increase the knowledge on the way we process the intensity of others' emotions, as well as the extent to which engaging in facial mimicry biases the judgement of congruent emotions when facemasks occlude the lower part of both emotional and neutral faces.

2.3 Methods

2.3.1 Participants

A total of 51 subjects (32 females) aged 18-43 years (mean age = 27.7, SD = 6.2) were recruited by posting announcements on social networks about a study concerning "facial expression recognition". Participants were randomly assigned to either one of three groups, according to the perceptual-motor task they were asked to perform (i.e., either imitate, counter-imitate, or simulate facial expressions). All had normal or corrected-to-normal vision and were naïve to the purposes of the study. Participants provided written informed consent, and the procedures were approved by the ethics committee at the Department of Psychology and were in accordance with the ethical standards of the 1964 Declaration of Helsinki. Participation in the study was voluntary and no compensation was given for it.

2.3.2 Visual stimuli

The stimuli were selected from the Karolinska Directed Emotional Faces picture set—KDEF (Lundqvist et al., 1998) and included twelve still images (half males, half female). The employment of still visual stimuli, rather than video clips, allowed to control the exact moment the facial expression was shown. Each actor/actress was presented with two emotional expressions (i.e., either angry or joyful) and with a neutral expression as well. Furthermore, each picture was duplicated and manipulated using Photoshop so to have an additional set of the same faces covered by a sanitary facemask while preserving the shape, the size, and the color of the original pictures (see fig. 1, edited by Calbi et al. 2021). The background color of the pictures did not vary across the different faces.

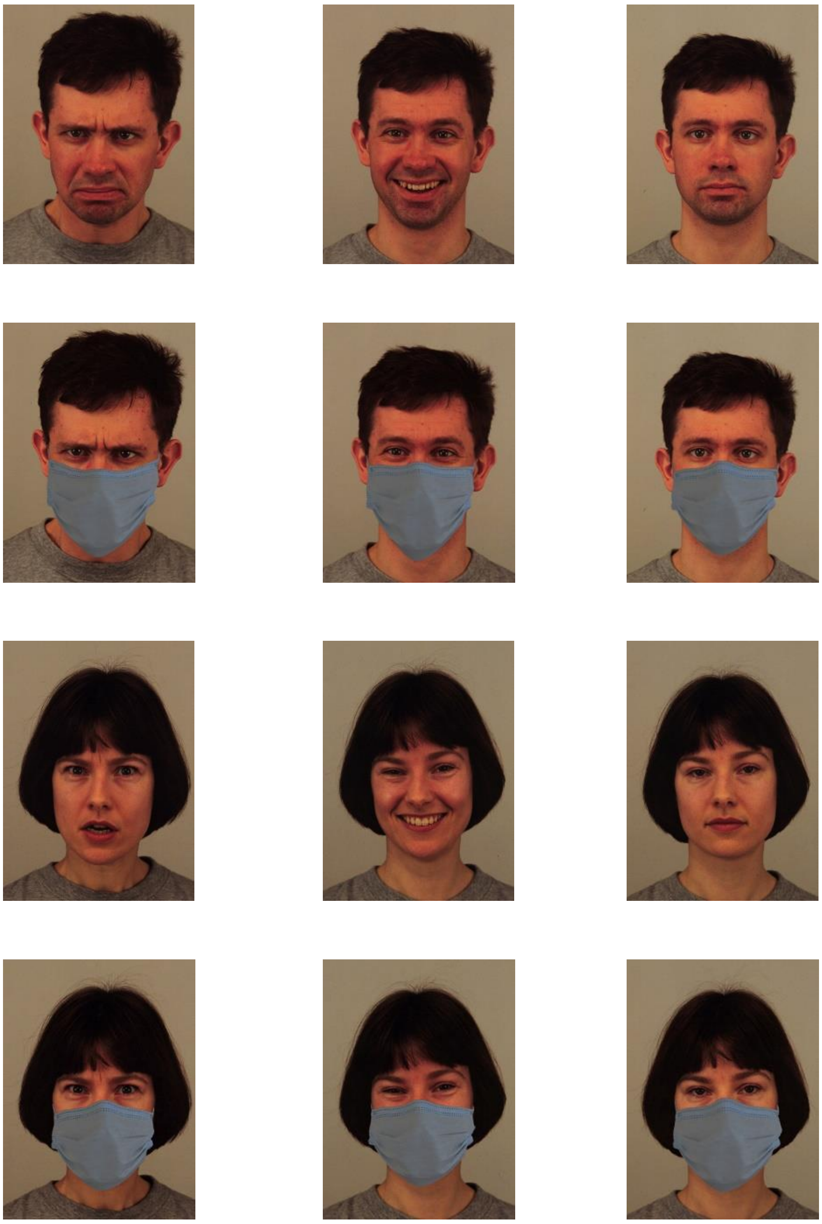


Fig. 1. Example of the stimuli for angry, neutral, and joyful facial expressions, in both unmasked and masked versions (edited by Calbi et al., 2021, original dataset from the Karolinska Directed Emotional Faces – KDEF, Lundkvist et al. 1998).

2.3.3 Emotion intensity task

An Intel® Core™ i7 laptop running OpenSesame 3.3.5 (Mathôt et al., 2012) was used for presenting stimuli on a 15.6-in. color screen monitor and collecting responses from the left mouse button. Participants were seated at about 60 cm from the computer screen. Each trial started with the appearance of a fixation cross for 500 ms, followed by the presentation of the target stimulus (i.e., either a joyful, angry, or neutral face) for 500 ms. Therefore, the presentation of the target face was above the threshold of most typical unconcealed expressions (see Ekman, 1993). Since the presentation of the facial expressions was supraliminal, we designed a dependent variable that reflected intensity ratings of emotional faces rather than a categorical collection of joy/anger/neutral responses, aiming to stretch any difference in emotion perception and avoid ceiling effects. With this aim, we asked participants to rate the intensity of each facial expression presented by using a continuous scale. Indeed, participants' responses were given on a 1000-pixel long bounded rectangle on the screen. The scale was anchored by "joy" at one extremity and "anger" at the other, with the central point associated to the neutral label (for neutral faces) (figure 2). Therefore, participants' responses were converted to numerical values, reflecting the number of pixels along the horizontal axis of the response rectangle, starting from the pixel on the extreme left (pixel -500) to the extreme right (pixel 500) of the response bar. This scale allowed participants to modulate their ratings (ranging from -500 to 500) by choosing to click on intermediate points of the horizontal axis representing the scale, ratings close to the middle point (corresponding to 0) indicated a neutral facial expression. The correspondence between the side of the scale (left or right) and the emotion associated (joy or anger) was randomized and counterbalanced within participants. We administered to all participants 2 blocks of 144 trials each: 3 facial expressions (anger, happiness, neutral) x 12 actors (male, female) x 2 face covering (mask, nomask) x 2 (repetition). Prior to experimental blocks, subjects completed a short practice block of 6 trials to familiarize with the task. Each block lasted about 20 minutes.

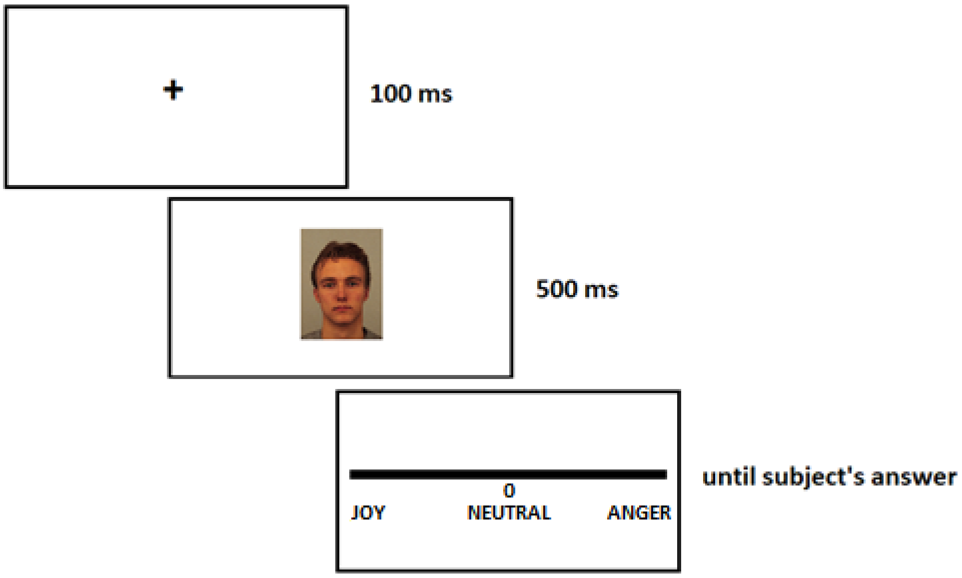


Fig. 2. Illustration of a trial of the emotion intensity task. Each trial begins with the fixation cross, then emotional face representing a neutral, happy, or angry expression for which the participant's emotion intensity judgement is required

2.3.4 Dependent measures

Although subjects were instructed to respond as quickly and accurately as possible, the visual scale we designed did not allow to collect meaningful RTs. Indeed, since the scale was a horizontal bar, the response times were closely linked to the distance covered by the mouse cursor from its appearance point to the point of the scale chosen as the response. Therefore, being the mouse cursor always presented at the center of the screen, the higher the rating the higher the reaction time (further distance from the center of the screen). For this reason, we did not include reaction times in our analyses.

Moreover, we administered the Italian adaptation of the emotional contagion scale (Lo Coco et al., 2014; see Appendix) originally designed by Doherty (1997), assessing a more overt affective form of empathy. The questionnaire comprises 15 items measuring the tendency to acquire other's emotion. It includes 5 basic emotions: anger (e.g., "It irritates me to be around angry people"), fear (e.g., "I notice myself getting tense when I'm around people who are stressed out"), sadness (e.g., "I get filled with sorrow when people talk about the death of their loved ones"), happiness (e.g., "When someone smiles warmly at me, I smile back and feel warm inside"), and love (e.g., "I melt when the one I love holds me close"). Each basic emotion is represented by three items and scored on a five-point Likert scale from (1) *not at all* to (5) *always*. Although we were only interested in items pertaining joy and anger, we decided to administer the full version of the emotional contagion questionnaire since it only takes few minutes to be completed. Furthermore, we reasoned that having the relevant items interspersed between items investigating unrelated emotional dimensions would have made unlikely that participants guessed the link between the trained facial emotion and the responses to the questionnaire.

Finally, we presented participants with two open-ended questions examining whether they grasped the real purpose of the study ("What do you think is being investigated in this study? Do you know the research question of this study? Please describe underneath") (taken from Stel et al., 2008; translated in Italian language).

2.3.5 General procedure

The experimenter explained to the subjects that their first assignment would be to undergo an active session in which they had to generate facial expressions. No direct reference to their internal emotional state was done. It was also anticipated that the immediately following task would be to judge a series of stimulus faces presented on the screen.

In particular, the active sessions we designed were meant to be an emotional training, it consisted of a perceptual-motor task involving concurrent observation and execution of facial expressions. The observed stimuli were emotional faces (i.e., happy or angry) that triggered participants to display either congruent or incongruent facial expressions. An additional group of participants performed self-generated intentional facial expression with no visual reference, this group is referred to as “simulation” group. Thus, participants were randomly assigned to either the *imitation, counter-imitation,* or *simulation* group.

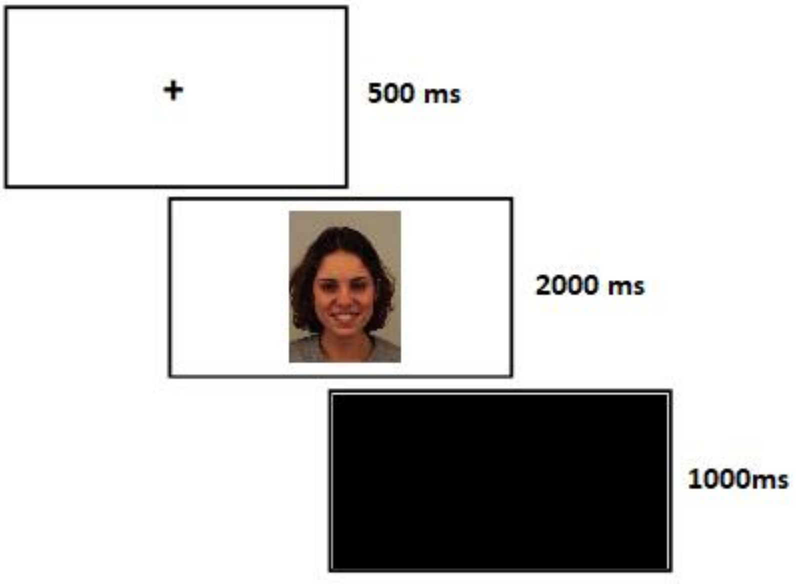
In the imitation group subjects were directed to mimic either angry or happy facial expressions presented in still photographs (see fig 3); whereas in the counter-imitation group participants were previously instructed to enact the opposing emotion to that observed (i.e., smiling when presented with angry faces, and frowning when happy faces were shown. See fig. 4). In other words, we manipulated between subjects the participant’s/actor’s facial expression congruence. In a randomized blocked design, participants completed two emotional training sessions, where either happy or angry faces were generated separately. In both the imitation and counter-imitation groups, each session included the presentation of faces expressing just one emotion (i.e., either joy or anger). In particular, either 90 happy or 90 angry uncovered faces were shown for each training session, corresponding to 9 actors (4 males) taken from the Karolinska Directed Emotional Faces picture set—KDEF (Lundqvist et al., 1998), and repeated 10 times within the session. Thus, subjects underwent two emotional trainings lasting about 7 minutes each.

2.3.6 Imitation/Counter-imitation groups

The trial started with the appearance of a fixation cross for 500 ms, followed by a facial stimulus which remained on the screen for 2000 ms. Depending on the group they belong, participants were instructed to start performing the imitative (or counter-imitative) behavior as soon as the stimulus was presented and for its entire duration (see figures 3 and 4). Therefore, the imperative cue to perform the facial expression was the stimulus onset. The two-second time window chosen to reproduce an emotional face is in accordance with a previous study in which 2s were given to tense and relax facial muscles in response to a visual cue (Hennenlotter et al., 2005). Each trial ended with a black screen shown for 1000ms which participants were instructed to interpret as stop signal, thus prompting them to return to a neutral facial expression until the next trial. The emotional training was not designed to be difficult, so very few mistakes would be expected. Indeed, a short preliminary practice block confirmed that all subjects were accurate at following the instructions and performing such visuo-motor training. Participants completed the emotion intensity task twice, right after each perceptual-motor session (i.e., imitation or counter-imitation) which, again, was emotion specific (i.e., they had to mimic either happy or angry faces).

In sum, the sequence of assignments for both groups was the following: (i) provide sociodemographic information, (ii) perform the emotional training session (i.e., imitation or counter-imitation), (iii) complete the emotional contagion scale, (iv) execute the emotion intensity task - short break - and again (v) perform the training session on the other emotion, (vi) execute the emotion intensity task, (vii) answer to open-ended questions about the purpose of the experiment. Half of the participants performed the imitation (or counter-imitation) of joyful faces first, whereas the other half imitated (or counter-imitated) angry faces first. Therefore, there were two possible time courses of events for both groups, based on the order between the imitative (or counter-imitative) sessions where either joyful or angry faces were presented. All subjects underwent both the joyful and angry facial expression trainings. Therefore, half participants imitated (or counter-imitated joyful expressions before the imitation (or counter-imitation) of angry faces, whereas the other half imitated (counter-imitated) angry faces before the imitation (counter-imitation) of joyful expressions. To make sure that participants were performing the motor training correctly, the experimenter visually inspected them online from a remote device connected to the laptop used for the experiment. Such manipulation check was implemented through a videocall between the remote device and the laptop, participants were unaware of it so to avoid that they felt observed and focused on the camera during the experiment. Subjects were not videotaped; no recordings of the emotional trainings were stored. Participants’ accuracy during the training was assessed qualitatively, with motor responses (i.e., performing either 90 smiles or 90 frownings) observed by the experimenter during the task, and resulting in almost no errors noted. This was expected given that the motor training was very simple and well understood by subjects, who also completed a practice block before starting the training.

We administered the emotional contagion scale just once to reduce the possibility that participants became aware that we were interested in how the mimicry manipulation modulates their perception of other's emotional display. Furthermore, a test and re-test on a 15-item questionnaire within a temporal gap of only 25 minutes could have turned out to be an invalid measure of emotion perception change.



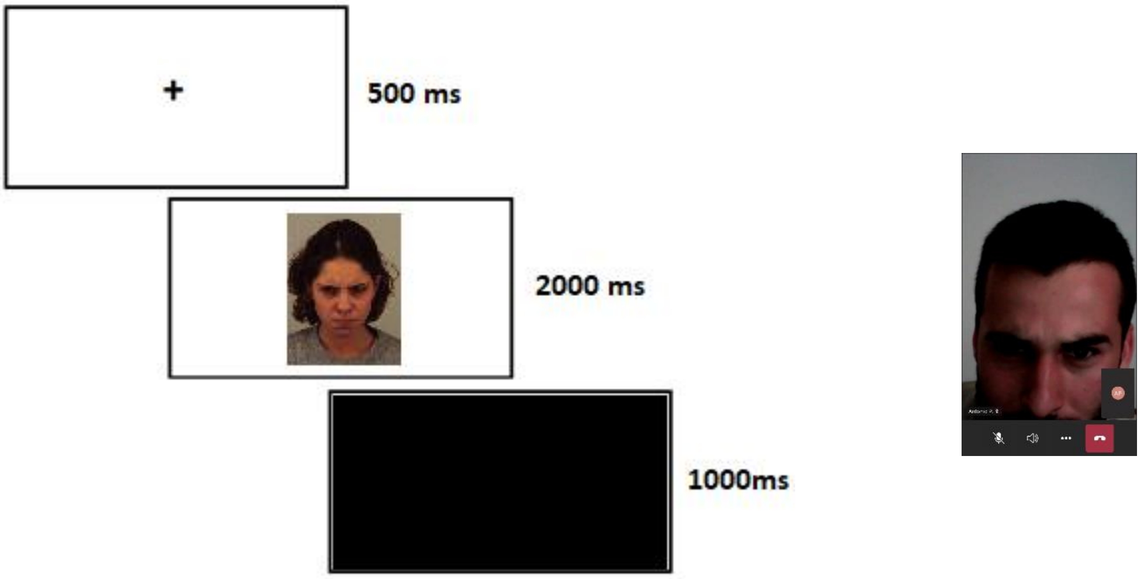
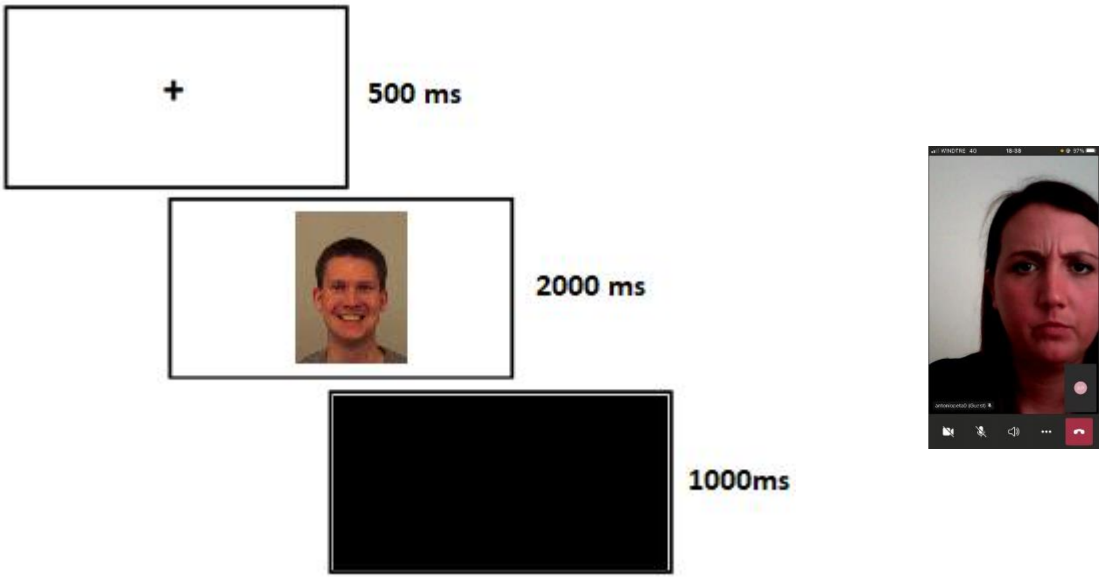


Fig. 3. ***Imitation***. Example of a trial in training session for the imitation group. Each trial started with a fixation cross anticipating the appearance of the emotional face. Participants had to imitate the facial expression presented on the screen and hold it until the offset of the visual stimulus (i.e., 2s). Two imitation sessions were performed separately, one for each emotion (i.e., anger vs. joy, in a counterbalanced order). In the upper figure the participant was imitating joyful expressions, whereas in the lower figure he was imitating angry expressions.



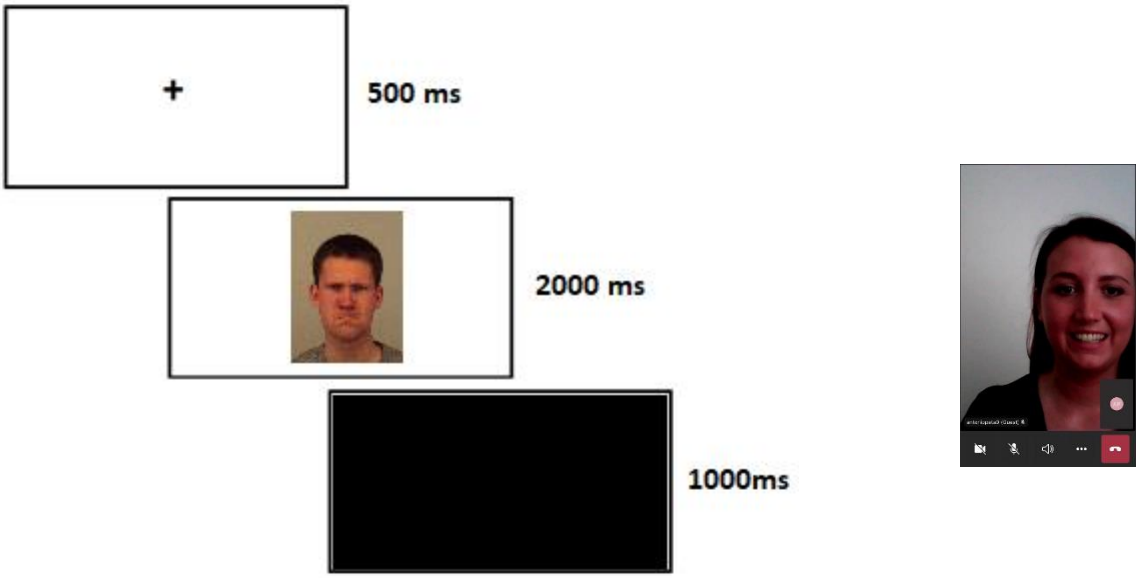
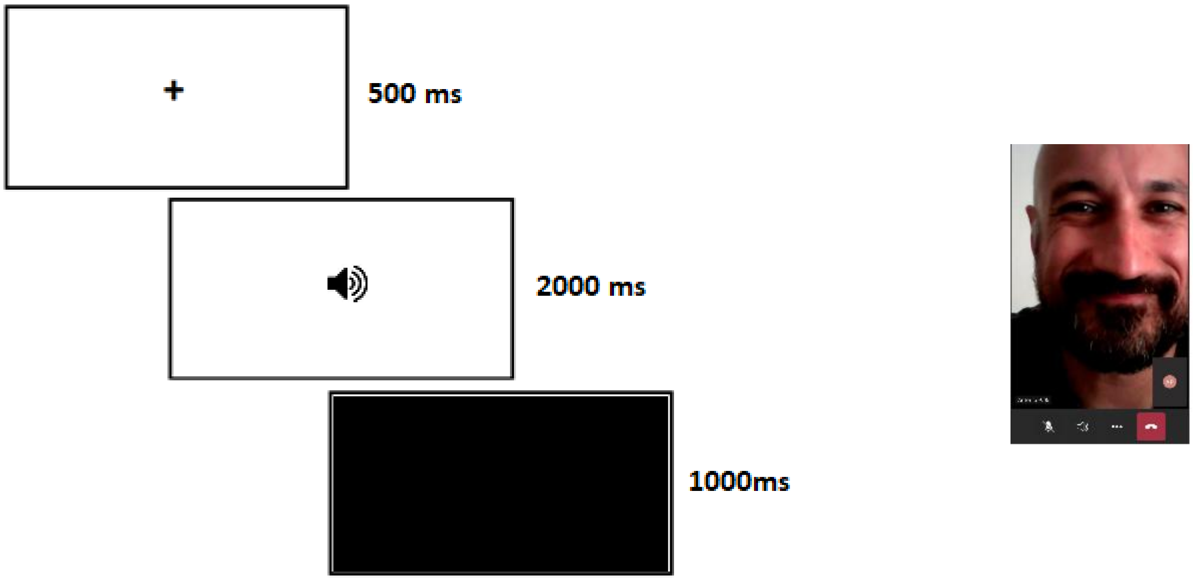


Fig. 4. ***Counter-Imitation***. Example of a trial in training session for the counter-imitation group. Each trial started with a fixation cross anticipating the appearance of the emotional face. Participants were instructed to express a facial expression referring to the opposing emotion as compared to that presented on the screen. Once the emotional face appeared, participants showed the opposing facial expression and held it until the offset of the visual stimulus (i.e., 2s). As for the imitation group, two counter-imitation sessions were performed separately, one for each emotion (i.e., anger vs. joy, in a counterbalanced order). In the upper figure the participant was counter-imitating joyful expressions, whereas in the lower figure she was counter-imitating angry expressions.

2.3.7 Simulation group

The simulation group was supposed to serve as a control condition to assess the effect of expressive behavior alone on the subsequent perception of others' emotional display. This condition was designed to be optimally comparable with regard to the instructions provided to subjects in the imitation and counter-imitation groups. Indeed, the same procedure as in the other two groups was employed, with the only difference that this time participants had no models to imitate/counter-imitate, they were rather asked to perform a self-generated facial expression. To make the training as natural as possible, participants in this group were simply told to "produce emotional faces", without explaining to them how to accomplish the goal. Therefore, while in the other two groups participants were asked to reproduce (in a congruent or incongruent fashion) the expression shown by a stimulus face, participants in the simulation group had to pose a specific emotional expression (i.e., joy or anger) according to previous instructions. In particular, each trial started with the appearance of a fixation cross for 500 ms, followed by an auditory stimulus (i.e., a beep) lasting 2000 ms and prompting subjects to either smile or frown (according to the instructions received before the session) as soon as the tone was audible and for its entire duration. In other words, the "beep" tone cued participants to generate and hold a facial expression as long as it was audible. Each trial ended with a black screen shown for 1000ms, which signaled to participants that they could return to a neutral face until the next trial started (see. Figure 5). As for the other groups, participants completed the emotion intensity task right after performing two distinct facial motor training: one for the simulation of joyful faces, and another for the simulation of angry faces. Regarding the length of the emotional training session, a total of 90 facial expressions were performed for each session, thus its duration completely resembled that of the other groups. As for the manipulation check, the experimenter assessed online whether participants did indeed show the facial expressions for the entire duration of emotional training. Finally, the experimenter conducted a debriefing about the real aim of the study.

a) "Instruction to smile while the sound is on"



b) "Instruction to frown while the sound is on"

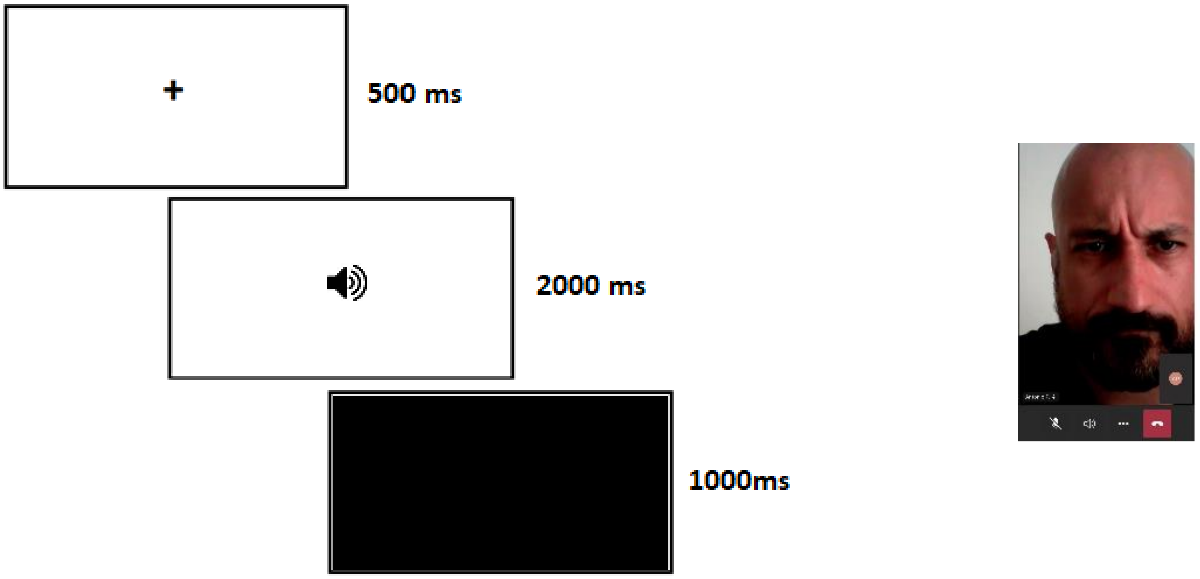


Fig. 5. ***Simulation***. Example of a trial in the training session for the simulation group. Each trial started with a fixation cross anticipating the appearance of the "beep" tone. Before the session began, the experimenter instructed participants to associate to the sound a facial expression for the emotion of either joy or anger. Thus, as soon as the acoustic stimulus was audible, participants showed the facial expression and held it until the offset of the tone (i.e., 2s). As for the other groups, two simulation sessions were performed separately, one for each emotion (i.e., anger vs. joy, in a counterbalanced order). In the upper figure (a) the participant was generating joyful expressions, whereas in the lower figure (b) he was enacting angry expressions.

2.3.8 Experimental design

A 3 x 2 x 2 x 2 mixed design was used, with the group (imitation vs. counter-imitation vs. simulation) manipulated between subjects, whereas subject’s training sessions (joy vs. anger), the emotion of the stimuli (joy vs. anger), the face covering of the stimuli (mask vs. nomask) were the within-subjects independent variables.

2.3.9 Data analyses

Participants provided the emotion intensity ratings on a continuous scale ranging from -500 to 500, with either “joy” or “anger” associated to the left and right end of the scale. Thus, the scale included 2 specular subscales, one from -500 to 0 and the other from 0 to 500, each associated to a distinct emotion. Negative values were converted into positive ones so that higher values corresponded to higher intensity ratings for both the emotions, making them more easily comparable. Indeed, the bias potentially induced by the between-subject factor was defined as the observers’ difference in judging the emotional faces on the congruent as compared to the incongruent trials. In particular, the 2-level congruence factor distinguished participants’ responses in: “same” referring to the ratings on the pictures with the same facial expression as that trained; whereas the “other” label reflected the ratings on the faces showing the opposite facial expression as compared to that repeatedly posed during the training. Thus, the data analyses were carried out by means of a 4-way ANOVA with the “Group” (i.e., 3 levels: “Imitation”, “Counter-Imitation”, “Simulation”) as the between subject factor; whereas the following variables were manipulated within subjects: (i) the “Emotion” of the visual stimuli (i.e., 2 levels: “joy”, “fear”), (ii) whether the facial stimuli were or were not covered by a surgical “Mask” (i.e., 2 levels: “mask”, “nomask”), (iii) the “Congruence” between the emotion seen during the task and the targeted emotion during the training (2 levels: “same”, “other”). Post-hoc analyses were performed using the Bonferroni test to correct for multiple comparisons. Partial eta^2 was computed as a measure of effect size for the main effects and interactions.

As for the questionnaire assessing the emotion contagion (EC), we computed the total scores from items 2,3,11, and 5,7,10 measuring the susceptibility to other's joy and anger, respectively (see Appendix). Higher values reflected higher tendency to get involved by other's emotional state. Then, we compared the EC scores following the generation of either joyful or angry expressions. To this aim, we performed independent *t*-tests comparing the scores of the EC subscale measuring susceptibility to other's joy and fear between the groups of participants trained to joyful *vs*. angry expressions. This allowed us to verify whether the potential effects of the training on the subsequent emotion intensity ratings were paralleled by a corresponding bias on a more explicit form of empathy assessed by the EC scale.

Neutral faces were analyzed separately, we wanted to see whether the emotional training could also bias the perception of non-emotional faces. Such bias would have been reflected in participants' ratings as the shift from the central point of the scale (i.e., 0), which marks the area of the scale associated with the "neutral" label. Therefore, a series of one-sample *t*-tests were run to analyse if ratings for neutral faces were significantly biased towards any of the emotional ends of the scale (i.e., significantly differ from the test value of 0).

2.4 Results

The ANOVA showed significant main effects of Group ($F_{2,48} = 14.901$, $p < 0.001$, eta$^2 = 0.37$; "simulation" = mean 329.46 ± SEM 6.69 vs. "imitation" = mean 377.63 ± SEM 7.40 vs. "counter-imitation" = mean 357.88 ± SEM 8.70, see fig. 6); Congruence ($F_{1,48} = 45.021$, $p < 0.001$, eta^2 = 0.48; "same" = mean 371.11 ± SEM 6.28 vs. "other" = mean 332.86 ± SEM 6.03); and Mask ($F_{1,48}$ = 328.749, $p < 0.001$, eta$^2 = 0.87$; "mask" = mean 313.32 ± SEM 6.61 vs. "nomask" = mean 390.65

± SEM 4.58). Although no main effect of Emotion was observed ($F_{1,48} = 1.320$, $p = 0.26$, $eta^2 = 0.03$; “joy”= mean 346.16 ± SEM 6.27 vs. “anger”= mean 357.81 ± SEM 6.31), it resulted a significant interaction Emotion x Mask ($F_{1,48} = 19.625$; $p < 0.001$; $eta^2 = 0.29$), showing that covering the lower part of the face with a surgical mask differently impacts intensity ratings for joyful and angry facial stimuli (see fig. 7).

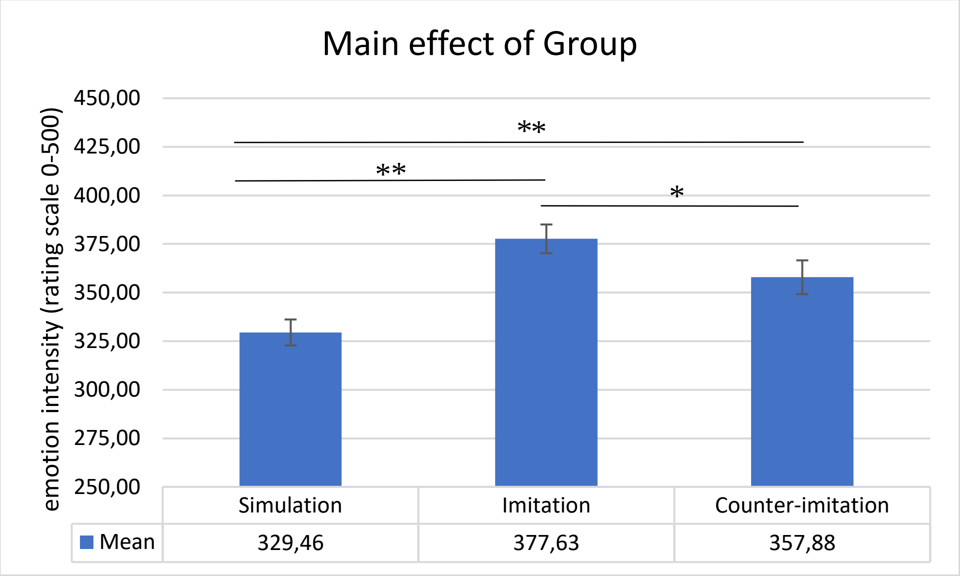


Fig. 6. Main effect of Group. Error bars represent the standard error of the mean (SEM). * denotes significant differences between the conditions (* p = 0.01; ** p < .0001).

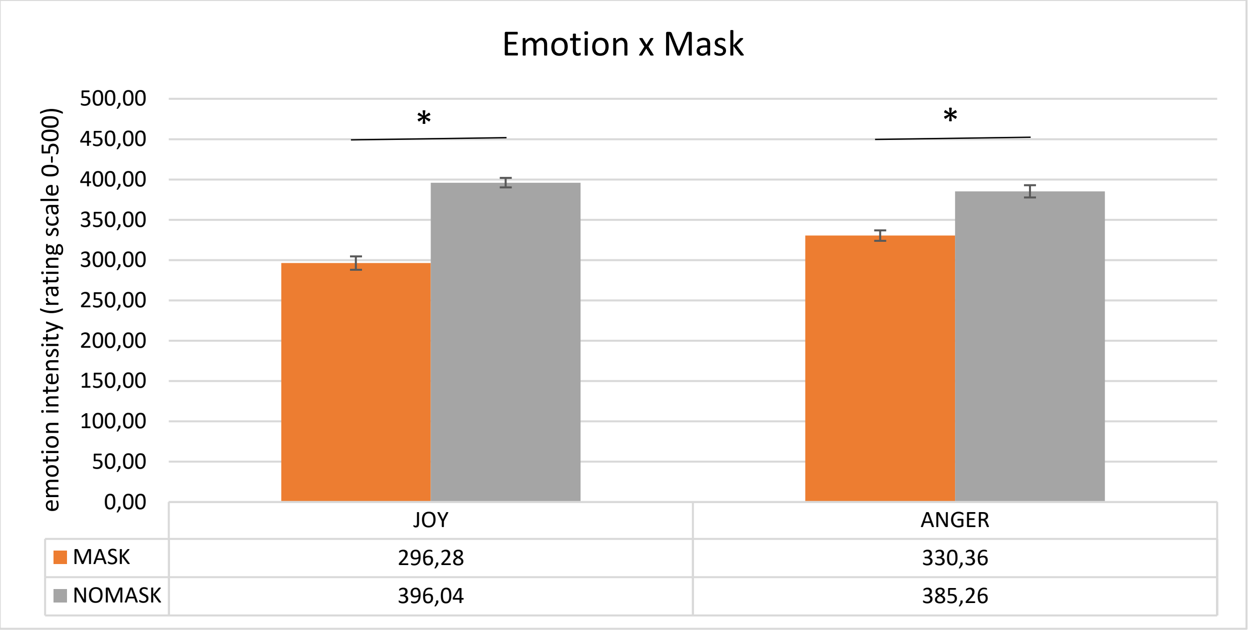


Fig. 7. Emotion x Mask interaction. Emotion intensity ratings for both joyful and angry faces, either covered or uncovered by a surgical facemask. Error bars represent the standard error of the mean (SEM). * denotes significant differences between the conditions ($p < 0.001$).

According to the main effect of Mask, the intensity ratings were significantly higher when judging unmasked rather than masked faces for both emotions (i.e., “joy mask” = mean 296.28 ± SEM 8.32 vs. “joy nomask” = mean 396.04 ± SEM 5.88, $p < 0.001$; “anger mask” = mean 330.36 ± SEM 6.47 vs. “anger nomask” = mean 385.26 ± SEM 7.61, $p < 0.001$). We conducted additional analyses to compare such effect between the emotions, to see whether masking faces differently affects the judgement of joyful and angry expressions. To this aim, we computed an index obtained subtracting ratings for masked faces (i.e., mask condition) from ratings for unmasked faces (i.e., nomask condition). This operation was done for both angry and joyful facial stimuli, higher values reflected higher difference in the ratings. Therefore, we run a paired samples *t*-test comparing the two indexes and found a significant difference ($t_{100} = - 4.31$; $p < 0.001$), indicating a higher index for joyful faces as compared to angry facial expressions (see fig. 8).

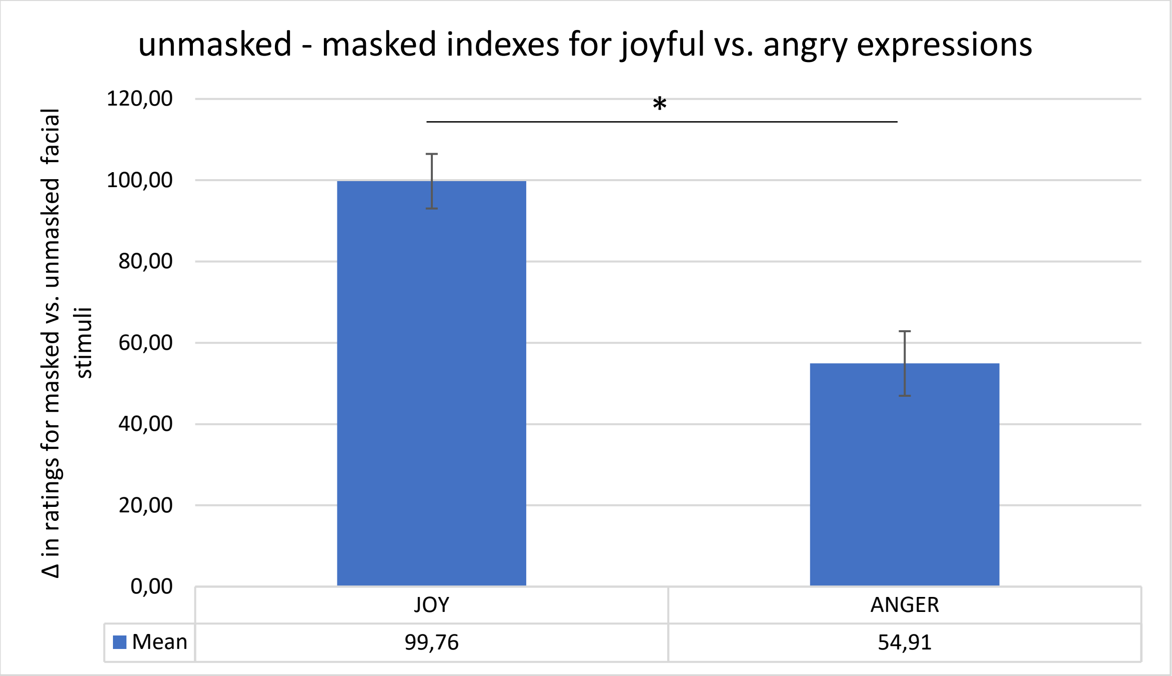
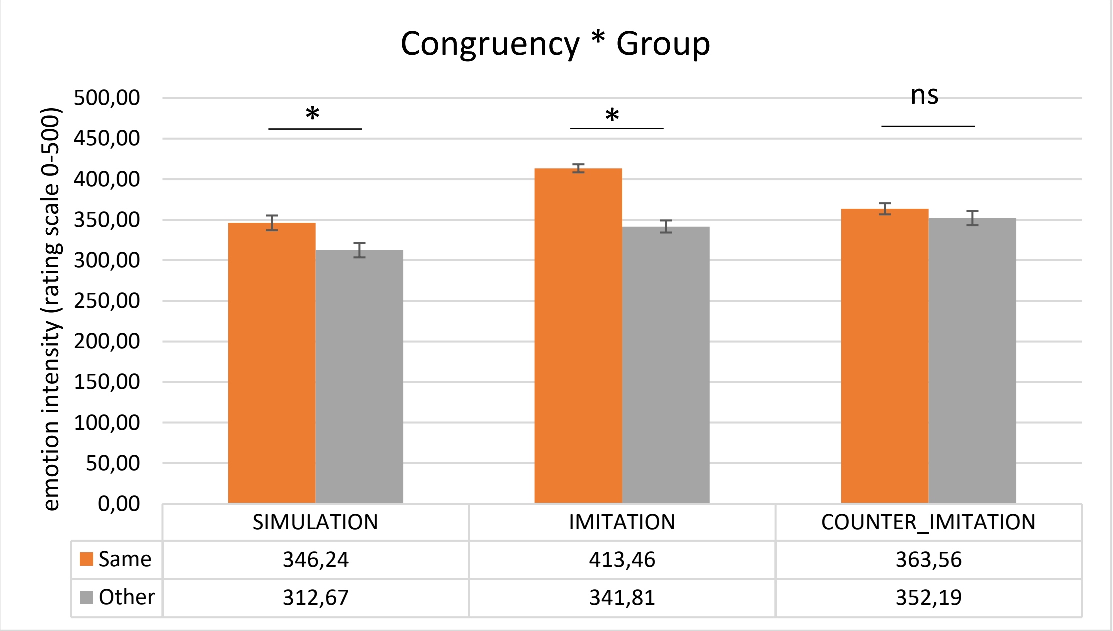


Fig. 8. Unmasked – masked indexes on joy and anger intensity ratings, calculated by subtracting ratings for masked facial stimuli (i.e., "mask" condition) from ratings for unmasked facial stimuli (i.e., "nomask" condition). Error bars represent the standard error of the mean (SEM). * denotes significant difference between the conditions ($p < 0.001$).

Importantly, it was qualified a significant Congruence x Group interaction ($F_{2,48} = 8.399$; $p < 0.001$; $eta^2 = 0.26$). Bonferroni post-hoc tests indicated a significant difference between the "same" and "other" conditions for the "simulation" and "imitation" groups only (i.e., simulation same = mean 346.24 ± SEM 9.11 vs. simulation other = mean 312.67 ± SEM 8.96, $p < 0.01$; imitation same = mean 413.46 ± SEM 4.96 vs. imitation other = mean 341.81 ± SEM 7.42, $p < 0.001$; counter-imitation same = mean 363.56 ± SEM 6.81 vs. counter-imitation other = mean = 352.19 ± SEM 8.91, $p = 1$) (see fig. 9).



	SIMULATION	IMITATION	COUNTER_IMITATION
🟧 Same	346,24	413,46	363,56
■ Other	312,67	341,81	352,19

Fig. 9. Congruence x Group interaction. Emotion intensity ratings for “same” and “other” trials, averaged for each group. Error bars represent the standard error of the mean (SEM). Error bars represent the standard error of the mean (SEM). * denotes significant differences between the conditions ($p < 0.001$).

Therefore, it resulted that the congruence effect (i.e., positive difference resulting from the “same” minus “other” subtraction) significantly influenced the performance of participants who prior to the emotion intensity task were involved in either expressions simulation or imitation. To further explore this result, we conducted an independent *t*-test contrasting the congruence effects between the simulation and the imitation groups. As a result, the imitation group exhibited a congruence effect more than double that of the simulation group (i.e., congruence effect in the imitation group = mean 71.66 ± SEM 6.11 vs. congruence effect in the simulation group = mean 33.57 ± SEM 11.88; see fig. 10), demonstrating that engaging in emotional imitation favors the following ratings of the congruent emotion more than getting involved in self-generated emotional expressions ($t_{34} = - 4.31$; $p = 0.01$).

Interestingly, the 3-way interaction Congruence x Group x Mask did not reach significance ($F_{2,48} = 1.841$; $p = 0.17$; $eta^2 = 0.07$), suggesting that the congruence effect observed in the simulation and imitation groups is independent from mouth and nose covering of the emotional stimuli.

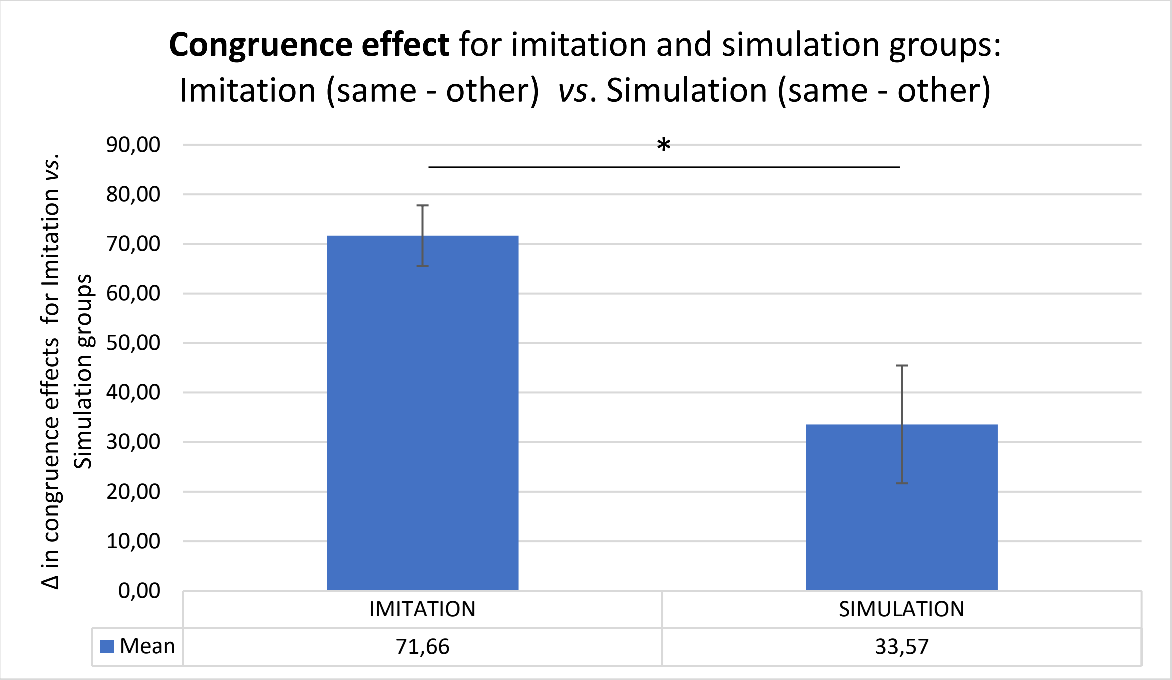


Fig. 10. Comparison between the congruence effect for the imitation and simulation groups, calculated by subtracting ratings for “other” trials from ratings for “same” trials. Error bars represent the standard error of the mean (SEM). * denotes significant differences between the conditions (p = 0.01).

Each participant engaged in both joy and anger facial motor training sessions, meaning that two separate expressive sessions were performed, one for each emotion. Consequently, it can be that the interaction Congruence x Group is dependent by the order of the training sessions. For instance, it can happen that the emotional training is effective only during the first session, resulting to have null aftereffects when a different emotion is targeted in a later training session. To explore this possibility, it was run an ANOVA with an additional 2-level variable named “Order” (i.e., first half vs. second half of the experiment), allowing us to test whether the congruence effect is constant across the two sessions of the experiment. The Congruence x Order interaction did not reach significance ($F_{1,48} = 0.061$; $p = 0.81$; $eta^2 = 0.001$), as well as the 3-way interaction Congruence x Group x Order ($F_{2,48} = 0.344$; $p = 0.71$; $eta^2 = 0.01$). These results revealed that both the emotional trainings effectively modulated the ratings of the emotional faces subsequently presented.

Regarding the non-emotional pictures, we conducted a series of one-sample *t*-tests analyzing whether the imitation sessions could modulate the following emotion intensity ratings of neutral faces as well. To this aim, we contrasted the mean ratings of either masked or unmasked neutral faces, as a function of the imitation of either joyful or angry expressions, against the test value of 0 (associated with the "neutral" label). It resulted that after engaging in joy imitation training, ratings for unmasked neutral faces demonstrated a significant shift from the central point of the scale towards the end of the scale anchored to the "joy" label (mean ± SEM= -6.80 ± 5.83; $t_{14} = - 1.69$, $p = 0.05$) (see fig.11). Differently, after training on imitating angry expressions, the ratings for both masked and unmasked neutral faces were biased towards the extremity of the scale anchored to the "anger" label (i.e., neutral anger mask: mean ± SEM = -52.46 ± 8.58, $t_{14} = - 7.24$, $p < 0.001$; neutral anger nomask: mean ± SEM = -41.72 ± 7.72, $t_{14} = - 6.82$; $p < 0.001$) (see fig.12). Interestingly, a paired samples *t*-test comparing the ratings for neutral masked vs. unmasked faces, after training on angry expressions, showed a significant difference ($t_{14} = 1.76$; $p < 0.05$), indicating that neutral faces wearing a facemask were rated as significantly more angry than unmasked faces.

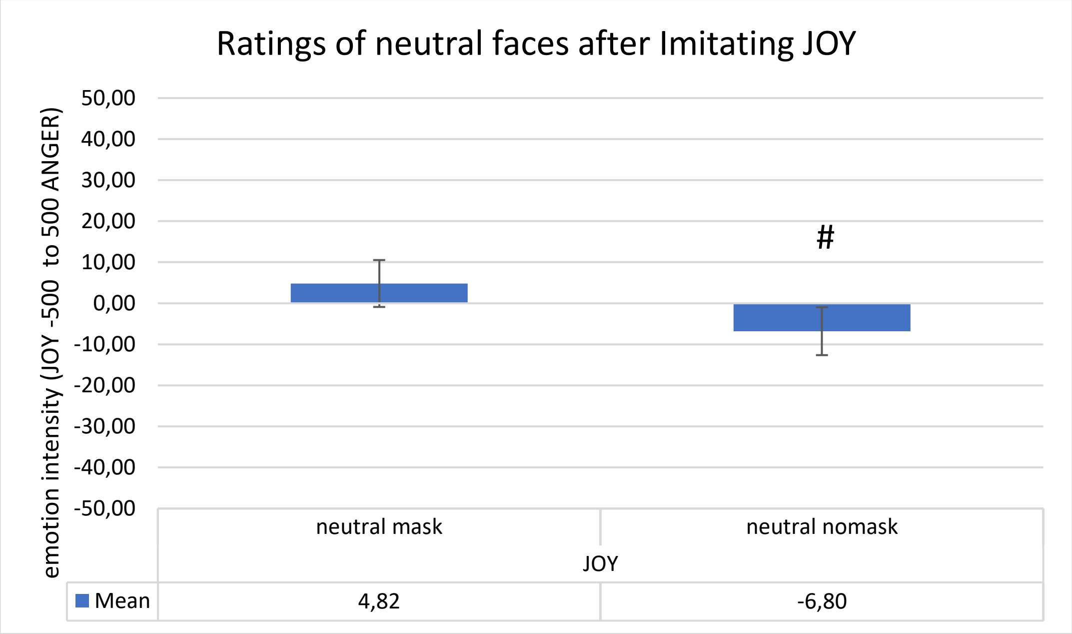


Fig. 11. Emotion intensity ratings of neutral faces either wearing or not a facemask, following the imitation session of joyful faces. # denotes significant difference from the test value of 0 (p = 0.05), corresponding to the neutral label. Error bars represent the standard error of the mean (SEM).

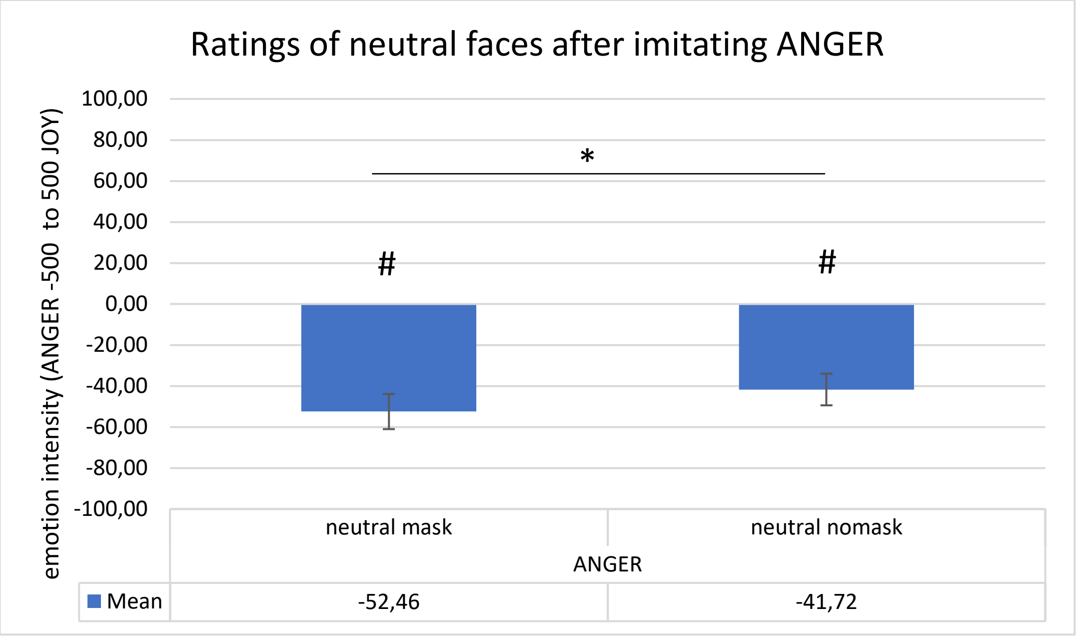
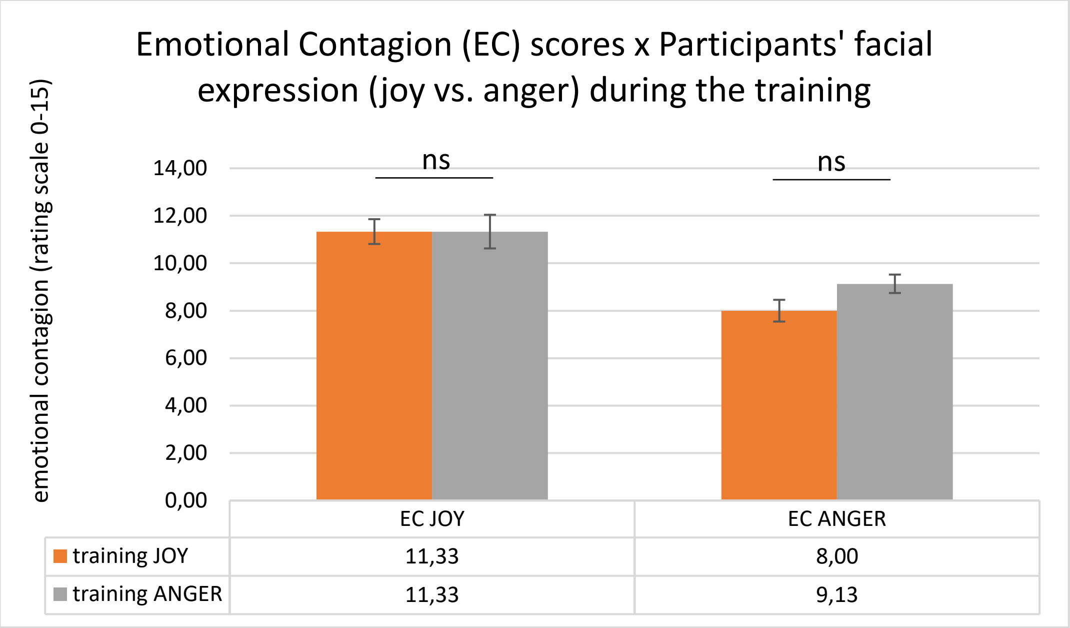


Fig. 12. Emotion intensity ratings of neutral faces either wearing or not a facemask, following the imitation session of angry faces. # denotes significant difference from the test value of 0 ($p < 0.001$) corresponding to the neutral label. * indicate significant difference between the ratings for masked vs. unmasked neutral faces ($p < 0.05$). Error bars represent the standard error of the mean (SEM).

To control for non-specific effects of the experimental manipulation, we conducted additional independent *t*-tests comparing participants' tendency to get affected by other's joy and anger, depending on the facial expression showed during the training (i.e., either joyful or angry). Interestingly, we found no significant modulation of the emotional contagion scores for both emotions as a function of the expressive training (i.e., EC joy: after training joy = mean 11.33 ± SEM 0.52 vs. after training anger = mean 11.33 ± SEM 0.71, $t_{28} = 0$, $p = 1$; EC anger: after training joy = mean 8.00 ± SEM 0.46 vs. after training anger = mean 9.13 ± SEM 0.39, $t_{28} = - 1.89$; $p = 0.07$) (see fig. 13). Thus, it suggests that the facial motor training influenced the subsequent emotion intensity task but not a more cognitive self-report measure of emotional contagion susceptibility.



	EC JOY	EC ANGER
🟧 training JOY	11,33	8,00
▨ training ANGER	11,33	9,13

Fig. 13. Scores on the items measuring the EC susceptibility to either other's joy or anger, depending on the emotion previously trained (i.e., either joy or anger, manipulated within-subject). Error bars represent the standard error of the mean (SEM).

Finally, during the debriefing, the experimenter encouraged participants to speculate about the purpose of the study and to write down their thoughts. Overall, the analyses of participants' answers suggested that they were not aware of the experimental hypotheses of the study. Indeed, none of them detected a connection between the emotional training sessions and the dependent measures. In particular, most participants (= 15) indicated that the study was about the recognition of emotions, others (= 11) thought we were interested to study pandemics aftereffects or the facemask influence on emotion perception. The rest of the subjects (= 4) all reported different possible purposes of the study without mentioning the influence of our mimicry (or self-generated facial expression) manipulations. Therefore, demand characteristics cannot provide a valid explanation for our findings.

2.5 Discussion

Facial expressions bring information about social dynamics and other's emotional states, providing cues on how to regulate one's behavior in response to others. Accordingly, social-cognitive skills such as identifying emotional facial displays are important predictors of functional social behavior in clinical samples (Hooker & Park, 2002).

In the present study, we explored the effectiveness of a behavioral training in which healthy subjects were asked to produce facial expressions in response to other's emotions. Importantly, we tested the training-induced aftereffects on the intensity judgements of other's facial expressions, either congruent or incongruent to previous behavioral training. This is relevant since emotion recognition tasks based on the sole analyses of the hit rate might fail to catch the manipulation effects on supraliminal facial expressions (Kastendieck et al., 2021). In the same way, a measure of perceived emotion intensity could provide an index for the interaction quality among individuals; for instance, lower perceived affect could be considered as a rejection of the person with whom someone is interacting.

In particular, we focused on how the training-induced learning differentially impacted the processing of high-intensity, low-intensity, and neutral facial expressions. As for low-intensity stimuli, we decided to use faces covered by a surgical facemask. Currently, the way facemasks influence social-cognition represents a particular hot topic since the international mass adoption of sanitary facemasks, aiming to prevent the spread of the coronavirus (COVID-19) disease (Coclite et al., 2020). Relatedly, several studies suggest that by covering other's facial display, facemasks might undermine spontaneous facial mimicry in the observer, which in turn facilitates empathic behavior and social connections (Dimberg et al., 2011; Hess & Fischer, 2013; Mancini et al., 2013; Tramacere & Ferrari, 2016; Palagi et al., 2020).

Our results indicated that a training strategy based on the observation and execution (i.e., imitation) of congruent facial expressions represent a simple, yet effective, tool for inducing improvements in emotional discriminatory abilities. The congruence effect revealed a pattern of results such that emotion intensity ratings for smiles were higher following the imitation of smiling faces, whereas frowning faces were rated as angrier following the imitation of angry expressions. These findings resemble previous stimulus-response compatibility effects (Brass et al., 2000; Otte et al., 2011; Cross & Iacoboni, 2014; for a recent review see Cracco et al. 2018). For instance, Shaham et al. (2020) found that participants' RTs for frowning or smiling were significantly shorter when presented with corresponding angry or happy vocalization, compared to the incongruent condition in which the emotional content of the stimuli did not match participants' expression. In contrast, Campbell et al.'s (2018) results indicated that RTs were unaffected by the match/mismatch between the action observed and that executed. However, a key difference between Campbell et al's manipulation and ours might account for the diverging pattern of results. Indeed, those authors randomly forthwarned participants to either imitate or counter-imitate (i.e., either hand opening or closing) within the same experimental block. Differently, in our study we manipulated the joy *vs*. anger training in separate blocks. Therefore, it seems plausible to assume that we elicited a stronger action-specific training, which eventually led to significant stimulus-response congruence aftereffects. Importantly, the congruence effect we observed equally biased the ratings of masked and unmasked faces. These findings indicate that training with high-intensity (i.e., uncovered) emotional expressions promotes learning that can significantly be transferred to both uncovered as well as covered facial expressions. We have not tested the reversed order, in which training with noisier facial expressions possibly impacts the processing of high-intensity emotional faces. However, existing literature has already showed that training-induced aftereffects are only observed when subjects are presented with clear stimuli rather than noisy displays during the perceptual learning (Dosher & Lu, 2005).

In addition, our analyses indicated that, to some degree, the learning impacts the judgement of neutral faces as well. Indeed, the perceived emotion intensity of neutral faces was biased towards the emotion previously trained. Interestingly, the training differently influenced the intensity ratings of neutral masked and unmasked faces. In particular, after training on joyful expressions, only neutral unmasked faces were significantly biased towards joy. Differently, imitating angry expressions significantly pushed the ratings for both masked and unmasked neutral faces towards the anger extremity of the scale. Our findings are complementary with those of a previous study in which the coupled presentation of neutral faces and emotion labels (i.e., sad or happy) congruently biased participants facial expressions (Hess & Fischer, 2014). Interestingly, participants' facial reactions were independent from their explicit emotional state (Hess & Fischer, 2014).

However, the emotion intensity bias that we observed for neutral faces partly contrasts with Du et al.'s (2016) results. Indeed, those authors found that training on happy expressions led to improved (rather than biased) discriminatory ability on neutral faces. If training on emotional expressions brought improvement in processing non-emotional faces as well, then our participants should not had shown a bias in reading neutral faces. However, in partly accordance with Du et al.'s findings, training on joyful expressions led to a lower congruence effect for neutral (unmasked) faces as compared to training on angry faces. Moreover, we administered a continuous scale for the emotion intensity ratings, whereas Du et al. (2016) used a 2-alternative forced choice task instead. Therefore, our dependent measure most likely had higher capacity to discriminate between the training conditions (Komorita & Graham, 1965).

As for neutral masked faces, the congruence effect was stronger following the "anger training" as compared to the "joy training". Such differential congruence effect may stem from stereotypical beliefs about masked faces. For instance, Agneta et al. (2011) found that subjects were more prone to associate negative emotions to covered faces as compared to fully visible ones. Therefore, such negativity bias added to the anger training aftereffects might have resulted in additive influences when it came to judge masked non-emotional faces. Similar phenomena might account for the lack of training-induced bias on the ratings of masked neutral faces following the imitation of joyful expressions. Indeed, although engaging in the repeated imitation of joyful expressions, participants subsequently presented with neutral masked faces might have considered them as less happy because the key element of a smiling face (i.e., the mouth) was occluded by the sanitary mask ((Blais et al., 2012; Calvo & Nummenmaa, 2008; Eisenbarth & Alpers, 2011; Nusseck et al., 2008; Schurgin et al., 2014; Smith et al., 2005; Wegrzyn et al., 2017). Therefore, equal and opposite effects of a negativity bias towards masked faces and a training-induced bias for joyful expressions resulted in (correctly) rating non-emotional masked faces as neutral. However, a recent study clarified that the vast majority of the interviewed subjects regularly wear facemasks; relatedly, they did not report explicit negative attitudes towards the use of facemasks as they firmly supported the concept that “it is generally reasonable to wear masks in public in the context of the COVID-19 pandemic” (Kastendieck et al., 2021). This suggests that the use of masked faces as emotional stimuli should not have had brought important confounding variables to our study.

Although we found significant congruence effect in the simulation group as well, it was remarkably smaller than that observed for subjects whose training included the presentation of a congruent visual reference (i.e., the “imitation” group). Indeed, besides the engagement of the motor system, our imitation program included a visual reference entailing a coherent emotional meaning, it might have triggered the activation of multiple neural systems that contributed to determine a stronger effect (Russo-Ponsaran et al., 2015). Nonetheless, participants’ performance in the simulation group is in line with the conceptualizations of the embodied simulation theory on how we comprehend other’s emotions. Accordingly, “the fundamental mechanism that allows us a direct experiential grasp of the mind of others is not a conceptual reasoning but direct simulation of the observed events through the mirror mechanisms” (Gallese et al., 2004). Consistent with this view, processing others’ facial expression is associated to congruent neural and bodily states in the observer (Niedenthal et al., 2010; Leslie et al., 2004). Our results reflected specular mechanisms in terms of the specificity of the learning aftereffects, being the congruence effect a measure of the facilitating influence for a specific set of trials (i.e., “same”) among all those presented during the emotion intensity task (i.e., “same” and “other”). Such high specificity of the perceptual-motor task influence can be regarded as a reflection of the plasticity of facial expression representations.

As for the counter-imitation condition, when the emotional stimuli were incongruent with participants’ facial display no congruence effect was found. However, overall ratings for the counter-imitation group demonstrated to be significantly higher as compared to the simulation group. Although speculative, it could be that the counter-imitation condition represented a training for both emotions (i.e., one visually perceived and the other reproduced by participants). In other words, the emotional meaning activated by the visual stimuli, and participants’ incongruent sensorimotor activity might have created a non-specific yet facilitating effect, reflected in the overall higher ratings in this group as compared to the simulation group.

As predicted by the facial feedback theory, engaging in the reproduction of affective faces may be associated to self-reports of the corresponding emotion, reflecting a cognitive mechanism termed as “emotional contagion” (for a review, Hatfield et al. 2014). To control for this effect, following the training we administered a self-report questionnaire assessing the susceptibility to others’ emotion: The emotional contagion scale (Italian adaptation of Lo Coco et al., 2014; originally designed by Doherty, 1997). Relevantly, we compared the scores on the susceptibility to other’s anger and joy as a function of the training underwent right before (i.e., reproducing joyful *vs*. angry expressions). Interestingly, we found that our emotion-specific training did not differentially influence the emotional contagion scores on both subscales (i.e., EC joy and EC anger). These results indicate that actively engaging in the generation of emotional expressions determined asymmetric influence on the affective and cognitive measures that we used. This is consistent with previous research suggesting that emotional (or affective) and cognitive perspective-taking are partially dissociable forms of empathy (Stel et al., 2008; Healey & Grossman, 2018; Fantozzi et al., 2021).

2.6 Limitations

There are several limitations to this study. First, the study involved a small sample of participants. It represents a note of caution in interpreting our findings since the limited coverage of the population stand against strong assertions about the generalizability of our results. Second, the adoption of static facial photographs might reduce the ecological validity of the study. However, previous results indicate that training-induced meliorative effects on emotion recognition applies on dynamic faces as well (Marsh et al., 2010). Third, we used the same emotional pictures during the training and the following emotion intensity task. It might leave the doubt that the observed congruence effect is rather a “stimulus familiarity effect”, since participants were possibly more familiar with the faces presented during the training as compared to the novel nontrained emotional photographs. However, previous studies have consistently shown that (i) training on emotion discrimination abilities generalize to different faces with the same expression, (ii) the facilitation is gender independent, and (iii) that learning effects are even transferred to congruent but low-intensity emotional faces. (Marsh et al., 2010; Du et al., 2016). Importantly, the improvements observed in the imitation group in relation to the counter-imitation group precludes an explanation of the training effects based on mere familiarity with presented expressions. Indeed, in the counter-imitation training as well, participants were repeatedly exposed to (incongruent) emotional stimuli that were then presented again in the emotion intensity task. Nevertheless, participants who engaged in a counter-imitation training did not show a significant congruence effect. Rather, similarity between the training and the task might be advisable for future research aiming to investigate the neurobiological changes potentially caused by the training, since it would increase the likelihood that the same cognitive mechanisms are addressed in both the training and the test phase.

Fourth, the length of the training (i.e., 90 trials for each block) might appear arbitrary, yet it was determined on the base of previous research from our lab (unpublished). We defined a total number of facial expression repetitions that would likely be both effective and easily tolerated by participants, trying to avoid any longer duration of the training that volunteers might not have been interested in. Similarly, Otte et al.'s study (2011) included two experimental blocks of 80 trials each in which participants were first presented with an emotional face and shortly after they had to produce either a congruent or incongruent facial expression (i.e., smile or frown). Relevantly, such short dual-task procedure revealed strong stimulus-response compatibility effects on both reaction times and error rates. Therefore, considered the almost same length between Otte et al.'s experimental block and our training session, it is plausible to consider appropriate a 90-trials training session. However, while our results indicated that a relatively short and simple training yield positive effects, more concentrated and longer training may determine stronger effects or lead to an asymptote (Miller, 1956). Future research is needed to explore whether changing the parameters of the training may effectively modulate the emotional perceptual function as well.

Another limitation of the study can be that it lacks an additional control group in which subjects' mimicry is not required during the training. It would have allowed to rule out the possibility that passive viewing of facial emotions, without associating any active facial motor response to it, is sufficient to produce enhanced facial emotion processing. For instance, in a classic study it was found that by simply observing other's facial expressions it is induced a slight activity in the viewer's corresponding facial muscles (Dimberg, 1982). However, neuroimaging data revealed that passive observation of facial expressions elicits lower activity within the underlying neural systems as compared to an active condition in which facial mimicry is required. Indeed, Carr et al. (2003) demonstrated that observation and imitation induces greater neural activity in the superior temporal sulcus than the mere exposure to the emotions. Therefore, it is plausible to expect a corresponding pattern of results in behavioral performance, where participants undergoing a perceptual-motor training would obtain higher facilitating effects as compared to those obtainable in a simplified perceptual training.

Finally, it is noteworthy that our block design training on angry vs. happy facial expressions might have induced congruent emotional states. Therefore, some sort of training-induced mood might represent an alternative explanation for the congruence effect we observed. Accordingly, it was found that listening to emotion vocalizations implicitly induce congruent facial movements and self-reported concordant emotional states (Hawk et al. 2012, study 2). Similarly, observing emotional expressions can evoke congruent emotional experiences in the observer (Olszanowski et al., 2020). We did not collect self-reported states about the emotions felt by participants after each training, thus we cannot exclude such alternative explanation. We thought that testing and re-testing participants' emotional states, within the relatively short duration of the experiment, could have resulted to not be sensitive enough to catch potential changes in participant's mood. However, if our results were fully explained by participants' internal emotional states, then there should not have been room for further improvement in the congruence effect for the imitation group as compared to the simulation group. Indeed, participants in both groups engaged in the generation facial expressions, the only difference was that in the imitation group participants had also the support of concurrent emotional stimuli acting as models.

2.7 Future research

Our study included healthy and young volunteers; adaptations might be needed for the translation of such training into clinical practice with elderly. Indeed, it can be that older adults would be less enthusiast of complying with computerized training because of a priori stigma towards technology. However, even elderly can be prone to use technological devices within personalized rehabilitation settings, stimulating their self-efficacy and preventing any feelings of inadequacy to take place (Vaportzis et al., 2017).

We studied subjects' intensity judgements of well-visible emotional faces. Indeed, target stimuli were presented for a duration of 500 ms, that recent research suggests as the threshold between macro and micro-expressions (Matsumoto & Hwang, 2018). However, during most social interactions people show subtle and faster facial expressions, especially during conversations, that might not result as evident as supraliminal emotional stimuli. Therefore, future research might benefit from the adoption of spontaneous and rapidly presented emotional faces, allowing to test the perimeter of training effects.

Moreover, it would be interesting to study the neural bases that impact the outcomes of training programs. For instance, social-cognitive trainings combined with transcranial magnetic stimulation protocols may represent more powerful and long-term therapeutic actions, favoring not only modifications in behavioral performance but also neuro-plasticity processes (Lage et al., 2016). Finally, long-term follow-up monitoring of training aftereffects would be desirable to clarify whether and how such learning significantly facilitates socio-cognitive dynamics of real-life situations as well.

2.8 Conclusion

In conclusion, we showed that a behavioral intervention, based on a perceptual-motor training involving facial expressions, improved healthy participants' ability to discriminate between joyful and angry faces. While being aware of sample size limitation, we suggest that an observation and imitation approach is more effective than simply engaging in facial expression generation. Importantly, the training revealed to be effective only when congruence between the facial emotion presented and participants' facial expression was met. Moreover, training effects were observed independently of the fact that target emotional faces wore a surgical facemask, suggesting that beneficial effects of such training programs can extend to low intensity emotional faces. We also highlighted the specificity of the aftereffects by showing the uncorrelation between the outcomes on an emotion intensity judgement task and on a self-reported measure of emotional contagion susceptibility.

3 CHAPTER III

Looking *forward* to going *back*: Transcranial magnetic stimulation of function specific re-entrant neural networks to enhance visual perception of emotional expressions

3.1 Abstract

This research paper aims at clarifying the network-based dynamics that causally determine visual perception of emotional faces. A non-invasive transcranial magnetic stimulation (TMS) protocol was implemented to target specific neural pathways involving re-entrant input from high order brain regions into the visual cortex (V1) and test their causal contribution to visual perception. We focused on visual temporo-occipital networks (Superior Temporal Sulcus-V1) which are recruited when processing emotional faces and susceptible to plastic modification. We used cortico-cortical paired associative stimulation (ccPAS) to target STS-V1 and plastically modulated the strength of its cortico-cortical connectivity. We tested the effects of this plastic exogenous manipulation on emotion-specific re-entrant circuits by administering state-dependent ccPAS during presentation of specific emotional expressions. This allowed us to target functionally specific yet spatially overlapping re-entrant neural networks active during visual processing of an emotion and test whether reinforcing these networks bias visual perception of specific emotions. This will provide insights into the organization and functions of re-entrant brain circuits contributing to vision.

3.2 Introduction

Social cognition refers to the cognitive processes enabling individuals to comprehend themselves, others, and the intersubjective dynamics of the social interactions. Facial emotion recognition is a fundamental socio-cognitive process, both voluntary and spontaneous facial expressions often convey others' feelings in a meaningful way, and the capacity to interpret such nonverbal messages represent an advantage in interpersonal communication. Indeed, social interactions are driven by the ability to grasp the "messages" sent by the face. For instance, higher emotion recognition skills have been shown to be associated to personality traits favoring positive social relationships (Hall et al., 2009). Conversely, deficient socio-cognitive functioning has demonstrated to be related to poor real-life outcomes pertaining to occupational status, community functioning, social problem solving, and social skills in general (Couture et al., 2006). Thus, emotion perception might be considered a critical skill for the accurate understanding of social dynamics in general, also determining one's behavior adaptation to a certain situation through emotion regulation and empathy (Joseph & Newman, 2010). For these reasons, there is substantial interest towards the discovery of training protocols aimed to target mental abilities referring to social cognition, rehabilitate abnormal neural mechanisms, and therefore improve behavioral outcomes in people's daily interactions.

The visual system and the temporal cortex underlie the processing of biological inputs such as bodies and faces (Astafiev et al. 2004; Cazzato et al. 2015). The seminal work of Haxby and colleagues (2000) is among the first to systematically define neuroimaging studies that have highlighted the neural areas that preferentially respond to faces. A "Core system" of the visual analysis of faces was identified, consisting of the inferior occipital gyrus (occipital face area, OFA), lateral fusiform gyrus (fusiform face area, FFA), and superior temporal sulcus (STS). In particular, OFA represents the starting site of the neural signal in response to the presentation of faces, it preferentially processes the individual parts that make up the face (e.g., the eyes and the mouth) and produces a first representation of it (Gauthier et al., 2000; Haxby et al., 2000; Calder & Young, 2005). Neural network models propose the extension of a ventral path that reaches the FFA (McCarthy et al., 1997) and would be responsible for the elaboration of invariant characteristics of the face, which contribute to the discrimination of identity (Grill-Spector et al., 2004; Rotshtein et al., 2005). In addition, a dorsal neural pathway is also recognized, which again starting from OFA projects into the posterior portion of the temporal sulcus, an area that processes variable aspects of the face such as the movement of the lips, the direction of the eyes, therefore the facial expression more generally (Hoffman & Haxby, 2000; Winston et al., 2004). Starting from the study by Allison and colleagues (2000), the role of STS in face processing has been thoroughly investigated in the last twenty years. Neuroimaging studies have replicated the prevailing feature of this cortical area, which would mainly be engaged in response to moving rather than static faces (Handwerker et al., 2019; Pitcher et al., 2011; 2019; Schultz & Pilz, 2009; Thomas et al., 2007). These studies confirm that the analysis of the changing aspects of the face lead to an increased activity in pSTS, presumably also because of the cortical inputs it receives from motion-selective areas (O'Toole et al., 2002; Gschwind et al., 2012), making it central in the study of emotional faces. Indeed, neuroanatomical studies on non-human primates have identified a cortical pathway that projects along the STS and reaches the amygdala (Aggleton et al., 1980; Stefanacci & Amaral, 2000). Additional imaging studies revealed that social cognitive tasks involve interconnected brain regions which demonstrate an interplay between subcortical and cortical structures, still maintaining a considerable level of functional specialization (Brüne 2005; Dima et al. 2011; Pessoa & Adolphs 2010; Shamay-Tsoory 2011).

Thus, the neurocognitive system including the STC (superior temporal cortex), the SRC (somatosensory-related cortex), and the amygdala is particularly involved in emotion processing rather than identity recognition tasks, therefore differentiating a system preferentially tuned to facial expression rather than invariant features of the faces (Vuilleumier & Pourtois, 2007). Further evidence from neuropsychology highlights the functional specialization of such a neural circuit by showing that lesions in any area of that network would impair emotion recognition but not the elaboration of other facial features (Adolphs, 2010; Adolphs et al., 2000; Pitcher et al., 2008). For instance, schizophrenic patients suffer aberrant neural activity directly associated to impaired facial emotion recognition which eventually leads to dysfunctional behavioral outcomes (Namiki et al., 2007; Hooker & Park, 2002). Therefore, evidence of abnormal neural functioning in clinical populations such as patients suffering from schizophrenia (Aleman & Kahn, 2005; Barch, 2005), encourage researchers to investigate for stimulating protocols aiming to facilitate cognitive processing through neuroplastic changes, such as improved neural attunement and cortical growth (Ohl & Scheich, 2005; Polley et al., 2006).

Several studies have consistently shown how the first brain responses to visual stimuli consist of a flow of neural activity that proceeds from the primary visual cortex to higher-level areas, for an increasingly detailed processing of visual information (Lamme, 2006). Causal evidence of this comes from chronometric transcranial magnetic stimulation (TMS) studies, in which the neural activity of a given brain area is perturbed at variable post-presentation timing of the stimulus. By doing so, the analysis of the performance of the task assigned to the participant allows to find out at what moment the stimulated area is most susceptible to external perturbation with TMS. This approach allowed not only to replicate the criticality of a given cortical area in visual processing, but also to establish the direction and speed in which the underlying neural nodes are engaged. For example, Pitcher (2014) gave participants a match-to-sample expression recognition task of emotional faces in which a match face was followed by a target face. Relevantly, during the presentation of the target face, a pair of TMS pulses (double TMS, dTMS) separated by 40 ms (Inter stimulus interval, ISI) were sent on rOFA and rpSTS with the intention of inhibiting the recognition task. Performance was found to be significantly impaired when rOFA was stimulated 60 and 100ms after the onset of the target stimulus. Instead, as regards rpSTS, the inhibitory effect of the dTMS was observed in a time window ranging from 60 to 140ms post onset of the probe stimulus. These results demonstrate once again that the processing of emotional faces begins with a first flow of neural activity that goes from low-level areas (rOFA) to higher-level areas (rpSTS), reflecting a first passage of feedforward information into the visual system (Pitcher et al., 2012). The final stage of a perceptual activity would be in the awareness of the visual information processed. According to the first theories, awareness would be acquired through the so-called recurrent or re-entering neural activity, in which cortico-cortical feedback activity proceeds from higher level areas to the primary visual cortex (Lamme & Roelfsema, 2000; Pascual-Leone & Walsh, 2001; Lamme, 2006). For instance, Borgomaneri et al (in prep) compared the contribution of feedforward vs. feedback neural processing on the processing of emotional faces through a cortico-cortical paired associative stimulation (ccPAS) protocol. The ccPAS session involved paired and repeated offline stimulation of right posterior STS (rpSTS) and right V1 (rV1), targeting for the first time simultaneously 2 nodes of the neural network (i.e., right STS and V1) involved in emotional faces processing (Pitcher, 2014). Crucially, the ISI between the TMS pulses and the directionality of stimulation was manipulated, so as to define the optimal conditions for the induction of cortical plasticity. An increase of the performance in the task (in terms of emotion discrimination accuracy) was found only when the stimulation occurred in the temporal-occipital direction, demonstrating that visual back projections have a critical role on emotional perception. Remarkably, the ccPAS-induced perceptual improvement on emotion recognition was found only when an inter-pulses timing of 200ms (but not 100ms nor synchronous stimulation) was used (Borgomaneri et al., in prep).

3.2.1 Aim of the study

Growing literature reports how the influence of TMS interacts with the state of the brain, considering that the possibility of inducing long-term potentiation (LTP) or long-term depression (LTD)-like effects depends on previous and ongoing synaptic activity (Edwards et al., 2019). For instance, studies suggest that the susceptibility of motor areas to respond to external modulations depends on both the baseline neural activity at the stimulation site and its functional connectivity with remote areas (Grefkes et al., 2010; Càrdenas-Morales et al., 2014). Similarly, susceptibility to report visual phosphenes (i.e., artificial light sensations) induced by TMS delivered over the occipital pole seems to be associated with spontaneous fluctuations in the pre-stimulus oscillatory alpha activity, representing an index of visual cortex excitability within and across participants (Romei et al., 2008a; Romei et al., 2008b). Other studies show that the direction and magnitude of the effects induced by repetitive TMS (rTMS) interact with the behavioral activation of the stimulated region (Fujiwara & Rothwell, 2004). The influence of cognitive processes on TMS-induced neuroplastic changes was also noted. For example, Conte and colleagues (2007) found that the effect of a 5 Hz-rTMS protocol on the amplitude of MEPs depended on attentional processes: The amplitude of MEPs was greater when participants looked at the hand whose motor representation was stimulated than under "relaxed" and "non-target hand" control conditions. In short, neurostimulation approaches have progressively moved from more classical “interference” protocols towards more “information-based” interventions where the state and activity of the target neural substrate has been taken into account to begin to define the conditions that determine a given direction and extent of the TMS induced effects (Pascual-Leone et al., 2000; Romei et al., 2016b; Pitcher et al., 2021).

In this project, state-dependent TMS effects were tested by implementing an innovative dual-coil brain stimulation protocol, namely state-dependent ccPAS, aimed at modulating the ability to correctly recognize facial expressions selectively, as a function of the state-dependent manipulation. To do so, the ccPAS was paired with concurrent emotional faces presentation, which served the purpose of inducing a target brain state by repeatedly exposing a given emotional configuration during the state-dependent intervention. This procedure would allow for the evaluation of potential LTP-like induced effects specifically associated with the induced brain state, thus, boosting functionally specific neural pathways leading to an increased performance on the behavioral outcome that quantifies the cognitive processing efficiency. This paradigm would allow to target functionally specific neural pathways, rather than indiscriminately target all neurons in a stimulated cortical area (which would be obtained by the implementation of a simple offline ccPAS), so that the plasticity eventually induced by the ccPAS would influence the processing efficiency of a specific cognitive function associated with the brain-state induced. To provide neurophysiological proof of emotion-specific tuning within the temporal cortex, Morin et al. (2015) recorded the neural activity of 637 neurons from the inferior temporal cortex of monkeys that were rewarded for passively viewing images of conspecific facial expressions (neutral, threat, and fear grin). As a preliminary result, those authors found that approximately 44% (278/637) of the neurons were responsive to face stimuli. Importantly, of the 278 face-responsive neurons sampled, 23% (65/278) were preferentially tuned to specific facial expressions. Indeed, a subset of neurons was more responsive to threat expressions than fear grin (n = 44/65), whereas for the other subset of neurons the firing response to threat was less intense than for fear grin (n = 21/65). Therefore, Morin et al.'s (2015) findings provided evidence for the existence of neurons that, although spatially overlapped (i.e., located within the same area), demonstrated some degree of functional specialization.

Starting from these premises, we wanted to investigate the possibility of a selective modulation in the emotion recognition accuracy due to the state-dependent ccPAS protocol. In particular, the accuracy on joyful faces is expected to be enhanced following a ccPAS session in which the coupled TMS pulses are associated to the presentation of joyful faces; whereas improved recognition rates for fearful expressions would be expected when ccPAS is associated to the presentation of fearful faces. Crucially, such selective influence on the performance, based on the emotion attended during the state-dependent ccPAS protocol, would contrast with a general improvement in emotion recognition accuracy which could also occur due to the stimulating protocols. For example, a participant attending joyful faces during the ccPAS could also become better at detecting fearful faces (or vice versa) because of an improved general ability to recognize others' nonverbal emotions, or possibly due to a boosting effect on the awareness of the emotional faces.

As for the pre/post testing sessions, we chose to present emotional faces for a very short timeframe so as to make our stimuli presentation more congruent with subtle micro expressions that pertain social interactions. Indeed, micro expressions have a particular relevance since they represent implicit emotions that there is no way to deceive, occurring in the actor's face for less than 0.5 s, and differing from macro expressions that usually have a duration ranging from 0.5 s to 4 s (Ekman, 2004). As for the ccPAS experimental condition, we targeted re-entrant (i.e., feedback) projections from the STS to the early visual cortex (V1), consistent with models exploring the visual system of primates in which it is suggested that through feedback processing mechanisms the activity in the higher-level cortical areas influences the activity in the lower-level cortical areas (Lamme & Roelfsema, 2000). A control ccPAS condition was also included, where the stimulation directionality was reversed (i.e., first pulse delivered on V1 and the second one on STS) so as to induce a feedforward flow of neural activity. Targeting STS and V1 was motivated by the fact that among non-clinical individuals these regions are particularly involved during face emotion recognition than face identity discrimination, and lesions determine impairments in emotion recognition but not identity discrimination. (Adolphs et al., 2000; Adolphs et al., 2003; Pitcher et al., 2008).

We hypothesized that by targeting both feedforward and re-entrant projections between STS and early visual cortex (V1), we would be able to compare potential LTP-like effects, evaluating the performance on the behavioral task designed, after having stimulated functionally specific neural pathways, so as to quantify the emotional processing efficiency before and after the ccPAS. Consistently with recent literature (Chiappini et al., 2018), it should be observed a specific facilitation effect following the feedback ccPAS. It would result in a transitory improvement of the performance in the behavioral task, selectively for the emotion of joy or fear, depending on the experimental group to which the participant was assigned. This result would confirm that, although stimulating the same neural network, it is possible to selectively enhance the performance on the detection of the targeted emotion, rather than indiscriminately affect the general ability of the participants in the designed emotion perception task. Furthermore, we wanted to investigate whether and how baseline emotion accuracy (i.e., prior to ccPAS) was associated to the potential performance changes induced by the ccPAS protocol.

3.3 Methods

3.3.1 Participants

60 participants (25 males; average age 23.1, SD 2.7) volunteered for the study and were randomly assigned to one of the four experimental groups aiming to control for the ccPAS directionality (i.e., STS-to-V1 vs. V1-to-STS) and the emotional state-dependency condition (i.e., either presenting joyful or fearful facial expressions during the ccPAS session). All participants were right-handed according to a standard handedness inventory (Briggs & Nebes, 1975), and had normal or corrected-to-normal visual acuity in both eyes. None of the participants reported history of mental or neurological diseases and no contraindications to the TMS were described (Wassermann, 1998). All of them were naïve with respect to the experimental hypotheses. Participants gave their written informed consent, and the procedures were approved by ethics committee at the Department of Psychology and were in accordance with the ethical standards of the 1964 Declaration of Helsinki. No discomfort or adverse effects during TMS were reported or noticed.

3.3.2 Visual stimuli

The stimuli were selected from the NimStim database (Tottenham et al., 2009) and included faces belonging to 16 different actors, 8 women and 8 men. An expression of fear and one of joy were selected for each actor. Furthermore, for each facial expression the corresponding mirrored version on the vertical plane was created, so that the set of stimuli contained 64 photographs of emotional faces in total. Each face was cropped using an elliptical stencil to exclude hair, ears, and neck to rule out an effect of any other physical components except a facial expression (Goshen-Gottstein & Ganel, 2000; Sweeny et al., 2009; Lee et al., 2011; Martin & Greer, 2011). Mosaic pattern pictures made up of fragments of each target face were created, by means of the MATLAB system, to be employed as masks stimuli, each preserving the elliptical form, the color and the spatial frequency of the original picture (Martens et al., 2006; Sato & Aoki, 2006; Yang et al., 2011).

3.3.3 Emotion discrimination task

The stimuli were presented on a 21-inch Samsung Syncmaster monitor; subjects were seated maintaining the head at about 60 cm from the center of the screen. The experiments were programmed using Matlab software to control picture presentation and to trigger TMS. Each emotion discrimination block included 120 stimuli, both joyful and fearful male and female faces were presented. Each trial started with the appearance of a blank screen (800 ms), indicating the beginning of the trial, followed by the presentation of the target stimulus (i.e., either joyful or fearful face) for 17 ms. However, one issue with the tachistoscopic presentation is that the retinal image of the presented stimulus remains longer than intended, introducing a confound in the assessment (Matsumoto et al., 2000). To address this problem, we included a slide immediately after the target presentation in which the pixels of the same expressor's emotional face was scrambled so as to create a corresponding mask stimulus (presented for 33ms). Therefore, such a procedure of backward masking prevented any aftereffects of the target images. As a final slide for each trial, a black screen was presented until the subject's answer (fig.1). The subject's task was to discriminate the emotion expressed by the face (two alternative forced choice task) as accurately and quickly as possible by pressing and releasing (with the right hand) two different keys (according to each possible response: "happy" or "fear") on a standard keyboard. Response-button correspondence was randomized across subjects. Each block lasted approximately 4 minutes. The dependent variables are the response accuracy and reaction times.

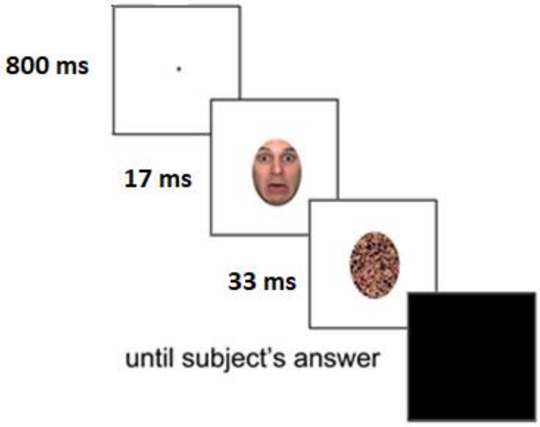


Fig. 1. Illustration of an experimental trial. Each trial begins with the fixation cross, then the emotional face representing either happiness or fear for which the participant's response is required

3.3.4 Experimental design

The experiment involved the administration of 6 testing sessions at different time intervals: before the ccPAS (Pre), immediately after the stimulation (Post0), and then after regular intervals of 20 minutes from each other (i.e., Post20, Post40, Post60, Post80 minutes after ccPAS) to observe the time course of any aftereffects induced by the stimulation protocols. The experimental design is mixed, with the variables time elapsed after the brain stimulation (i.e., 5 levels: post0, post20, post40, post60, post80 minutes), and emotion expressed by the target visual stimuli (fearful or joyful faces) manipulated within subjects; whereas the stimulation directionality groups (i.e., experimental group STS-to-V1 vs. control group V1-to-STS) and the emotion displayed during the ccPAS (either joy or fear) were the between-subjects variables. Thus, participants were randomly assigned to one of four groups, defined for convenience as "joy", "fear", "inverse joy", and "inverse fear". For the experimental groups, i.e. "joy" and "fear", the first TMS pulse was given on the right STS (while the subjects were observing a face that expressed joy or fear, respectively) followed by the second impulse given ipsilaterally on V1. Differently, for the control groups, i.e. “inverse joy” and “inverse fear”, the first TMS pulse was given on the right side of V1, followed by an impulse on the right STS. Thus, the stimulation directionality in the control groups is reversed, that is why the ccPAS in the control groups is not expected to lead to any facilitation on the subsequent emotion discrimination task, in line with the already reported specific directionality effects of the ccPAS protocol (Pascual-Leone & Walsh, 2001; Romei et al., 2016a; Chiappini et al., 2018).

3.3.5 State-dependent ccPAS

ccPAS was delivered by means of a Magstim BiStim2 machine (Magstim Company, UK) via two 50 mm figure-of-eight coils (fig. 2). 90 pairs of pulses were continuously delivered at a rate of 0.1 Hz, making the stimulation session last about 15 minutes (Veniero et al., 2013). We decided to adopt such brain stimulation parameters (i.e., frequency and total pairs of pulses) since a previous TMS-fMRI study had already proven to reliably target inter-areas synaptic efficacy, as demonstrated by an amplified PMv-M1 BOLD coupling after the ccPAS intervention (e.g., Johnen et al., 2015). According to the Hebbian learning paradigm, the repeated coupled stimulation of one area (conditioning pulse) followed by a second area (test pulse), with an inter-pulses interval resembling the physiological timing of communication between those areas, would improve the synaptic efficiency between the two sites, making the second area more receptive to input from the first. Each pair of stimuli consisted of two monophasic transcranial magnetic pulses. The pulses were triggered remotely using a computer that controlled both stimulators. The targeted areas were right STS and V1. For both areas, intensity of TMS was set at 60% of the maximum stimulator output. The ccPAS protocol was manipulated between two different groups of participants (i.e., feedforward V1-to-STS *vs*. feedback STS-to-V1 stimulation order). Importantly, during the ccPAS session both joyful and fearful faces were presented for a duration that made them clearly recognizable, as they remained visible for 550 ms. Participants were instructed to passively observe the facial expressions throughout the entire duration of the ccPAS session. However, the crucial experimental manipulation was that only facial expressions afferent to a specific emotion were presented in correspondence with the coupled TMS pulses (fig. 3). This procedure would allow to recruit emotion-specific neurons while simultaneously activating the cortical neural pathways through ccPAS. By doing so, we aimed to induce Hebbian plasticity (Hebb, 1949) in functionally specific neural networks connecting STS and V1. The inter pulses delay was set at 200 ms on the basis of TMS-EEG preliminary data that were part of a study investigating STS connectivity during action observation and execution (Borgomaneri et al. in prep.). In particular, at about 200 ms after STS stimulation (i.e., delivering single pulses) it was seen a maximal peak of activity in V1. Thus, such an inter pulses interval would reflect a stimulation protocol that mimics the timing of communication between two brain areas involved in the given task, potentially able to induce Spike Timing Dependent Plasticity (Pascual-Leone & Walsh, 2001). Indeed, such TMS-induced cortical inputs are supposed to drive Hebbian plasticity when near simultaneous activations of distinct nodes of a neural pathway occurs. To prevent a possible attentional decrease due to the repetitive nature of the task, we included a sub task in which participants had to press the space bar of the keyboard when the same actor was presented twice consecutively within the same trial.

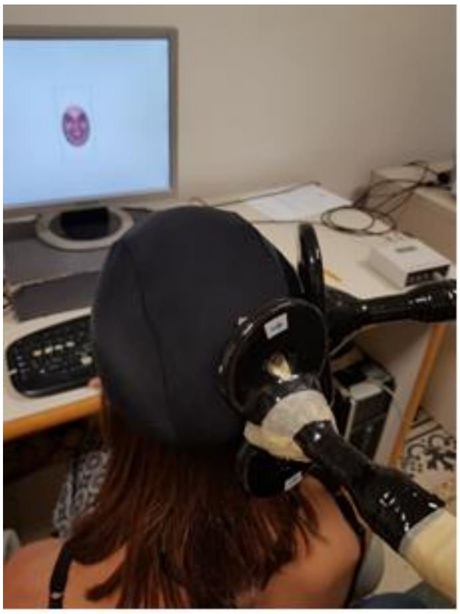


Fig. 2. Positioning of the coils during the cortico-cortical paired associative stimulation (ccPAS).

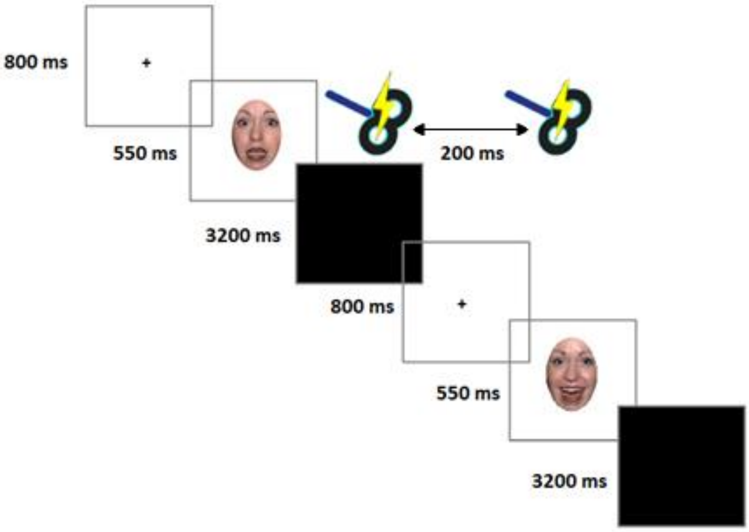


Fig. 3. Timeline of the sequence of events for each trial during the ccPAS, example from the ccPAS group “fear”.

3.3.6 Neuronavigation

Coil position was identified on each participant’s scalp with the SofTaxic Navigator system (Electro Medical Systems) (Urgesi et al., 2007b, 2007a; Bertini et al., 2010; Serino et al., 2011). Skull landmarks (nasion, inion, and 2 preauricular points) and about 100 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital). Coordinates in Talairach space were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template. The right STS scalp location was identified by means of the SofTaxic Navigator system and marked with a pen. Mean coordinates ± standard deviation corresponded to Brodmann area 21 in the posterior part of the right STS (x = 58.01 ± 2.11, y = -48.03 ± 3.59, z = 8.23 ± 1.21). For the stimulation of V1 we identified the scalp location that corresponded best to the visual cortex (x = 19, y = −98, z = 1, (Serino et al., 2011)).

3.3.7 Data analyses

Accuracy rates (% of correct responses) and reaction times (milliseconds) were recorded as dependent variables. As for accuracy, an index was created in which the accuracy values of the “Post” sessions were compared to the accuracy values of the “Pre” ccPAS session. Specifically, accuracy rates obtained after ccPAS were divided by the values obtained in the baseline performance. Therefore, a 5-level “Time” factor (0, 20, 40, 60, and 80 minutes after the ccPAS) expressed as a post/pre ratio in the accuracy values was obtained. By doing so, any value higher than 1 (or 100%) indicates enhanced performance, whereas values lower than 1 (or 100%) reflected a decrease in performance, compared to baseline values. Relevantly, the accuracy rates were described as a function of the emotion observed during the ccPAS protocol, so as to measure the influence of the state-dependent stimulation depending on the ccPAS being applied concurrently to the presentation of either joyful or fearful faces. Therefore, a 2-level congruence factor was created with the level “Same” for the performance on the detection of the same emotion associated to the ccPAS and the level “Other” for the performance on the detection of the emotion not previously associated to the ccPAS. The data analyses were carried out by means of a 4-way ANOVA with the “Group” (i.e., 2 levels: “STS-V1”, “V1-STS”) and the target “Emotion” associated with the ccPAS (2 levels: “joy”, “fear”) as between subject factors; whereas we had the "Congruence" between the emotion seen during the task and the target emotion associated with the ccPAS (2 levels: "same", "other") and the "Time" defined in relation to the moment of stimulation (5 levels: "Post0", "Post20", "Post40", "Post60", and "Post80") as the within subjects factors. Post-hoc analyses were performed using both the Duncan and LSD test to correct for multiple comparisons. Partial eta^2 was computed as a measure of effect size for the main effects and interactions.

3.4 Results

A first analysis was conducted to ensure that no significant differences could be observed at baseline across the different conditions. Indeed, it could be conceivable that participants might be randomly clustered in different groups with different abilities to recognize emotions, for example with one group showing a higher performance already at baseline. Therefore, we tested any differences between the pre-ccPAS accuracy rates among the "same" and "other" conditions for the both the STS-V1 and V1-STS stimulation groups. Crucially, it was found no significant difference between the 4 baseline accuracy rates (i.e., mean ± SEM for "STS-V1 same": 0.69 ± 0.03; "STS-V1 other": 0.72 ± 0.02; "V1-STS same": 0.74 ± 0.02; "V1-STS other": 0.69 ± 0.02; all $p > 0.05$). Next, we investigated the change on accuracy rates following the ccPAS protocol (post/pre accuracy values) as a function of the stimulation directionality (i.e., STS-V1 vs. V1-STS) and congruence (same vs. other trials). Here, the Group x Congruence ANOVA on post/pre accuracy values showed a significant interaction ($F_{1,56} = 5.42$; $p = 0.02$; eta$^2 = 0.08$). Post hoc analysis with Duncan test showed that for "same" trials following the STS-to-V1 ccPAS (mean ± SEM: 1.10 ± 0.03) an increase in the performance relative to the group undergoing the opposite order of stimulation occurred (mean ± SEM: 1.00 ± 0.03) ($p < 0.04$). Furthermore, when running post hoc analysis with LSD test also the difference between "same" (mean ± SEM: 1.10 ± 0.03) and "other" (mean ± SEM: 1.01 ± 0.03) within the STS-V1 group reached significance ($p < 0.03$), with the accuracy improvement for "same" trials being significantly higher than “other” trials (fig. 4). No other main effects nor interactions reached significance (all F < 2.28; all p > 0.13). To further investigate the aftereffects of the ccPAS protocol on emotion discrimination performance, a series of one-sample t-tests against the test value of 1 were conducted, thus testing the combined mean performance after ccPAS against a standard value reflecting equality in the post/pre ratio (i.e., null ccPAS aftereffects), (tab 1). Only the condition “same” for STS-V1 group showed a significant change in the direction of an improvement in the performance after the stimulation protocol (p = .008, all other p > .12).

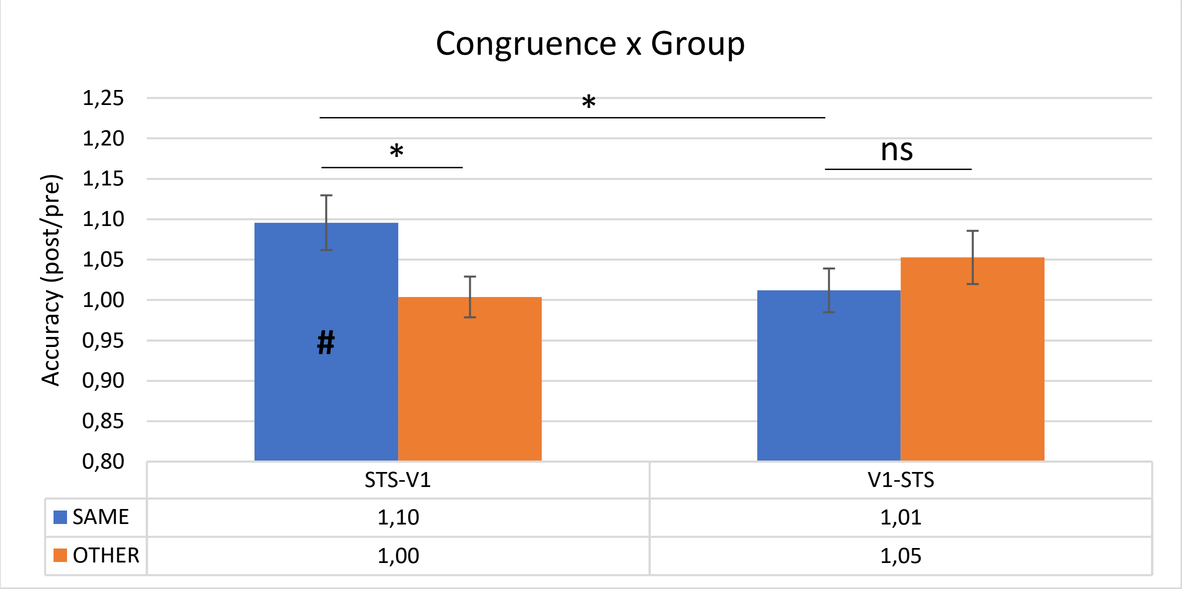


Fig. 4. Performance (mean accuracy post ccPAS/mean accuracy pre ccPAS) obtained in the different ccPAS groups (STS-V1, V1-STS) for same and other trials. * denotes significant differences in the change of performance following ccPAS (p < 0.05). # denotes significant difference in performance for post ccPAS aggregated sessions as compared to pre ccPAS, as measured by one-sample t-Tests against the value of 1 (no change) (p < 0.05).

One-sample t-Tests

	Test Value = 1					
					95% Confidence Interval of the Difference	
	T	Df	Sig. (2-tailed)	Mean Difference	Lower	Upper
STS-V1 Same	2,824	29	,008	,096	,026	,165
STS-V1 Other	,129	29	,898	,007	-,103	,117
V1-STS Same	,138	29	,891	,004	-,052	,059
V1-STS Other	1,599	29	,121	,053	-,015	,120

Tab 1. One-sample t-tests.

The same ANOVA was then conducted on post/pre reaction times (RTs) values which showed only a significant main effect of time ($F_{4,224} = 13.78$; $p < 0.001$; $eta^2 = 0.19$) (Fig. 5). It was observed a linear trend reflecting participants becoming significantly faster as they repeated the emotion discrimination task (all $p < 0.05$), most likely because of practice effects. Importantly, such a pattern rules out a speed-accuracy trade-off, showing that higher accuracy following ccPAS cannot be explained by corresponding slower response times. No other main effects or interactions reached significance (all $F < 1.59$; all $p > 0.17$).

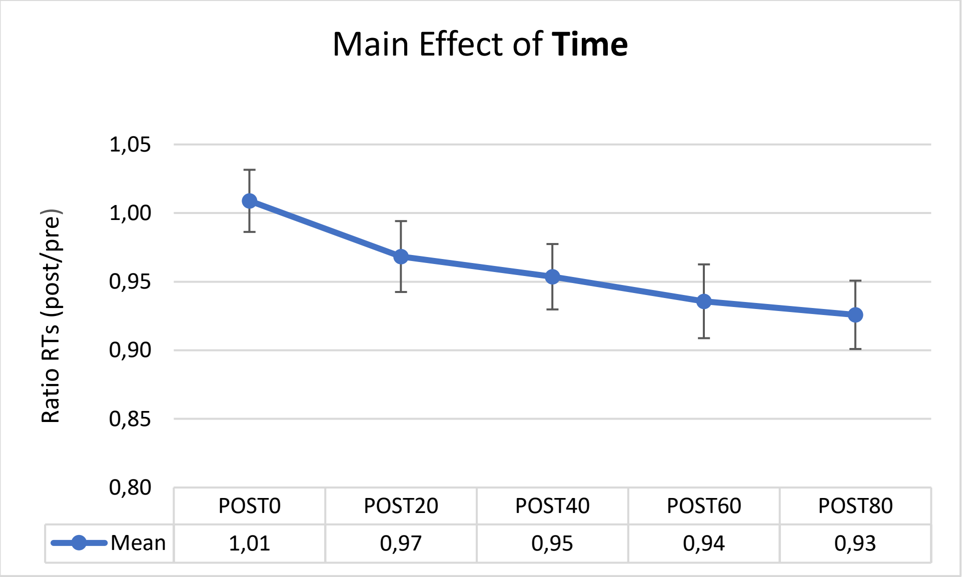


Fig. 5. Trend line Reaction Times for averaged post ccPAS testing sessions as compared to baseline levels.

Finally, in order to test for the potential relationship between the performance at baseline vs. the performance following ccPAS in the congruent experimental group (i.e., STS-V1), we conducted a median split on baseline accuracy rates for the STS-V1 group only, focusing on “same” trials so that two groups of low- and high -performers at baseline were created. The rationale behind this was that we wanted to explore whether the baseline performance could modulate the ccPAS aftereffects. We focused only on the congruent trials in the STS-V1 group as it was the only group that was significantly influenced by the stimulating protocol, resulting in an improvement of the accuracy for congruent trials only (i.e., “same”) (fig. 4). In principle, one could expect that higher gain could be observed for those participants having a lower baseline level. The median accuracy value at baseline resulted to be .70 (i.e., 70%), so below this threshold participants were included in the low responders (low_resp) group (N = 14), whereas those with a performance higher than .70 were included in the high responders (high_resp) group (N= 16). The mean accuracy value for low responders resulted to be .54, whereas high responders had a mean performance of .81 at baseline (Tab. 2). One sample t-tests of the mean accuracy at baseline were run for both low and high responders against the test value of .50 corresponding to chance performance. It was found that only high responders significantly differ from the test value (Tab. 3), suggesting that the two groups significantly differ from each other with respect to the ability to perform the emotion discrimination task at baseline. Moreover, a score reflecting the ratio between the post (averaged for post0, post20, post40, post60, and post80 testing sessions) and the pre (i.e., baseline) sessions for both low (M= 1.21, SEM= 0.05) and high (M= 0.99, SEM= 0.03) responders was created (tab. 4, upper section). A two-sample *t*-test showed significant difference between groups ($p < 0.001$; see tab. 5). These results indicate that an improvement in the accuracy following the STS-V1 ccPAS only occurs when the baseline performance is relatively low, or better, at chance level. Additional analyses were run in order to investigate the significance of the change in the performance post ccPAS. To do so, we conducted one-sample t-tests against the test value of 1, reflecting no change in the post testing sessions as compared to the baseline (i.e., post/pre = 1), for both low and high responders. Results indicated that only the low responders group performed significantly better after the ccPAS protocol (see tab. 6).

Moreover, an index was computed to quantify the facilitating effect of congruence (i.e., “same” as compared to “other” trials) following the STS-to-V1 stimulation. To this aim, the following formula [(Post / Pre “same”) / (Post / Pre “other”)] was applied for both low (M= 1.23, SEM= 0.08) and high responders (M= 1.00, SEM= 0.04) (tab. 4, lower section). Again, the *t*-test showed a significant between groups difference ($p < 0.001$; see tab. 6), indicating that the state-dependent ccPAS boosting effect on emotion recognition is evident only for participants that started from a weaker baseline performance, possibly due to higher room for improvement in this group. In further analyses we compared the mean facilitating indexes for low and high responders against the test value of 1 (see tab. 7). Again, it was found that only low responders significantly benefit from the congruence effect.

One-Sample Statistics				
	N	Mean	Std. Deviation	Std. Error Mean
PRE_**low_resp**_same_STSV1	14	,5450	,10726	,02867
PRE_**high_resp**_same_STSV1	16	,8125	,07151	,01788

Tab. 2.

One-Sample Test						
	Test Value = .50					
	T	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
PRE_**low_resp**_same_STSV1	1,570	13	,140	,04500	-,0169	,1069
PRE_**high_resp**_same_STSV1	17,481	15	,000	,31250	,2744	,3506

Tab. 3.

		N	Mean	SEM
Ratio Post/Pre_Same_ STS-V1	**Low_resp**	14	1,21	0,05
	High_resp	16	0,99	0,03
Facilitation INDEX_same/other_ STS-V1	**Low_resp**	14	1,23	0,08
	High_resp	16	1,00	0,04

Tab. 4

	Low_resp	**High_resp**
Mean	1,21	0,99
Variance	0,04	0,01
Observations	14	16
Hyphothesized Mean Difference	0	
Df	28	
t Stat	3,980512	
P(T<=t) one-tail	0,000221	
t Critical one-tail	1,701131	
P(T<=t) two-tail	0,000443	
t Critical two-tail	2,048407	

Tab. 5

	Low_resp*_RATIO POST/PRE_Same_STS-V1*
Mean	1,21
Variance	0,04
Observations	14
Hyphothesized Mean	1
Df	13
t Stat	4,127959
P(T<=t) one-tail	0,000595
t Critical one-tail	1,770933
P(T<=t) two-tail	0,001189
t Critical two-tail	2,160369

	High_resp*_RATIO POST/PRE_Same_STS-V1*
Mean	0,99
Variance	0,01
Observations	16
Hyphothesized Mean	1
Df	15
t Stat	-0,2733
P(T<=t) one-tail	0,394176
t Critical one-tail	1,75305
P(T<=t) two-tail	0,788351
t Critical two-tail	2,13145

Tab. 6

Low_resp *facilitating index for same as compared to other conditions [(POST/PRE same) / (POST/PRE other)]*		
Mean	1,23	
Variance	0,08	
Observations	14	
Hyphothesized Mean	1	
Df	13	
t Stat	2,988069	
P(T<=t) one-tail	0,005238	
t Critical one-tail	1,770933	
P(T<=t) two-tail	0,010477	
t Critical two-tail	2,160369	

High_resp *facilitating index for same as compared to other conditions [(POST/PRE same) / (POST/PRE other)]*	
Media	1,00
Varianza	0,02
Osservazioni	16
Differenza ipotizzata per le medie	1
Gdl	15
Stat t	-0,10976
P(T<=t) una coda	0,457026
t critico una coda	1,75305
P(T<=t) due code	0,914051
t critico due code	2,13145

Tab. 7

3.5 Discussion

Emotion processing performance has been significantly associated to social functioning in a way that the ability to interpret emotional information is crucial to decipher people’s mental state and intentions (Couture et al., 2006). Research on the neural changes induced by social cognitive remediation programs indicate that altered neurocognitive systems demonstrate susceptibility to neuroplastic modifications (Eack et al., 2010; Subramaniam et al., 2012). However, the nature of the causal relationship between cognitive rehabilitation programs and the neural changes is still not definitive. For instance, affective training in patients suffering schizophrenia was found to inhibit neural activation in regions underlying facial emotion processing, such as the occipital lobe and superior temporal sulcus, indicating increased efficiency of the targeted neural network (Luckhaus et al., 2013). In contrast, Habel et al. (2010) found increased neural activity in the occipital lobe and parietal cortex subsequent to the same training protocol of affect recognition in schizophrenic patients. Thus, rehabilitation programs for individuals with troubles on accurately perceiving emotions represent an important line of research. Already tested social-cognitive training programs are available in clinical practice and have proven to induce ameliorative effects on behavioral outcomes on clinical samples (Wykes et al., 2011; Kurtz & Richardson, 2012). However, there is no cognitive modification without related changes in the brain. Social neuroscientists have revealed that the social brain is characterized by intricate neural interconnections between deeper structures and cortical regions (Burns 2004; 2006). Thus, the emerging idea is that social cognition concerns an extensive range of interrelated neural networks showing a certain degree of functional specialization (Fujiwara et al. 2015). Correspondingly, neuroimaging research have demonstrated that understanding other's emotions involves a complex communication between the occipital lobe, the superior temporal sulcus, the premotor cortex, and the parietal lobe (Van Overwalle, 2009). In particular, temporal and occipital lobes are considered to represent a "core system" responsible for facial emotion recognition, whereas a "long range" system projects from the middle portion of the STS to the prefrontal cortex and the amygdala (Gobbini & Haxby 2007; Fox et al. 2009). Accordingly, previous research with fMRI has shed light on the cortical regions responsible for face processing (Haxby & Hoffman, 2000; Winston et al., 2004), identifying a greater haemodynamic response in the right posterior STS during facial expression recognition as compared to identity recognition tasks.

Non-invasive human brain stimulation is recently moving beyond the notion of simply enhancing or impairing cognitive functions, following an information-based approach in which neurostimulation protocols are informed by biologically-inspired parameters (Romei et al., 2016b). It is a current challenge trying to increase the knowledge on plastic adaptation of functional networks, focusing on the connectivity between brain areas. In this respect, the development of the ccPAS protocol has been inspired by Hebbian-like plasticity principles and by virtue of mimicking pre- and post-synaptic neural activation in a neural network by means of repeated dual coil stimulations, spike-timing dependent plasticity (STDP) mechanisms have been likely implemented in recent research (Giudali et al., 2021; Momi et al., 2020; Nord et al., 2019; Zibman et al., 2019). Indeed, it has been shown that cortical plasticity occurs only when the external manipulation best mimics the spatiotemporal dynamics of the targeted neural network (Romei et al., 2016a). Recently, Chiappini and colleagues (2018) demonstrated the influence exerted by the ccPAS on the perceptual involvement of V5-V1 back projections underlying visual motion perception, which resulted functionally malleable, in a state-dependent manner. While ccPAS studies have classically focused on motor networks (Rizzo et al., 2009; Koganemaru et al., 2009; Buch et al., 2011; Arai et al., 2011; Lu et al., 2012; Veniero et al., 2013), in the present study we extended the research investigation on emotion detection, aiming to shedding new light in the network-based neural dynamics responsible for emotion processing.

The purpose of this research was to explore the causal role of non-invasive brain stimulation on emotional face processing. In particular, we investigated to what extent the recognition of emotional facial expressions is enhanced following LTP-like effects induced by multi-coil TMS intervention on the cortical right pSTS-V1 neural pathway. Indeed, neuroplastic changes induced by the ccPAS protocol are determined by the strengthening of the neural coordination of the targeted nodes. In our study, we repeatedly delivered near-coincident cortical inputs from “higher” (i.e.,STS) to “lower” (i.e., V1) levels of the visual processing hierarchy. This stimulating protocol determined an improvement on the emotion recognition ability, indicating that ccPAS can be considered a suitable tool to drive brain remodeling at a neural network level, and consequently influence a certain behavior.

Crucially, we repeatedly activated “online” the neural pathway between STS and V1, implementing an innovative state dependent ccPAS protocol. Indeed, simultaneously with the TMS pulses given on STS-V1, faces expressing a specific emotion (i.e., either joy or fear) were presented in order to modulate the activation of the neurons that encode for a particular facial expression. Behaviourally, we expected an emotion specific effect on performance, namely, the adaptation to a specific emotional expression combined with the ccPAS-induced LTP-like effects would result in an enhanced ability to detect the congruent facial expression when presented subsequently. In particular, to test the influence of the ccPAS on the emotion perception, participants had to perform a discrimination task of emotional faces before and after the ccPAS. It resulted that the brain stimulation effectively leads to an improvement of the performance in the behavioral task. At a neural level, adaptation results in a decreased neural response to the adapting stimulus (i.e., in this case the facial expressions presented during the ccPAS) by diminishing the neuron’s resting potential (Sanchez-Vives et al., 2000; Engel et al., 2005). Therefore, passively viewing emotional expressions would bias the baseline level of its underlying neural activity. It is important to keep in mind that during our ccPAS session there was not adaptation to a specific facial expression (i.e., either joy or fear), rather both emotional expressions were presented with equal frequency and number of trials. Thus, it occurred equal adaptation to both facial expressions (i.e., joyful and fearful), so the neural response to both facial emotions was equally “depressed” by the continuous presentation throughout the ccPAS session. However, the crucial manipulation was that ccPAS was delivered during the presentation of a specific emotional expression (i.e., either joy or fear), allowing a selective boosting of the neural response associated to either joyful or fearful expressions, thus increasing the specific signal-to-noise ratio for that emotion, and eventually improving the accuracy of participants in detecting it. Accordingly, we obtained that the ccPAS protocol specifically enhanced the encoding processes for the emotional faces congruent to that seen during the brain stimulation, resulting in a functionally specific perceptual improvement. Indeed, we observed an increasing accuracy in the perception of emotional faces that expressed the emotion congruent (i.e., “same” trials) with that seen during the ccPAS session, regardless of the emotion (joy or fear), suggesting that it is possible to target specific neural subpopulations by selectively incrementing their processing efficacy. If our ccPAS protocol affected the emotional features encoded by all neural populations equally, no emotion-specific boosting effect in the following facial expression discrimination task would be shown. However, participants’ ability to detect the congruent emotion (i.e., corresponding to what they viewed when the ccPAS pulses were delivered) was selectively enhanced, whereas such pattern of results was not shown for the incongruent emotion. As neural populations tuned to the other (i.e., incongruent) emotion possibly did not benefit from the ccPAS-induced synaptic potentiation. Such specific behavioral improvement indicates that the perception of the specific features encoded by the ccPAS-targeted neural network (i.e., same trials) is biased to the disadvantage of the other (incongruent) emotional displays. The state dependent effects that we demonstrated are in accordance with Silvanto et al.'s study (2008), in which the activity of specific neural subpopulations was manipulated (in an adaptation paradigm) before TMS to the visual cortex, allowing them to investigate the relationship between the baseline level of neural activity and the perceptual consequences of TMS. Those authors found that TMS selectively facilitated the perception of the stimulus features encoded by the least active neural populations, whereas impaired the perception of the nonadapted stimulus features. In other words, adaptation reduced the neural activation in response to the adapted stimulus features, therefore a TMS intervention - which "adds" neural activation – brought back suprathreshold activation levels (necessary to perceive that specific stimulus features). On the other hand, it was observed an inhibitory TMS effect on the nonadapted features. As for nonadapted stimulus characteristics, the neural activation was not reduced by the adaptation paradigm, therefore the neural firing rate already had the potential to trigger the perceptual threshold. Thus, TMS would not increase the signal level (already at the roof) but would possibly add noise, provoking a decrease in the signal/noise ratio associated with a given cognitive process, eventually resulting in inhibited perceptual functions.

However, while our results are suggestive of the occurrence of Hebbian network plasticity, these represent only indirect evidence since our study lacks a measure of the neurobiological correlates of ccPAS on STS-V1. Nonetheless, previous literature has shown that mastering a certain skill is associated with changes in the brain circuit responsible for that practice-induced learning (Kleim et al., 2002; Merzenich, 2013), revealing synaptic modifications such as increased connection strength. On the other hand, ccPAS has shown to strengthen the stimulated network connection and reduce connectivity in non-stimulated and yet connected areas (Johnen et al., 2015), as well as modulating neural oscillatory coherence between stimulated areas (Sel et al., 2021). Notably, the ccPAS beneficial aftereffects observed in our study were attributable to the specific stimulation directionality going from STS to the primary visual cortex. Indeed, no similar results were obtained by administering the state-dependent ccPAS in a feedforward manner. Thus, only backward projections seem to be sensitive to plastic enhancement of emotion perception, in line with their role of top-down modulation claimed in the literature (Gilbert & Li, 2013; Wyatte et al., 2014). Hence, the neural activity in early visual areas does not simply reflect the processing of sensory input but is also influenced by the information coming from higher level areas (Hochstein & Ahissar, 2002). Importantly, feedforward ccPAS resulted in null rather than negative behavioral aftereffects, further demonstrating the riskless properties of the state-dependent ccPAS protocol designed. Moreover, it demonstrates that it is unlikely that the ccPAS parameters that we set (i.e., intensity, frequency, and duration of brain stimulation) exert disrupting effects on the targeted neuron populations, as we aimed to induce a primary excitatory effect on the targeted STS-to-V1 neural network, which would promote state dependent plasticity. On the contrary, the adoption of high-frequency TMS procedures (e.g., theta-burst stimulation) might have induced inhibitive effects on performance (Huang et al., 2005), but the way these hypothetical perceptual aftereffects would be manifested in a ccPAS procedure is an open question. Accordingly, Handwerker et al. (2020) combined TBS and resting-state fMRI to map the remote effects of transient cortical disruption of the right posterior STS. Remarkably, it was found that TBS reduced resting-state connectivity between rpSTS and other-face-selective areas. In our study, individual's baseline ability to discriminate between facial expressions interacted with the effectiveness of the ccPAS intervention. It has already been highlighted that a limitation of PAS protocols is the high inter- and intra- individual variability of their effects. For instance, when considering PAS protocols over the motor cortex, a significant percentage of the tested participants are non-respondent to PAS, even within participants' analyses indicate that PAS aftereffects are not always consistent (e.g., Müller-Dahlhaus et al., 2008; López-Alonso et al., 2014; Campana et al., 2019; Minkova et al., 2019). Among the other factors that might preclude PAS effects are participants' attention during the intervention or participants' age and gender (Stefan et al., 2004). In our sample, the feedback ccPAS aftereffects were evident only for participants who had lower emotion recognition accuracy at baseline. Thus, it could be claimed that accuracy rates before ccPAS are relevant for before-after treatment improvement to emerge. These findings should not be surprising, since high-performers exhibited less room for improvement being already good at performing emotion recognition at baseline (ceiling effect). Anyway, these results can still be considered encouraging because such ccPAS protocol designed to train emotion recognition would eventually be directed to individuals who have significant socio-emotional perception deficits, therefore lower accuracy rates to begin with.

3.6 Limitations

The present study has some limitations. First, the study involved a relatively small sample of students who volunteered to participate in the experiments. It may have introduced a self-selection bias since our participants were a selected sample of the entire student population, therefore potentially having some peculiar personality characteristics. For example, Pieters et al (1992) found that healthy students volunteering in clinical research exhibit lower levels of state and trait anxiety as compared with the general norm. It might be relevant since it has been shown that participants with higher levels of trait anxiety perform significantly better at recognizing the emotion of fear as compared to participants with lower levels of trait anxiety (Surcinelli et al., 2006). Therefore, it would be advisable to include questionnaires of relevant personality traits in future studies, especially when recruiting participants who are asked to perform a fear recognition task. Another limitation might have been the use of static emotional pictures rather than moving (i.e., dynamic) faces. This might reduce the generalizability of our findings to more naturalistic settings. Accordingly, Khosdelazad et al., 2020 found that static pictures of stereotypical emotions are more easily recognized than dynamic stimuli. In addition, future research would benefit from the inclusion of more complex emotional states such as agitation, shyness, pleasure, satisfaction, etc., which are equally relevant in interpersonal relationships, and would also help to prevent ceiling effects. Lastly, in our study we used a single-blind design. Although our participants were not aware of which experimental group they belonged to, for practical reasons it was not possible to do the same with the experimenters. Ongoing research would benefit from the use of a double-blind design, where examiners naive with respect to the experimental conditions conduct baseline and post-TMS assessments.

3.7 Future research

These data for the first time show that the recognition of rapidly presented emotional faces can be trained with a ccPAS protocol, leading to promising prospects for future research aiming to increase the social communication skill and overall quality of life in individuals with psychopathologies. Neuroimaging studies should be performed in order to provide converging results of dependent neuroplastic changes in the social-cognitive cortical regions targeted with the ccPAS. Moreover, future studies should evaluate conditions within which the training is effective, focusing on key characteristics that make the ccPAS a useful rehabilitation protocol (e.g., the optimal length of ccPAS, varying the nature of the stimuli or their presentation time) and for how long after brain stimulation both the behavioral and neurophysiological aftereffects can be tracked. Importantly, it opens the door to the evaluation of the ccPAS beneficial impact on other social cognitive skills not measured in our study such as social inference, investigating the modulating effects on perception of more realistic and complex social situations. The ceiling effect observed for high-performers suggests that test stimuli beyond facial expressions (e.g., bodily postures, emotional auditory information, etc.) should be included in future research, alongside the presentation of non-stereotypical facial expressions (e.g., more subtle), in order to determine enough variability to allow for ccPAS modulatory influence to emerge. Similarly, it can also be possible that high-performers might need ccPAS with different parameters, such as higher intensity or frequency of brain stimulation.

3.8 Conclusion

In conclusion, in this study we showed that state-dependent feedback ccPAS intervention on STS and V1 can improve the recognition accuracy of emotional faces on healthy individuals. In particular, the state-dependent STS-to-V1 ccPAS paradigm determined a specific modulation of the aftereffects, causally demonstrating (at a behavioral level) that it is possible to boost the processing of a specific emotion for which the STS-V1 cortical pathway is particularly involved. These results provide insights into associative plasticity mechanisms, suggesting that it is possible to induce selective ccPAS plasticity-driven influences of either joyful or fearful faces (by their visual co-occurrence with the ccPAS session). The next challenge is to convert these findings into remediation protocols that train clinical subjects to accurately recognize emotions and have fulfilling social interactions.

4 GENERAL DISCUSSION

The aim of this thesis was to study the mechanisms underlying plastic modifications of functions and neural networks responsible for emotional processing. To do so, a set of behavioral and state-dependent brain stimulation experiments were implemented to investigate the role of facial mimicry (chapter II) and cortico-cortical paired associative stimulation (chapter III) on the way we process other's emotional expressions.

The first study, in chapter II, investigated the way a perceptual-motor training, based on the repeated execution of facial expressions (i.e., happy and angry), impacted the emotional intensity ratings of both high-intensity and low-intensity emotional and neutral others' facial expressions. As for low-intensity stimuli, faces covered by a surgical facemask were shown. Accordingly, the psychological factors regulating the relationship between wearing surgical masks and social cognition are of particular interest, especially because of the international mass adoption of sanitary facemasks aiming to prevent the spread of the coronavirus (COVID-19) disease (Coclite et al., 2020). Target stimuli were shown for a duration of 500 ms, making this presentation above the threshold of most typical unconcealed expressions. The measure of perceived emotion intensity was meant to provide an index of the interaction quality among individuals. For instance, lower perceived affect could be considered as a rejection of the person with whom someone is interacting. Results showed that observing and intentionally imitating other's emotional expressions significantly improved participants emotional discriminatory abilities when subsequently asked to judge the emotional intensity of others' congruent and incongruent facial expressions. Results reflected specular mechanisms in terms of the specificity of the learning aftereffects, being the congruence effect a measure of the facilitating influence for a specific set of trials (i.e., "same") among all those presented during the emotion intensity task (i.e., "same" and "other"). Specifically, the congruence effect revealed a pattern of results such that the emotion intensity ratings for smiles were higher following the imitation of smiling faces, whereas frowning faces were rated as angrier following the imitation of angry expressions. Such high specificity of the training-induced perceptual influence can be regarded as a reflection of the plasticity of specific facial expression representations. Furthermore, it was made a direct comparison of the training-induced congruence effect between the above mentioned "imitation" group and a "simulation" control group (i.e., participants produced facial expressions in response to auditory stimuli instead of other's facial expressions). Although it was found a significant congruence effect in the "simulation" group as well, it was remarkably smaller than that observed for subjects whose training included the presentation of a congruent visual reference (i.e., the "imitation" group). Indeed, besides the engagement of the motor system, the imitation training included a visual reference entailing a coherent emotional meaning, it might therefore have triggered the activation of multiple neural systems that contributed to determine a stronger effect (Russo-Ponsaran et al., 2015). Such findings demonstrated the advantages, in terms of empathic attunement, of a setting recreating the ideal context in which social relationships exist (i.e., seeing each other) as compared t to other forms of communication (e.g., phone call). Accordingly, "the fundamental mechanism that allows us a direct experiential grasp of the mind of others is not a conceptual reasoning but direct simulation of the observed events through the mirror mechanisms" (Gallese et al., 2004). Consistent with this view, processing others' facial expression is associated to congruent neural and bodily states in the observer (Niedenthal et al., 2010; Leslie et al., 2004).

Moreover, the congruence effect equally biased the ratings of masked and unmasked emotional faces. These findings indicate that training with high-intensity (i.e., uncovered) emotional expressions promoted learning that was significantly transferred to both uncovered as well as covered facial expressions. Additional data analyses indicated that, to some degree, the training-induced learning impacted the judgement of neutral faces as well. In particular, the training differently influenced the emotional intensity judgements of neutral masked and unmasked faces: After training on joyful expressions, only neutral unmasked faces were significantly biased towards joy; whereas, imitating angry expressions significantly pushed the ratings for both masked and unmasked neutral faces towards the anger extremity of the scale. Therefore, these findings provide evidence for the asymmetric influence that previous social interactions might exert in the subsequent judgments of other's masked neutral expressions. Depending on the fact that someone has previously been engaged in an unpleasant (e.g., nervous) inter-individual communication, the ongoing perception of other's ambiguous facial display, as it might be represented by a masked facial expression, is encoded as angrier than it really is. However, it might be speculated that this kind of "angry bias" towards neutral masked faces is mostly due to the fact that some might consider facemasks uncomfortable, and feel negative attitudes because of their automatic association with the ongoing covid-19 public health emergency. Even before the coronavirus outbreak, Agneta et al. (2011) found that subjects were more prone to associate negative emotions to covered faces as compared to fully visible ones. Nevertheless, a recent study clarified that the vast majority of the interviewed subjects regularly wear facemasks; relatedly, they did not report explicit negative attitudes towards the use of facemasks as they firmly supported the concept that “it is generally reasonable to wear masks in public in the context of the COVID-19 pandemic” (Kastendieck et al., 2021). This suggests that the use of masked faces as stimuli should not have had brought important confounding factors. Another objection to the study in chapter II might be that engaging in the reproduction of affective faces may be associated to self-reports of the corresponding emotion, reflecting a cognitive mechanism termed as “emotional contagion” (for a review, Hatfield et al. 2014). To control for this effect, right after the training it was administered a self-report questionnaire assessing the susceptibility to others’ emotion: The emotional contagion scale (Italian adaptation of Lo Coco et al., 2014; originally designed by Doherty, 1997). Relevantly, the scores on the susceptibility to other’s anger and joy as a function of the training underwent right before (i.e., reproducing joyful *vs*. angry expressions) were compared. Importantly, it was found that the emotion-specific training did not differentially influence the emotional contagion scores on both subscales (i.e., joy and anger). These results indicated that actively engaging in the generation of emotional expressions determined asymmetric influence on the affective (i.e., emotion intensity task) and cognitive (i.e., emotional contagion scale) measures used. This is consistent with previous research suggesting that emotional (or affective) and cognitive perspective-taking are partially dissociable forms of empathy (Stel et al., 2008; Healey & Grossman, 2018; Fantozzi et al., 2021).

The purpose of the second study, in chapter III, was to explore to what extent the recognition of emotional facial expressions is enhanced following a multi-coil TMS intervention on the cortical right pSTS-V1 neural pathway, aiming to induce LTP-like effects. Indeed, neuroplastic changes induced by the ccPAS protocol are determined by the strengthening of the neural coordination of the targeted nodes. Near-coincident cortical inputs from “higher” (i.e.,STS) to “lower” (i.e., V1) levels of the visual processing hierarchy were repeatedly delivered. Crucially, the neural pathway between STS and V1 was activated “online”, implementing an innovative state dependent ccPAS protocol. Specifically, simultaneously with the TMS pulses given on STS-V1, faces expressing a specific emotion (i.e., either joy or fear) were presented in order to modulate the activation of the neurons encoding for a specific emotional expression. At a neural level, adaptation results in a decreased neural response to the adapting stimulus (i.e., in this case the facial expressions presented during the ccPAS) by diminishing the neuron’s resting potential (Sanchez-Vives et al., 2000; Engel et al., 2005). Therefore, passively viewing emotional expressions was expected to bias the baseline level of its underlying neural activity. Importantly, during the ccPAS session there was not adaptation to a specific facial expression (i.e., either joy or fear), rather both emotional expressions were presented with equal frequency and number of trials. Thus, such procedure supposedly induced equal adaptation to both facial expressions (i.e., joyful and fearful), so that the neural response to both facial emotions was equally “depressed” by the continuous presentation throughout the ccPAS session. However, the crucial manipulation was that ccPAS was delivered during the presentation of a specific emotional expression (i.e., either joy or fear), allowing a selective boosting of the neural response associated to either joyful or fearful expressions, thus increasing the specific signal-to-noise ratio for that emotion and eventually improving the accuracy of participants in detecting it. This procedure allowed to keep equal the total number of joyful and fearful expressions presented within the same ccPAS intervention, so that any subsequent improvement in the accuracy rate for the recognition of a specific emotional expression could only have been due to the ccPAS protocol. Differently, in the study presented in chapter II, the block design training on angry *vs*. happy facial expressions might have induced congruent emotional states, so that the congruence effect might have been partly due to a training-induced mood, consistent with the emotional meaning of the facial expressions enacted. Accordingly, previous research demonstrated that listening to emotion vocalizations implicitly induce congruent facial movements and self-reported concordant emotional states (Hawk et al. 2012, study 2). Similarly, observing emotional expressions can evoke congruent emotional experiences in the observer (Olszanowski et al., 2020). Furthermore, the general procedure of the brain stimulation study (chapter III) allowed to tackle another limitation of the behavioral study. Indeed, the study presented in chapter II lacked an additional control group in which subjects' mimicry was not required during the training. It would have allowed to rule out the possibility that passive viewing of facial emotions, without associating any active facial motor response to it, was sufficient to produce enhanced facial emotion processing. For instance, in a classic study it was found that by simply observing other's facial expressions it is induced a slight activity in the viewer's corresponding facial muscles (Dimberg, 1982). Behaviourally, it was expected that the state-dependent brain stimulation induced an emotion specific effect on performance. In particular, the adaptation to a specific emotional expression combined with the ccPAS-induced LTP-like effects would result in enhanced ability to detect the congruent facial expression when presented subsequently. To test the influence of the ccPAS on the emotion perception, subjects underwent a two-alternative forced-choice task before and after the ccPAS, in which the emotion expressed by the target stimulus (i.e., either joyful or fearful face) was presented very rapidly (i.e., 17ms). Results indicated that participants' ability to detect the congruent emotion (i.e., corresponding to what they viewed when the ccPAS pulses were delivered) was selectively enhanced, regardless of the emotion (joy or fear), suggesting that it is possible to target specific neural subpopulations by selectively incrementing their processing efficacy. In contrast, such pattern of results was not shown for the incongruent emotion, since neural populations tuned to the other (i.e., incongruent) emotion possibly did not benefit from the ccPAS-induced synaptic potentiation. Such specific behavioral improvement indicates that the perception of the specific features encoded by the ccPAS-targeted neural network (i.e., same trials) is biased to the disadvantage of the other (incongruent) emotional displays. If the ccPAS protocol affected the emotional features encoded by all neural populations equally, no emotion-specific boosting effect in the following facial expression discrimination task would be shown. Likewise, if passively observing emotional expressions was sufficient to promote facilitation in the following discrimination task, then there would not have been differences in the emotion recognition accuracy post ccPAS. This result allowed to rule out the possibility that the congruence effect found in the imitation group of the behavioral study (chapter II) was only due to congruent visual stimulation rather than to the perceptual-motor synergic action of the training. This is consistent with neuroimaging data revealing that passive observation of facial expressions elicits lower activity within the underlying neural systems as compared to an active condition in which facial mimicry is required (Carr et al., 2003). Indeed, Carr et al. (2003) demonstrated that observation and imitation induces greater neural activity in the superior temporal sulcus than the mere exposure to the emotions. Therefore, it was plausible to expect a corresponding pattern of results in behavioral performance, where participants undergoing a perceptual-motor training would obtain higher facilitating effects as compared to those obtainable in a simplified perceptual training.

Notably, the ccPAS beneficial aftereffects found were attributable to the specific stimulation directionality going from STS to the primary visual cortex. Indeed, no similar results were obtained by administering the state-dependent ccPAS in a feedforward manner (i.e., from V1 to STS). Thus, only backward projections seem to be sensitive to plastic enhancement of emotion perception, in line with their role of top-down modulation claimed in the literature (Gilbert & Li, 2013; Wyatte et al., 2014). Hence, the neural activity in early visual areas does not simply reflect the processing of sensory input but is also influenced by the information coming from higher level areas (Hochstein & Ahissar, 2002).

5 GENERAL CONCLUSION

In sum, the present thesis project provides a broad methodological framework within which behavioral and brain stimulation studies were designed to investigate the functional and neural properties underlying emotion processing in healthy individuals.

In chapter II, we behaviorally explored the plasticity and learning mechanisms of facial expression representations (i.e., neutral, happy, and angry). It was shown that intentionally observing and imitating facial expressions biased the subsequent expression intensity judgements for the congruent, but not the incongruent, emotional expressions. Notably, although rated as overall less emotionally intense, masked faces did not undermine the emotion-specific aftereffects of the training-induced learning. These results provide evidence for training-specific perceptual learning processes in high-level vision for both low-intensity (i.e., masked) and high-intensity (i.e., unmasked) neutral and emotional faces. In chapter III, we used cortico-cortical paired associative stimulation (ccPAS) to target STS-V1 neural pathways and plastically modulated the strength of its cortico-cortical connectivity according to the Hebbian principles. Importantly, we tested these on emotion-specific re-entrant circuits by administering state-dependent ccPAS during the presentation of specific emotional expressions (i.e., either happy or fearful). Findings indicated specific perceptual improvements, namely increased recognition accuracy for the emotional faces that expressed the emotion congruent with that shown during the ccPAS. This suggests that it is possible to target specific neural subpopulations by selectively incrementing their processing efficacy.

APPENDIX

Italian adaptation of the emotional contagion scale (Lo Coco et al., 2014)

Soggetto n. …… **Età** …… **Sesso** **M** | **F**

Istruzioni

Le seguenti affermazioni riguardano i tuoi pensieri e sentimenti in una serie di situazioni.

Per ognuna delle affermazioni qui sotto, indica con una croce la casella che ritieni più vicina allatua esperienza.

1. Se la persona con cui sto parlando inizia a piangere, mi si riempiono gli occhi di lacrime

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

2. Quando mi sento giù, stare con una persona felice mi risolleva

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

3. Quando qualcuno/a mi sorride calorosamente, ricambio il sorriso e mi riempio di calore

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

4. Mi riempio di tristezza quando la gente parla della morte dei loro cari

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

5. Quando vedo i volti arrabbiati al telegiornale serro le mandibole e le mie spalle si stringono

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

6. Quando guardo negli occhi la persona che amo, la mia mente è piena di pensieri romantici

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

7. Mi irrita avere attorno gente arrabbiata

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

8. Guardare i volti pieni di paura delle vittime al telegiornale mi fa provare a immaginare come si possano sentire

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

9. Mi sciolgo quando la persona che amo mi tiene stretto/a

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

10. Divento teso/a quando sento per caso una lite furiosa

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

11. Avere attorno gente felice mi riempie la mente di pensieri felici

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

12. Quando la persona che amo mi tocca sento il mio corpo rispondere

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

13. Noto che divento teso/a quando la gente che mi sta attorno è stressata

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

14. Piango davanti a un film triste

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

15. Sentire le urla penetranti di un/una bambino/a terrorizzato nella sala d’attesa di un dentista mi rende nervoso/a

Mai	Raramente	Di solito	Molto spesso	Sempre
☐	☐	☐	☐	☐

REFERENCES

Abraham, W. C. (2008). Metaplasticity: tuning synapses and networks for plasticity. *Nature Reviews Neuroscience*, *9*(5), 387-387.

Abraham, W. C., & Bear, M. F. (1996). Metaplasticity: the plasticity of synaptic plasticity. *Trends in neurosciences*, *19*(4), 126-130.

Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Annals of the New York Academy of Sciences*, *1191*(1), 42.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *Journal of neuroscience*, *20*(7), 2683-2690.

Adolphs, R., Tranel, D., & Damasio, A. R. (2003). Dissociable neural systems for recognizing emotions. *Brain and cognition*, *52*(1), 61-69.

Aggleton, J. P., Burton, M. J., & Passingham, R. E. (1980). Cortical and subcortical afferents to the amygdala of the rhesus monkey (Macaca mulatta). *Brain research*, *190*(2), 347-368.

Aleman, A., & Kahn, R. S. (2005). Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? *Progress in neurobiology*, *77*(5), 283-298.

Allison, T., Puce, A., & McCarthy, G. (2000). Social perception from visual cues: role of the STS region. *Trends in cognitive sciences*, *4*(7), 267-278.

Antal, A., Terney, D., Poreisz, C., & Paulus, W. (2007). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience*, *26*(9), 2687-2691.

Arai, N., Müller-Dahlhaus, F., Murakami, T., Bliem, B., Lu, M. K., Ugawa, Y., & Ziemann, U. (2011). State-dependent and timing-dependent bidirectional associative plasticity in the human SMA-M1 network. *Journal of Neuroscience*, *31*(43), 15376-15383.

Artola, A., Bröcher, S., & Singer, W. (1990). Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. *Nature*, *347*(6288), 69-72.

Aspan, N., Vida, P., Gadoros, J., & Halasz, J. (2013). Conduct symptoms and emotion recognition in adolescent boys with externalization problems. *The Scientific World Journal, 2013*.

Astafiev, S. V., Stanley, C. M., Shulman, G. L., & Corbetta, M. (2004). Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nature neuroscience*, *7*(5), 542-548.

Balconi, M., & Canavesio, Y. (2016). Is empathy necessary to comprehend the emotional faces? The empathic effect on attentional mechanisms (eye movements), cortical correlates (N200 event-related potentials) and facial behaviour (electromyography) in face processing. *Cognition and Emotion*, *30*(2), 210-224.

Baranyi, A., & Fehér, O. (1981). Synaptic facilitation requires paired activation of convergent pathways in the neocortex. *Nature*, *290*(5805), 413-415.

Baranyi, A., & Szente, M. B. (1987). Long-lasting potentiation of synaptic transmission requires postnaptic modifications in the neocortex. *Brain Research*, *423*(1-2), 378-384.

Barch, D. M. (2005). The cognitive neuroscience of schizophrenia. *Annu. Rev. Clin. Psychol.*, *1*, 321-353.

Barlati, S., Deste, G., De Peri, L., Ariu, C., & Vita, A. (2013). Cognitive remediation in schizophrenia: current status and future perspectives. *Schizophrenia Research and Treatment, 2013*.

Baron-Cohen, S., Wheelwright, S., & Jolliffe, A. T. (1997). Is there a" language of the eyes"? Evidence from normal adults, and adults with autism or Asperger syndrome. *Visual cognition*, *4*(3), 311-331.

Bell, C. C., Han, V. Z., Sugawara, Y., & Grant, K. (1997). Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature*, *387*(6630), 278-281.

Bertini, C., Leo, F., Avenanti, A., & Ladavas, E. (2010). Independent mechanisms for ventriloquism and multisensory integration as revealed by theta-burst stimulation. *European Journal of Neuroscience*, *31*(10), 1791-1799.

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. (2003). Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. *Neuroimage*, *20*(3), 1685-1696.

Bi, G. Q., & Poo, M. M. (1998). Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. Journal of neuroscience, 18(24), 10464-10472.

Bienenstock, E. L., Cooper, L. N., & Munro, P. W. (1982). Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *Journal of Neuroscience*, *2*(1), 32-48.

Blais, C., Roy, C., Fiset, D., Arguin, M., & Gosselin, F. (2012). The eyes are not the window to basic emotions. *Neuropsychologia*, *50*(12), 2830-2838

Bliem, B., Müller-Dahlhaus, J. F. M., Dinse, H. R., & Ziemann, U. (2008). Homeostatic metaplasticity in the human somatosensory cortex. *Journal of Cognitive Neuroscience*, *20*(8), 1517-1528.

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31-39.

Bliss, T.V.P., & Gardner-Medwin, A.R. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. Journal of Physiology-London, *232*(2), 357-74.

Bölte, S., Feineis-Matthews, S., & Poustka, F. (2008). Brief report: Emotional processing in high-functioning autism—physiological reactivity and affective report. *Journal of autism and developmental disorders*, *38*(4), 776-781.

Borgomaneri, S., Bolloni, C., Sessa, P., & Avenanti, A. (2020). Blocking facial mimicry affects recognition of facial and body expressions. *PloS one*, *15*(2), e0229364.

Boroojerdi, B., Phipps, M., Kopylev, L., Wharton, C. M., Cohen, L. G., & Grafman, J. (2001). Enhancing analogic reasoning with rTMS over the left prefrontal cortex. *Neurology*, *56*(4), 526-528.

Brass, M., Bekkering, H., Wohlschläger, A., & Prinz, W. (2000). Compatibility between observed and executed finger movements: comparing symbolic, spatial, and imitative cues. *Brain and cognition*, *44*(2), 124-143.

Briggs, G. G., & Nebes, R. D. (1975). Patterns of hand preference in a student population. *Cortex*, *11*(3), 230-238.

Brown, T. H. (1986). Differential conditioning of associative synaptic enhancement in hippocampal brain slices. *Science*, *232*(4746), 85-87. Brüne, M. (2005). “Theory of mind” in schizophrenia: a review of the literature. *Schizophrenia bulletin*, *31*(1), 21-42.

Buch, E. R., Johnen, V. M., Nelissen, N., O'Shea, J., & Rushworth, M. F. (2011). Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. *Journal of Neuroscience*, *31*(48), 17669-17679.

Buch, E. R., Mars, R. B., Boorman, E. D., & Rushworth, M. F. (2010). A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. *Journal of Neuroscience*, *30*(4), 1395-1401.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., ... & Mintun, M. A. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *Journal of neuroscience*, *25*(34), 7709-7717.

Burns, J. K. (2004). An evolutionary theory of schizophrenia: Cortical connectivity, metarepresentation, and the social brain. *Behavioral and Brain Sciences*, *27*(6), 831-855.

Burns, J. (2006). The social brain hypothesis of schizophrenia. *World psychiatry*, *5*(2), 77.

Campbell, M. E., Mehrkanoon, S., & Cunnington, R. (2018). Intentionally not imitating: Insula cortex engaged for top-down control of action mirroring. *Neuropsychologia*, *111*, 241-251.

Calbi, M., Langiulli, N., Ferroni, F., Montalti, M., Kolesnikov, A., Gallese, V., & Umiltà, M. A. (2021). The consequences of COVID-19 on social interactions: an online study on face covering. *Scientific reports*, *11*(1), 1-10.

Calder, A. J., & Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. *Nature Reviews Neuroscience*, *6*(8), 641-651.

Calvo, M. G., & Nummenmaa, L. (2008). Detection of emotional faces: salient physical features guide effective visual search. *Journal of Experimental Psychology: General*, *137*(3), 471.

Campana, M., Papazova, I., Pross, B., Hasan, A., & Strube, W. (2019). Motor-cortex excitability and response variability following paired-associative stimulation: A proof-of-concept study comparing individualized and fixed inter-stimulus intervals. *Experimental brain research*, *237*(7), 1727-1734.

Cappa, S. F., Sandrini, M., Rossini, P. M., Sosta, K., & Miniussi, C. (2002). The role of the left frontal lobe in action naming: rTMS evidence. *Neurology*, *59*(5), 720-723.

Carbon, C. C. (2020). Wearing face masks strongly confuses counterparts in reading emotions. *Frontiers in Psychology*, *11*, 2526.

Cárdenas-Morales, L., Volz, L. J., Michely, J., Rehme, A. K., Pool, E. M., Nettekoven, C., ... & Grefkes, C. (2014). Network connectivity and individual responses to brain stimulation in the human motor system. *Cerebral Cortex*, *24*(7), 1697-1707.

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proceedings of the national Academy of Sciences*, *100*(9), 5497-5502.

Carr, E. W., & Winkielman, P. (2014). When mirroring is both simple and “smart”: how mimicry can be embodied, adaptive, and non-representational. *Frontiers in human neuroscience*, *8*, 505.

Casula, E. P., Pellicciari, M. C., Picazio, S., Caltagirone, C., & Koch, G. (2016). Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. *Neuroimage*, *143,* 204-213.

Catmur, C., Mars, R. B., Rushworth, M. F., & Heyes, C. (2011). Making mirrors: premotor cortex stimulation enhances mirror and counter-mirror motor facilitation. *Journal of Cognitive Neuroscience*, *23*(9), 2352-2362.

Cazzato, V., Mian, E., Serino, A., Mele, S., & Urgesi, C. (2015). Distinct contributions of extrastriate body area and temporoparietal junction in perceiving one's own and others' body. *Cognitive, Affective, & Behavioral Neuroscience*, *15*(1), 211-228.

Chafee, M. V., & Goldman-Rakic, P. S. (2000). Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *Journal of neurophysiology*, *83*(3), 1550-1566.

Chao, C. C., Karabanov, A. N., Paine, R., Carolina de Campos, A., Kukke, S. N., Wu, T., ... & Hallett, M. (2015). Induction of motor associative plasticity in the posterior parietal cortex–primary motor network. *Cerebral Cortex*, *25*(2), 365-373.

Chartrand, T. L., & Bargh, J. A. (1999). The chameleon effect: the perception–behavior link and social interaction. *Journal of personality and social psychology*, *76*(6), 893.

Chiappini, E., Silvanto, J., Hibbard, P. B., Avenanti, A., & Romei, V. (2018). Strengthening functionally specific neural pathways with transcranial brain stimulation. *Current Biology*, *28*(13), R735-R736.

Coclite, D., Napoletano, A., Gianola, S., Del Monaco, A., D'Angelo, D., Fauci, A., ... & Iannone, P. (2020). Face mask use in the community for reducing the spread of COVID-19: a systematic review. *Frontiers in medicine, 7.*

Cohen, A. S., Raymond, C. R., & Abraham, W. C. (1998). Priming of long-term potentiation induced by activation of metabotropic glutamate receptors coupled to phospholipase C. *Hippocampus*, *8*(2), 160-170.

Conte, A., Gilio, F., Iezzi, E., Frasca, V., Inghilleri, M., & Berardelli, A. (2007). Attention influences the excitability of cortical motor areas in healthy humans. *Experimental Brain Research*, *182*(1), 109-117.

Couture, S. M., Penn, D. L., & Roberts, D. L. (2006). The functional significance of social cognition in schizophrenia: a review. *Schizophrenia bulletin*, *32*(suppl_1), S44-S63.

Cowey, A., & Walsh, V. (2000). Magnetically induced phosphenes in sighted, blind and blindsighted observers. *Neuroreport*, *11*(14), 3269-3273.

Cracco, E., Bardi, L., Desmet, C., Genschow, O., Rigoni, D., De Coster, L., ... & Brass, M. (2018). Automatic imitation: A meta-analysis. *Psychological Bulletin*, *144*(5), 453.

Cross, K. A., & Iacoboni, M. (2014). To imitate or not: Avoiding imitation involves preparatory inhibition of motor resonance. *Neuroimage*, *91*, 228-236.

Crupi, D., Ghilardi, M. F., Mosiello, C., Di Rocco, A., Quartarone, A., & Battaglia, F. (2008). Cortical and brainstem LTP-like plasticity in Huntington's disease. *Brain research bulletin*, *75*(1), 107-114.

d'Alfonso, A. A., van Honk, J., Hermans, E., Postma, A., & de Haan, E. H. (2000). Laterality effects in selective attention to threat after repetitive transcranial magnetic stimulation at the prefrontal cortex in female subjects. *Neuroscience letters*, *280*(3), 195-198.

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., & Iacoboni, M. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nature neuroscience*, *9*(1), 28-30.

Davare, M., Lemon, R., & Olivier, E. (2008). Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. *The Journal of physiology*, *586*(11), 2735-2742.

Davare, M., Montague, K., Olivier, E., Rothwell, J. C., & Lemon, R. N. (2009). Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. *Cortex*, *45*(9), 1050-1057.

Day, B. L., Dressler, D., Maertens de Noordhout, A. C. D. M., Marsden, C. D., Nakashima, K., Rothwell, J. C., & Thompson, P. D. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *The Journal of physiology*, *412*(1), 449-473.

De la Rosa, S., Fademrecht, L., Bülthoff, H. H., Giese, M. A., & Curio, C. (2018). Two ways to facial expression recognition? Motor and visual information have different effects on facial expression recognition. *Psychological Science*, *29*(8), 1257-1269.

Delbeuck, X., Van der Linden, M., & Collette, F. (2003). Alzheimer'disease as a disconnection syndrome?. *Neuropsychology review*, *13*(2), 79-92.

Di Lazzaro, V., Pilato, F., Oliviero, A., Dileone, M., Saturno, E., Mazzone, P., ... & Rothwell, J. C. (2006). Origin of facilitation of motor-evoked potentials after paired magnetic stimulation: direct recording of epidural activity in conscious humans. *Journal of neurophysiology*, *96*(4), 1765-1771.

Di Lorenzo, F., Ponzo, V., Motta, C., Bonnì, S., Picazio, S., Caltagirone, C., ... & Koch, G. (2018). Impaired spike timing dependent cortico-cortical plasticity in Alzheimer’s disease patients. *Journal of Alzheimer's Disease*, *66*(3), 983-991.

Dima, D., Stephan, K. E., Roiser, J. P., Friston, K. J., & Frangou, S. (2011). Effective connectivity during processing of facial affect: evidence for multiple parallel pathways. *Journal of Neuroscience*, *31*(40), 14378-14385.

Dimberg, U. (1982). Facial reactions to facial expressions. *Psychophysiology*, *19*(6), 643-647.

Dimberg, U., Andréasson, P., & Thunberg, M. (2011). Emotional empathy and facial reactions to facial expressions. *Journal of Psychophysiology*, *25*(1), 26.

Do, M., Kirkovski, M., Davies, C. B., Bekkali, S., Byrne, L. K., & Enticott, P. G. (2018). Intra-and inter-regional priming of ipsilateral human primary motor cortex with continuous theta burst stimulation does not induce consistent neuroplastic effects. *Frontiers in human neuroscience*, *12*, 123.

Dosher, B. A., & Lu, Z. L. (2005). Perceptual learning in clear displays optimizes perceptual expertise: Learning the limiting process. *Proceedings of the National Academy of Sciences*, *102*(14), 5286-5290.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Changes in grey matter induced by training. *Nature*, *427*(6972), 311-312.

Du, Y., Zhang, F., Wang, Y., Bi, T., & Qiu, J. (2016). Perceptual learning of facial expressions. *Vision research*, *128*, 19-29.

Dudek, S. M., & Bear, M. F. (1993). Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. *Journal of Neuroscience*, *13*(7), 2910-2918.

Eack, S. M., Hogarty, G. E., Cho, R. Y., Prasad, K. M., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2010). Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. *Archives of general psychiatry*, *67*(7), 674-682.

Edwards, G., Agosta, S., Herpich, F., Contò, F., Parrott, D., Tyler, S., ... & Battelli, L. (2019). Prolonged neuromodulation of cortical networks following low-frequency rTMS and its potential for clinical interventions. Frontiers in psychology, 10, 529.

Egger, V., Feldmeyer, D., & Sakmann, B. (1999). Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex. *Nature neuroscience*, *2*(12), 1098-1105.

Eisenbarth, H., & Alpers, G. W. (2011). Happy mouth and sad eyes: scanning emotional facial expressions. *Emotion*, *11*(4), 860.

Ekman, P. (1993). Facial expression and emotion. *American psychologist*, *48*(4), 384.

Ekman, P. (2004). Emotions revealed. *Bmj*, *328*(Suppl S5).

Eldaief, M. C., Halko, M. A., Buckner, R. L., & Pascual-Leone, A. (2011). Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner. *Proceedings of the National Academy of Sciences*, *108*(52), 21229-21234.

Engel, S. A. (2005). Adaptation of oriented and unoriented color-selective neurons in human visual areas. *Neuron*, *45*(4), 613-623.

Fantozzi, P., Muratori, P., Caponi, M. C., Levantini, V., Nardoni, C., Pfanner, C., ... & Masi, G. (2021). Treatment with Methylphenidate Improves Affective but Not Cognitive Empathy in Youths with Attention-Deficit/Hyperactivity Disorder. *Children*, *8*(7), 596.

Feldman, D. E. (2009). Synaptic mechanisms for plasticity in neocortex. *Annual review of neuroscience*, *32*, 33-55.

Feldman, D. E. (2012). The spike-timing dependence of plasticity. *Neuron*, *75*(4), 556-571.

Fiori, F., Chiappini, E., & Avenanti, A. (2018). Enhanced action performance following TMS manipulation of associative plasticity in ventral premotor-motor pathway. *NeuroImage*, *183,* 847-858.

Fischer, A. H., Gillebaart, M., Rotteveel, M., Becker, D., & Vliek, M. (2012). Veiled emotions: the effect of covered faces on emotion perception and attitudes. *Social Psychological and Personality Science*, *3*(3), 266-273.

Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience, 16*(3), 159-172.

Fox, C. J., Iaria, G., & Barton, J. J. (2009). Defining the face processing network: optimization of the functional localizer in fMRI. *Human brain mapping*, *30*(5), 1637-1651.

Frank, M. G., & Ekman, P. (1997). The ability to detect deceit generalizes across different types of high-stake lies. *Journal of personality and social psychology, 72*(6), 1429.

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends in cognitive sciences*, *9*(10), 474-480.

Friston, K. J. (2002). Dysfunctional connectivity in schizophrenia. *World Psychiatry, 1*(2), 66.

Froemke, R. C., & Dan, Y. (2002). Spike-timing-dependent synaptic modification induced by natural spike trains. *Nature, 416*(6879), 433-438.

Froemke, R. C., Letzkus, J. J., Kampa, B., Hang, G. B., & Stuart, G. (2010). Dendritic synapse location and neocortical spike-timing-dependent plasticity. *Frontiers in synaptic neuroscience*, *2*, 29.

Froemke, R. C., Poo, M. M., & Dan, Y. (2005). Spike-timing-dependent synaptic plasticity depends on dendritic location. *Nature*, *434*(7030), 221-225.

Fujiwara, T., & Rothwell, J. C. (2004). The after effects of motor cortex rTMS depend on the state of contraction when rTMS is applied. *Clinical Neurophysiology*, *115*(7), 1514-1518.

Fujiwara, H., Yassin, W., & Murai, T. (2015). Neuroimaging studies of social cognition in schizophrenia. *Psychiatry and Clinical Neurosciences*, *69*(5), 259-267.

Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in cognitive sciences*, *8*(9), 396-403.

Gamboa, O. L., Antal, A., Moliadze, V., & Paulus, W. (2010). Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Experimental brain research*, *204*(2), 181-187.

Gangitano, M., Valero-Cabré, A., Tormos, J. M., Mottaghy, F. M., Romero, J. R., & Pascual-Leone, Á. (2002). Modulation of input–output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex. Clinical Neurophysiology, 113(8), 1249-1257.

Gauthier, I., Tarr, M. J., Moylan, J., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). The fusiform "face area" is part of a network that processes faces at the individual level. *Journal of cognitive neuroscience*, *12*(3), 495-504.

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., & Classen, J. (2008). Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. *Cerebral cortex*, *18*(9), 2046-2053.

Gilbert, C. D., & Li, W. (2013). Top-down influences on visual processing. *Nature Reviews Neuroscience*, *14*(5), 350-363.

Gilson, M., Masquelier, T., & Hugues, E. (2011). STDP allows fast rate-modulated coding with Poisson-like spike trains. *PLoS Comput Biol*, *7*(10), e1002231.

Gobbini, M. I., & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia*, *45*(1), 32-41.

Goshen-Gottstein, Y., & Ganel, T. (2000). Repetition priming for familiar and unfamiliar faces in a sex-judgment task: evidence for a common route for the processing of sex and identity. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *26*(5), 1198.

Golan, O., Baron-Cohen, S., Hill, J. J., & Rutherford, M. D. (2007). The 'Reading the Mind in the Voice'test-revised: a study of complex emotion recognition in adults with and without autism spectrum conditions. *Journal of autism and developmental disorders*, *37*(6), 1096-1106.

Goldsworthy, M. R., Müller-Dahlhaus, F., Ridding, M. C., & Ziemann, U. (2014). Inter-subject variability of LTD-like plasticity in human motor cortex: a matter of preceding motor activation. *Brain Stimulation*, *7*(6), 864-870.

Grefkes, C., Nowak, D. A., Wang, L. E., Dafotakis, M., Eickhoff, S. B., & Fink, G. R. (2010). Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. *Neuroimage*, *50*(1), 233-242.

Grice, K. O., Vogel, K. A., Le, V., Mitchell, A., Muniz, S., & Vollmer, M. A. (2003). Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. *American Journal of Occupational Therapy*, *57*(5), 570-573.

Grill-Spector, K., Knouf, N., & Kanwisher, N. (2004). The fusiform face area subserves face perception, not generic within-category identification. *Nature neuroscience*, *7*(5), 555-562.

Grol, M. J., Majdandžić, J., Stephan, K. E., Verhagen, L., Dijkerman, H. C., Bekkering, H., ... & Toni, I. (2007). Parieto-frontal connectivity during visually guided grasping. *Journal of Neuroscience*, *27*(44), 11877-11887.

Groppa, S., Werner-Petroll, N., Münchau, A., Deuschl, G., Ruschworth, M. F., & Siebner, H. R. (2012). A novel dual-site transcranial magnetic stimulation paradigm to probe fast facilitatory inputs from ipsilateral dorsal premotor cortex to primary motor cortex. *Neuroimage, 62*(1), 500-509.

Gschwind, M., Pourtois, G., Schwartz, S., Van De Ville, D., & Vuilleumier, P. (2012). White-matter connectivity between face-responsive regions in the human brain. *Cerebral cortex, 22*(7), 1564-1576.

Guidali, G., Roncoroni, C., & Bolognini, N. (2021). Paired associative stimulations: Novel tools for interacting with sensory and motor cortical plasticity. *Behavioural Brain Research, 414*, 113484.

Habel, U., Koch, K., Kellermann, T., Reske, M., Frommann, N., Wölwer, W., ... & Schneider, F. (2010). Training of affect recognition in schizophrenia: neurobiological correlates. *Social neuroscience, 5*(1), 92-104.

Haber, S. N., & Behrens, T. E. (2014). The neural network underlying incentive-based learning: implications for interpreting circuit disruptions in psychiatric disorders. *Neuron, 83*(5), 1019-1039.

Hall, J. A., Andrzejewski, S. A., & Yopchick, J. E. (2009). Psychosocial correlates of interpersonal sensitivity: A meta-analysis. *Journal of Nonverbal behavior, 33*(3), 149-180.

Hamada, M., Hanajima, R., Terao, Y., Arai, N., Furubayashi, T., Inomata-Terada, S., ... & Ugawa, Y. (2007). Quadro-pulse stimulation is more effective than paired-pulse stimulation for plasticity induction of the human motor cortex. *Clinical neurophysiology, 118*(12), 2672-2682.

Hamada, M., Hanajima, R., Terao, Y., Okabe, S., Nakatani-Enomoto, S., Furubayashi, T., ... & Ugawa, Y. (2009). Primary motor cortical metaplasticity induced by priming over the supplementary motor area. *The Journal of physiology, 587*(20), 4845-4862.

Handwerker, D. A., Ianni, G., Gutierrez, B., Roopchansingh, V., Gonzalez-Castillo, J., Chen, G., ... & Pitcher, D. (2020). Theta-burst TMS to the posterior superior temporal sulcus decreases resting-state fMRI connectivity across the face processing network. *Network Neuroscience*, *4*(3), 746-760.

Hannah, R., & Rothwell, J. C. (2017). Pulse duration as well as current direction determines the specificity of transcranial magnetic stimulation of motor cortex during contraction. *Brain stimulation*, *10*(1), 106-115.

Harris, J. A., Clifford, C. W., & Miniussi, C. (2008). The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation? *Journal of Cognitive Neuroscience*, *20*(4), 734-740.

Hasan, A., Bergener, T., Nitsche, M. A., Strube, W., Bunse, T., Falkai, P., & Wobrock, T. (2013). Impairments of motor-cortex responses to unilateral and bilateral direct current stimulation in schizophrenia. *Frontiers in psychiatry*, *4*, 121.

Hasan, A., Nitsche, M. A., Herrmann, M., Schneider-Axmann, T., Marshall, L., Gruber, O., ... & Wobrock, T. (2012). Impaired long-term depression in schizophrenia: a cathodal tDCS pilot study. *Brain stimulation*, *5*(4), 475-483.

Hasan, A., Nitsche, M. A., Rein, B., Schneider-Axmann, T., Guse, B., Gruber, O., ... & Wobrock, T. (2011). Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by transcranial direct current stimulation. *Behavioural brain research*, *224*(1), 15-22.

Hatfield, E., Bensman, L., Thornton, P. D., & Rapson, R. L. (2014). New perspectives on emotional contagion: A review of classic and recent research on facial mimicry and contagion.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in cognitive sciences*, *4*(6), 223-233.

Hawk, S. T., Fischer, A. H., & Van Kleef, G. A. (2012). Face the noise: embodied responses to nonverbal vocalizations of discrete emotions. *Journal of personality and social psychology*, *102*(4), 796.

Healey, M. L., & Grossman, M. (2018). Cognitive and affective perspective-taking: evidence for shared and dissociable anatomical substrates. *Frontiers in neurology*, *9*, 491.

Hebb, D. O. (1949). The organization of behavior; a neuropsychologigal theory. *A Wiley Book in Clinical Psychology*, *62*, 78.

Hennenlotter, A., Schroeder, U., Erhard, P., Castrop, F., Haslinger, B., Stoecker, D., ... & Ceballos-Baumann, A. O. (2005). A common neural basis for receptive and expressive communication of pleasant facial affect. *Neuroimage*, *26*(2), 581-591.

Hess, G., Aizenman, C. D., & Donoghue, J. P. (1996). Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. *Journal of neurophysiology*, *75*(5), 1765-1778

Hess, G., & Donoghue, J. P. (1996). Long-term potentiation and long-term depression of horizontal connections in rat motor cortex. *Acta neurobiologiae experimentalis*, *56*(1), 397-405.

Hess, U., & Fischer, A. (2013). Emotional mimicry as social regulation. *Personality and social psychology review*, *17*(2), 142-157.

Hess, U., & Fischer, A. (2014). Emotional mimicry: Why and when we mimic emotions. *Social and personality psychology compass*, *8*(2), 45-57.

Hill, E. L., & Frith, U. (2003). Understanding autism: insights from mind and brain. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1430), 281-289.

Hochstein, S., & Ahissar, M. (2002). View from the top: Hierarchies and reverse hierarchies in the visual system. *Neuron*, *36*(5), 791-804.

Hoffman, E. A., & Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature neuroscience*, *3*(1), 80-84.

Holmgren, C. D., & Zilberter, Y. (2001). Coincident spiking activity induces long-term changes in inhibition of neocortical pyramidal cells. *Journal of Neuroscience*, *21*(20), 8270-8277.

Hooker, C., & Park, S. (2002). Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry research, 112*(1), 41-50.

Houdé, O., Zago, L., Mellet, E., Moutier, S., Pineau, A., Mazoyer, B., & Tzourio-Mazoyer, N. (2000). Shifting from the perceptual brain to the logical brain: The neural impact of cognitive inhibition training. *Journal of cognitive neuroscience*, *12*(5), 721-728.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*(2), 201-206.

Iacoboni, M. (2005). Neural mechanisms of imitation. *Current opinion in neurobiology, 15*(6), 632-637.

Ilić, N. V., Sajić, J., Mišković, M., Krstić, J., Milanović, S., Vesović-Potić, V., ... & Ilić, T. V. (2009). The efficacy of two protocols for inducing motor cortex plasticity in healthy humans–TMS study. *Gen Physiol Biophys, 28*, 228-34.

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., & Katila, T. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*, *8*(16), 3537-3540.

Jahanshahi, M., & Rothwell, J. (2000). Transcranial magnetic stimulation studies of cognition: an emerging field. *Experimental Brain Research, 131*(1), 1-9.

Jenness, J. L., Hankin, B. L., Young, J. F., & Gibb, B. E. (2015). Misclassification and identification of emotional facial expressions in depressed youth: A preliminary study. *Journal of Clinical Child & Adolescent Psychology, 44*(4), 559-565.

Johansen-Berg, H., Behrens, T. E. J., Robson, M. D., Drobnjak, I., Rushworth, M. F. S., Brady, J. M., ... & Matthews, P. M. (2004). Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proceedings of the National Academy of Sciences, 101*(36), 13335-13340.

Johnen, V. M., Neubert, F. X., Buch, E. R., Verhagen, L., O'Reilly, J. X., Mars, R. B., & Rushworth, M. F. (2015). Causal manipulation of functional connectivity in a specific neural pathway during behaviour and at rest. *Elife*, *4*, e04585.

Joseph, D. L., & Newman, D. A. (2010). Emotional intelligence: an integrative meta-analysis and cascading model. *Journal of applied psychology*, *95*(1), 54.

Jung, P., & Ziemann, U. (2009). Homeostatic and nonhomeostatic modulation of learning in human cortex. *Journal of Neuroscience*, *29*(17), 5597-5604.

Kähkönen, S., Komssi, S., Wilenius, J., & Ilmoniemi, R. J. (2005). Prefrontal transcranial magnetic stimulation produces intensity-dependent EEG responses in humans. *Neuroimage*, *24*(4), 955-960.

Kähkönen, S., Wilenius, J., Komssi, S., & Ilmoniemi, R. J. (2004). Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation. *Clinical Neurophysiology*, *115*(3), 583-588.

Kalia, M. (2008). Brain development: anatomy, connectivity, adaptive plasticity, and toxicity. *Metabolism*, *57*, S2-S5.

Kamke, M. R., Hall, M. G., Lye, H. F., Sale, M. V., Fenlon, L. R., Carroll, T. J., ... & Mattingley, J. B. (2012). Visual attentional load influences plasticity in the human motor cortex. *Journal of Neuroscience*, *32*(20), 7001-7008.

Kammer, T. (1998). Phosphenes and transient scotomas induced by magnetic stimulation of the occipital lobe: their topographic relationship. Neuropsychologia, 37(2), 191-198.

Kampa, B. M., Letzkus, J. J., & Stuart, G. J. (2007). Dendritic mechanisms controlling spike-timing-dependent synaptic plasticity. *Trends in neurosciences*, *30*(9), 456-463.

Karabanov, A., Ziemann, U., Hamada, M., George, M. S., Quartarone, A., Classen, J., ... & Siebner, H. R. (2015). Consensus paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. *Brain stimulation*, *8*(5), 993-1006.

Kastendieck, T., Zillmer, S., & Hess, U. (2021). (Un) mask yourself! Effects of face masks on facial mimicry and emotion perception during the COVID-19 pandemic. *Cognition and Emotion*, 1-11.

Katz, L. C., & Shatz, C. J. (1996). Synaptic activity and the construction of cortical circuits. *Science*, *274*(5290), 1133-1138.

Khosdelazad, S., Jorna, L. S., McDonald, S., Rakers, S. E., Huitema, R. B., Buunk, A. M., & Spikman, J. M. (2020). Comparing static and dynamic emotion recognition tests: Performance of healthy participants. *Plos one*, *15*(10), e0241297.

Kim, J. H., Lee, J. M., Jo, H. J., Kim, S. H., Lee, J. H., Kim, S. T., ... & Saad, Z. S. (2010). Defining functional SMA and pre-SMA subregions in human MFC using resting state fMRI: functional connectivity-based parcellation method. *Neuroimage*, *49*(3), 2375-2386.

Kim, S. J., Udupa, K., Ni, Z., Moro, E., Gunraj, C., Mazzella, F., ... & Chen, R. (2015). Effects of subthalamic nucleus stimulation on motor cortex plasticity in Parkinson disease. *Neurology*, *85*(5), 425-432.

Kleim, J. A., Barbay, S., Cooper, N. R., Hogg, T. M., Reidel, C. N., Remple, M. S., & Nudo, R. J. (2002). Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiology of learning and memory*, *77*(1), 63-77.

Koch, G., Ponzo, V., Di Lorenzo, F., Caltagirone, C., & Veniero, D. (2013). Hebbian and anti-Hebbian spike-timing-dependent plasticity of human cortico-cortical connections. *Journal of Neuroscience*, *33*(23), 9725-9733.

Koganemaru, S., Mima, T., Nakatsuka, M., Ueki, Y., Fukuyama, H., & Domen, K. (2009). Human motor associative plasticity induced by paired bihemispheric stimulation. *The Journal of physiology*, *587*(19), 4629-4644.

Kohl, S., Hannah, R., Rocchi, L., Nord, C. L., Rothwell, J., & Voon, V. (2019). Cortical paired associative stimulation influences response inhibition: cortico-cortical and cortico-subcortical networks. *Biological psychiatry*, *85*(4), 355-363.

Koivisto, M., Mäntylä, T., & Silvanto, J. (2010). The role of early visual cortex (V1/V2) in conscious and unconscious visual perception. *Neuroimage*, *51*(2), 828-834.

Komorita, S. S., & Graham, W. K. (1965). Number of scale points and the reliability of scales. *Educational and Psychological Measurement*, *25*(4), 987-995.

Komssi, S., Aronen, H. J., Huttunen, J., Kesaniemi, M., Soinne, L., Nikouline, V. V., et al. (2002). Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clinical Neurophysiology, *113*(2), 175-184.

Komssi, S., Kahkonen, S., & Ilmoniemi, R. J. (2004). The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation [Article] Human Brain Mapping, *21*(3), 154-164.

Knoblauch, A., Hauser, F., Gewaltig, M. O., Körner, E., & Palm, G. (2012). Does spike-timing-dependent synaptic plasticity couple or decouple neurons firing in synchrony?. *Frontiers in computational neuroscience*, *6*, 55.

Kret, M., & De Gelder, B. (2012). Islamic headdress influences how emotion is recognized from the eyes. *Frontiers in psychology*, *3*, 110.

Kret, M. E., & Fischer, A. H. (2018). Recognition of facial expressions is moderated by Islamic cues. *Cognition and emotion*, *32*(3), 623-631.

Kurtz, M. M., & Richardson, C. L. (2012). Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. *Schizophrenia bulletin*, *38*(5), 1092-1104.

Lage, C., Wiles, K., Shergill, S. S., & Tracy, D. K. (2016). A systematic review of the effects of low-frequency repetitive transcranial magnetic stimulation on cognition. *Journal of Neural Transmission*, *123*(12), 1479-1490.

Lamme, V. A. (2006). Towards a true neural stance on consciousness. Trends in cognitive sciences, 10(11), 494-501.

Lamme, V. A., & Roelfsema, P. R. (2000). The distinct modes of vision offered by feedforward and recurrent processing. *Trends in neurosciences*, *23*(11), 571-579.

Lamme, V. A., Super, H., & Spekreijse, H. (1998). Feedforward, horizontal, and feedback processing in the visual cortex. *Current opinion in neurobiology*, *8*(4), 529-535.

Lang, N., Harms, J., Weyh, T., Lemon, R. N., Paulus, W., Rothwell, J. C., & Siebner, H. R. (2006). Stimulus intensity and coil characteristics influence the efficacy of rTMS to suppress cortical excitability. Clinical neurophysiology, 117(10), 2292-2301.

Lee, S. Y., Kang, J. I., Lee, E., Namkoong, K., & An, S. K. (2011). Differential priming effect for subliminal fear and disgust facial expressions. *Attention, Perception, & Psychophysics*, *73*(2), 473-481.

Leslie, A. M., Friedman, O., & German, T. P. (2004). Core mechanisms in ‘theory of mind’. *Trends in cognitive sciences*, *8*(12), 528-533.

Letzkus, J. J., Kampa, B. M., & Stuart, G. J. (2006). Learning rules for spike timing-dependent plasticity depend on dendritic synapse location. *Journal of Neuroscience*, *26*(41), 10420-10429.

Levy, W. B., & Steward, O. (1983). Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. *Neuroscience*, *8*(4), 791-797.

López-Alonso, V., Cheeran, B., Río-Rodríguez, D., & Fernández-del-Olmo, M. (2014). Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain stimulation*, *7*(3), 372-380.

Lu, M. K., Tsai, C. H., & Ziemann, U. (2012). Cerebellum to motor cortex paired associative stimulation induces bidirectional STDP-like plasticity in human motor cortex. *Frontiers in human neuroscience*, *6*, 260.

Luckhaus, C., Frommann, N., Stroth, S., Brinkmeyer, J., & Wölwer, W. (2013). Training of affect recognition in schizophrenia patients with violent offences: behavioral treatment effects and electrophysiological correlates. *Social neuroscience*, *8*(5), 505-514.

Lundqvist, D., Flykt, A., & Ohman, A. (1998). Karolinska directed emotional faces set (KDEF). *Sweden: Department of Neurosciences, Karolinska Hospital Stockholm*.

Magee, J. C., & Johnston, D. (1997). A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science, 275*(5297), 209-213.

Mancini, G., Ferrari, P. F., & Palagi, E. (2013). In play we trust. Rapid facial mimicry predicts the duration of playful interactions in geladas. *PloS one, 8*(6), e66481.

Maringer, M., Krumhuber, E. G., Fischer, A. H., & Niedenthal, P. M. (2011). Beyond smile dynamics: mimicry and beliefs in judgments of smiles. *Emotion*, *11*(1), 181.

Marini, M., Ansani, A., Paglieri, F., Caruana, F., & Viola, M. (2021). The impact of facemasks on emotion recognition, trust attribution and re-identification. *Scientific Reports*, *11*(1), 1-14.

Markram, H., Gerstner, W., & Sjöström, P. J. (2011). A history of spike-timing-dependent plasticity. *Frontiers in synaptic neuroscience*, *3,* 4.

Markram, H., Gerstner, W., & Sjöström, P. J. (2012). Spike-timing-dependent plasticity: a comprehensive overview. *Frontiers in synaptic neuroscience, 4*, 2.

Markram, H., Lübke, J., Frotscher, M., & Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science*, *275*(5297), 213-215.

Mars, R. B., Klein, M. C., Neubert, F. X., Olivier, E., Buch, E. R., Boorman, E. D., & Rushworth, M. F. (2009). Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. *Journal of Neuroscience*, *29*(21), 6926-6931.

Marsh, P. J., Green, M. J., Russell, T. A., McGuire, J., Harris, A., & Coltheart, M. (2010). Remediation of facial emotion recognition in schizophrenia: Functional predictors, generalizability, and durability. *American Journal of Psychiatric Rehabilitation*, *13*(2), 143-170.

Mars, R. B., Jbabdi, S., Sallet, J., O'Reilly, J. X., Croxson, P. L., Olivier, E., ... & Rushworth, M. F. (2011). Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. *Journal of Neuroscience*, *31*(11), 4087-4100.

Martens, U., Schweinberger, S. R., Kiefer, M., & Burton, A. M. (2006). Masked and unmasked electrophysiological repetition effects of famous faces. *Brain Research*, *1109*(1), 146-157.

Martin, D., & Greer, J. (2011). Getting to know you: From view-dependent to view-invariant repetition priming for unfamiliar faces. *Quarterly Journal of Experimental Psychology*, *64*(2), 217-223.

Masquelier, T., Guyonneau, R., & Thorpe, S. J. (2008). Spike timing dependent plasticity finds the start of repeating patterns in continuous spike trains. *PloS one*, *3*(1), e1377.

Mathiowetz, V., Weber, K., Kashman, N., & Volland, G. (1985). Adult norms for the nine hole peg test of finger dexterity. *The Occupational Therapy Journal of Research*, *5*(1), 24-38.

Mathôt, S., Schreij, D., & Theeuwes, J. (2012). OpenSesame: An open-source, graphical experiment builder for the social sciences. *Behavior research methods*, *44*(2), 314-324.

Matsumoto, D., & Hwang, H. S. (2011). Evidence for training the ability to read microexpressions of emotion. *Motivation and emotion*, *35*(2), 181-191.

Matsumoto, D., & Hwang, H. C. (2018). Microexpressions differentiate truths from lies about future malicious intent. *Frontiers in psychology*, *9*, 2545.

Matsumoto, D., LeRoux, J., Wilson-Cohn, C., Raroque, J., Kooken, K., Ekman, P., ... & Goh, A. (2000). A new test to measure emotion recognition ability: Matsumoto and Ekman's Japanese and Caucasian Brief Affect Recognition Test (JACBART). *Journal of Nonverbal behavior*, *24*(3), 179-209.

Mazarakis, N. K., Cybulska-Klosowicz, A., Grote, H., Pang, T., Van Dellen, A., Kossut, M., ... & Hannan, A. J. (2005). Deficits in experience-dependent cortical plasticity and sensory-discrimination learning in presymptomatic Huntington's disease mice. *Journal of Neuroscience*, *25*(12), 3059-3066.

McCarthy, G., Puce, A., Gore, J. C., & Allison, T. (1997). Face-specific processing in the human fusiform gyrus. *Journal of cognitive neuroscience*, *9*(5), 605-610.

Mehta, U. M., Thirthalli, J., Aneelraj, D., Jadhav, P., Gangadhar, B. N., & Keshavan, M. S. (2014). Mirror neuron dysfunction in schizophrenia and its functional implications: a systematic review. *Schizophrenia research*, *160*(1-3), 9-19.

Merzenich, M. M. (2013). *Soft-wired: How the new science of brain plasticity can change your life*. Parnassus.

Miller, G. A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. *Psychological review*, *63*(2), 81.

Milnerwood, A. J., Cummings, D. M., Dallerac, G. M., Brown, J. Y., Vatsavayai, S. C., Hirst, M. C., ... & Murphy, K. P. (2006). Early development of aberrant synaptic plasticity in a mouse model of Huntington's disease. *Human molecular genetics, 15*(10), 1690-1703.

Miltner, W. H., Braun, C., Arnold, M., Witte, H., & Taub, E. (1999). Coherence of gamma-band EEG activity as a basis for associative learning. *Nature*, *397*(6718), 434-436.

Miniussi, C., & Thut, G. (2010). Combining TMS and EEG offers new prospects in cognitive neuroscience. *Brain topography*, *22*(4), 249.

Minkova, L., Peter, J., Abdulkadir, A., Schumacher, L. V., Kaller, C. P., Nissen, C., ... & Lahr, J. (2019). Determinants of inter-individual variability in corticomotor excitability induced by paired associative stimulation. *Frontiers in neuroscience, 13,* 841.

Momi, D., Neri, F., Coiro, G., Smeralda, C., Veniero, D., Sprugnoli, G., ... & Santarnecchi, E. (2020). Cognitive enhancement via network-targeted cortico-cortical associative brain stimulation. *Cerebral Cortex*, *30*(3), 1516-1527.

Morgante, F., Espay, A. J., Gunraj, C., Lang, A. E., & Chen, R. (2006). Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. *Brain*, *129*(4), 1059-1069.

Morin, E. L., Hadj-Bouziane, F., Stokes, M., Ungerleider, L. G., & Bell, A. H. (2015). Hierarchical encoding of social cues in primate inferior temporal cortex. *Cerebral Cortex*, *25*(9), 3036-3045.

Morris, R. G. M., Davis, S., & Butcher, S. P. (1990). Hippocampal synaptic plasticity and NMDA receptors: a role in information storage?. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *329*(1253), 187-204.

Mothersill, D., & Donohoe, G. (2019). Neural effects of cognitive training in schizophrenia: a systematic review and activation likelihood estimation meta-analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*(8), 688-696.

Müller-Dahlhaus, F., Lücke, C., Lu, M. K., Arai, N., Fuhl, A., Herrmann, E., & Ziemann, U. (2015). Augmenting LTP-like plasticity in human motor cortex by spaced paired associative stimulation. *PloS one*, *10*(6), e0131020.

Müller-Dahlhaus, J. F. M., Orekhov, Y., Liu, Y., & Ziemann, U. (2008). Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. *Experimental brain research*, *187*(3), 467-475.

Müller, J. F. M., Orekhov, Y., Liu, Y., & Ziemann, U. (2007). Homeostatic plasticity in human motor cortex demonstrated by two consecutive sessions of paired associative stimulation. *European Journal of Neuroscience*, *25*(11), 3461-3468.

Murakami, T., Müller-Dahlhaus, F., Lu, M. K., & Ziemann, U. (2012). Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. *The Journal of physiology*, *590*(22), 5765-5781.

Namiki, C., Hirao, K., Yamada, M., Hanakawa, T., Fukuyama, H., Hayashi, T., & Murai, T. (2007). Impaired facial emotion recognition and reduced amygdalar volume in schizophrenia. *Psychiatry Research: Neuroimaging*, *156*(1), 23-32.

Nestor, M. S., Fischer, D., & Arnold, D. (2020). “Masking” our emotions: Botulinum toxin, facial expression, and well-being in the age of COVID-19. *Journal of Cosmetic Dermatology*, *19*(9), 2154-2160.

Neubert, F. X., Mars, R. B., Buch, E. R., Olivier, E., & Rushworth, M. F. (2010). Cortical and subcortical interactions during action reprogramming and their related white matter pathways. *Proceedings of the National Academy of Sciences*, *107*(30), 13240-13245.

Nettekoven, C., Volz, L. J., Kutscha, M., Pool, E. M., Rehme, A. K., Eickhoff, S. B., ... & Grefkes, C. (2014). Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. Journal of Neuroscience, 34(20), 6849-6859.

Ni, Z., Charab, S., Gunraj, C., Nelson, A. J., Udupa, K., Yeh, I. J., & Chen, R. (2011). Transcranial magnetic stimulation in different current directions activates separate cortical circuits. *Journal of Neurophysiology*, *105*(2), 749-756.

Nicolo, P., Ptak, R., & Guggisberg, A. G. (2015). Variability of behavioural responses to transcranial magnetic stimulation: origins and predictors. Neuropsychologia, 74, 137-144.

Niedenthal, P. M., Mermillod, M., Maringer, M., & Hess, U. (2010). The Simulation of Smiles (SIMS) model: Embodied simulation and the meaning of facial expression. *Behavioral and brain sciences*, *33*(6), 417.

Noh, N. A., Fuggetta, G., Manganotti, P., & Fiaschi, A. (2012). Long lasting modulation of cortical oscillations after continuous theta burst transcranial magnetic stimulation. PloS one, 7(4), e35080.

Nord, C. L., Popa, T., Smith, E., Hannah, R., Donamayor, N., Weidacker, K., ... & Voon, V. (2019). The effect of frontoparietal paired associative stimulation on decision-making and working memory. *cortex*, *117*, 266-276.

Nusseck, M., Cunningham, D. W., Wallraven, C., & Bülthoff, H. H. (2008). The contribution of different facial regions to the recognition of conversational expressions. *Journal of vision*, *8*(8), 1-1.

O'Toole, A. J., Roark, D. A., & Abdi, H. (2002). Recognizing moving faces: A psychological and neural synthesis. *Trends in cognitive sciences*, *6*(6), 261-266.

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2007). Face to face: Blocking facial mimicry can selectively impair recognition of emotional expressions. *Social neuroscience*, *2*(3-4), 167-178.

Ohl, F. W., & Scheich, H. (2005). Learning-induced plasticity in animal and human auditory cortex. *Current opinion in neurobiology*, *15*(4), 470-477.

Olesen, P. J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nature neuroscience*, *7*(1), 75-79.

Olesen, P. J., Nagy, Z., Westerberg, H., & Klingberg, T. (2003). Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cognitive Brain Research*, *18*(1), 48-57.

Olszanowski, M., Wróbel, M., & Hess, U. (2019). Mimicking and sharing emotions: a re-examination of the link between facial mimicry and emotional contagion. *Cognition and Emotion*.

Otte, E., Jost, K., Habel, U., & Koch, I. (2011). Exploring cross-task compatibility in perceiving and producing facial expressions using electromyography. *Acta psychologica*, *138*(1), 187-192.

Palagi, E., Celeghin, A., Tamietto, M., Winkielman, P., & Norscia, I. (2020). The neuroethology of spontaneous mimicry and emotional contagion in human and non-human animals. *Neuroscience & Biobehavioral Reviews*, *111*, 149-165.

Park, H. J., & Friston, K. (2013). Structural and functional brain networks: from connections to cognition. *Science*, *342*(6158).

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science*, *292*(5516), 510-512.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience–virtual lesion, chronometry, and functional connectivity. Current opinion in neurobiology, 10(2), 232-237.

Peineau, S., Taghibiglou, C., Bradley, C., Wong, T. P., Liu, L., Lu, J., ... & Collingridge, G. L. (2007). LTP inhibits LTD in the hippocampus via regulation of GSK3β. *Neuron*, *53*(5), 703-717.

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a'low road'to'many roads' of evaluating biological significance. *Nature reviews neuroscience*, *11*(11), 773-782.

Pieters, M. S., Jennekens-Schinkel, A., Schoemaker, H. C., & Cohen, A. F. (1992). Self-selection for personality variables among healthy volunteers. *British journal of clinical pharmacology*, *33*(1), 101-106.

Pinkham, A. E., & Penn, D. L. (2006). Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. *Psychiatry research*, *143*(2-3), 167-178.

Pitcher, D. (2014). Facial expression recognition takes longer in the posterior superior temporal sulcus than in the occipital face area. *Journal of Neuroscience*, *34*(27), 9173-9177.

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *Journal of Neuroscience*, *28*(36), 8929-8933.

Pitcher, D., Goldhaber, T., Duchaine, B., Walsh, V., & Kanwisher, N. (2012). Two critical and functionally distinct stages of face and body perception. *Journal of Neuroscience*, *32*(45), 15877-15885.

Pitcher, D., Ianni, G., & Ungerleider, L. G. (2019). A functional dissociation of face-, body-and scene-selective brain areas based on their response to moving and static stimuli. *Scientific reports*, *9*(1), 1-9.

Pitcher, D., Japee, S., Rauth, L., & Ungerleider, L. G. (2017). The superior temporal sulcus is causally connected to the amygdala: a combined TBS-fMRI study. Journal of Neuroscience, 37(5), 1156-1161.

Pitcher, D., Parkin, B., & Walsh, V. (2021). Transcranial magnetic stimulation and the understanding of behavior. *Annual Review of Psychology*, *72*, 97-121.

Pitcher, D., Walsh, V., & Duchaine, B. (2011). The role of the occipital face area in the cortical face perception network. *Experimental brain research*, *209*(4), 481-493.

Player, M. J., Taylor, J. L., Alonzo, A., & Loo, C. K. (2012). Paired associative stimulation increases motor cortex excitability more effectively than theta-burst stimulation. *Clinical Neurophysiology*, *123*(11), 2220-2226.

Polley, D. B., Steinberg, E. E., & Merzenich, M. M. (2006). Perceptual learning directs auditory cortical map reorganization through top-down influences. *Journal of neuroscience*, *26*(18), 4970-4982.

Ponari, M., Conson, M., D'Amico, N. P., Grossi, D., & Trojano, L. (2012). Mapping correspondence between facial mimicry and emotion recognition in healthy subjects. *Emotion*, *12*(6), 1398.

Pötter-Nerger, M., Fischer, S., Mastroeni, C., Groppa, S., Deuschl, G., Volkmann, J., ... & Siebner, H. R. (2009). Inducing homeostatic-like plasticity in human motor cortex through converging corticocortical inputs. *Journal of neurophysiology*, *102*(6), 3180-3190.

Prado, J., Van Der Henst, J. B., & Noveck, I. A. (2010). Recomposing a fragmented literature: How conditional and relational arguments engage different neural systems for deductive reasoning.
Neuroimage, *51*(3), 1213-1221.

Prochazkova, E., & Kret, M. E. (2017). Connecting minds and sharing emotions through mimicry: A neurocognitive model of emotional contagion. *Neuroscience & Biobehavioral Reviews*, *80*, 99-114.

Ray, P. G., Meador, K. J., Epstein, C. M., Loring, D. W., & Day, L. J. (1998). Magnetic stimulation of visual cortex: factors influencing the perception of phosphenes. *Journal of Clinical Neurophysiology*, *15*(4), 351-357.

Ridding, M. C., & Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *The Journal of physiology*, *588*(13), 2291-2304.

Ribolsi, M., Lisi, G., Ponzo, V., Siracusano, A., Caltagirone, C., Niolu, C., & Koch, G. (2017). Left hemispheric breakdown of LTP-like cortico-cortical plasticity in schizophrenic patients. *Clinical Neurophysiology*, *128*(10), 2037-2042.

Rioult-Pedotti, M. S., Friedman, D., & Donoghue, J. P. (2000). Learning-induced LTP in neocortex. *Science*, *290*(5491), 533-536.

Rioult-Pedotti, M. S., Friedman, D., Hess, G., & Donoghue, J. P. (1998). Strengthening of horizontal cortical connections following skill learning. *Nature neuroscience*, *1*(3), 230-234.

Rizzo, V., Siebner, H. S., Morgante, F., Mastroeni, C., Girlanda, P., & Quartarone, A. (2009). Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a Hebbian mechanism. *Cerebral cortex*, *19*(4), 907-915.

Robertson, I. H., & Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. Psychological bulletin, 125(5), 544.

Robinson, G. B. (1986). Enhanced long-term potentiation induced in rat dentate gyrus by coactivation of septal and entorhinal inputs: temporal constraints. *Brain research*, *379*(1), 56-62.

Rogasch, N. C., & Fitzgerald, P. B. (2013). Assessing cortical network properties using TMS–EEG. *Human brain mapping*, *34*(7), 1652-1669.

Rolston, J. D., Wagenaar, D. A., & Potter, S. M. (2007). Precisely timed spatiotemporal patterns of neural activity in dissociated cortical cultures. *Neuroscience*, *148*(1), 294-303.

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., & Thut, G. (2008a). Spontaneous fluctuations in posterior α-band EEG activity reflect variability in excitability of human visual areas. *Cerebral cortex*, *18*(9), 2010-2018.

Romei, V., Chiappini, E., Hibbard, P. B., & Avenanti, A. (2016a). Empowering reentrant projections from V5 to V1 boosts sensitivity to motion. *Current Biology*, *26*(16), 2155-2160.

Romei, V., Rihs, T., Brodbeck, V., & Thut, G. (2008b). Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. *Neuroreport*, *19*(2), 203-208.

Romei, V., Thut, G., & Silvanto, J. (2016b). Information-based approaches of noninvasive transcranial brain stimulation. *Trends in Neurosciences*, *39*(11), 782-795.

Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., & Massimini, M. (2009). Natural frequencies of human corticothalamic circuits. *Journal of Neuroscience*, *29*(24), 7679-7685.

Rosenkranz, K., & Rothwell, J. C. (2006). Differences between the effects of three plasticity inducing protocols on the organization of the human motor cortex. *European Journal of Neuroscience*, *23*(3), 822-829.

Rotshtein, P., Henson, R. N., Treves, A., Driver, J., & Dolan, R. J. (2005). Morphing Marilyn into Maggie dissociates physical and identity face representations in the brain. *Nature neuroscience*, *8*(1), 107-113.

Russo-Ponsaran, N. M., Evans-Smith, B., Johnson, J., Russo, J., & McKown, C. (2016). Efficacy of a facial emotion training program for children and adolescents with autism spectrum disorders. *Journal of Nonverbal Behavior*, *40*(1), 13-38.

Rychlowska, M., Cañadas, E., Wood, A., Krumhuber, E. G., Fischer, A., & Niedenthal, P. M. (2014). Blocking mimicry makes true and false smiles look the same. *PLoS One*, *9*(3), e90876.

Sale, M. V., Ridding, M. C., & Nordstrom, M. A. (2007). Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation. *Experimental brain research*, *181*(4), 615-626.

Sanchez-Vives, M. V., Nowak, L. G., & McCormick, D. A. (2000). Cellular mechanisms of long-lasting adaptation in visual cortical neurons in vitro. *Journal of Neuroscience*, *20*(11), 4286-4299.

Santarnecchi, E., Momi, D., Sprugnoli, G., Neri, F., Pascual-Leone, A., Rossi, A., & Rossi, S. (2018). Modulation of network-to-network connectivity via spike-timing-dependent noninvasive brain stimulation. *Human brain mapping*, *39*(12), 4870-4883.

Santarnecchi, E., Polizzotto, N. R., Godone, M., Giovannelli, F., Feurra, M., Matzen, L., ... & Rossi, S. (2013). Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials. *Current Biology*, *23*(15), 1449-1453.

Sastry, B. R., Goh, J. W., & Auyeung, A. (1986). Associative induction of posttetanic and long-term potentiation in CA1 neurons of rat hippocampus. *Science*, *232*(4753), 988-990.

Sato, W., & Aoki, S. (2006). Right hemispheric dominance in processing of unconscious negative emotion. *Brain and cognition*, *62*(3), 261-266.

Sauseng, P., Klimesch, W., Schabus, M., & Doppelmayr, M. (2005). Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *International journal of Psychophysiology*, *57*(2), 97-103.

Schurgin, M. W., Nelson, J., Iida, S., Ohira, H., Chiao, J. Y., & Franconeri, S. L. (2014). Eye movements during emotion recognition in faces. *Journal of vision*, *14*(13), 14-14.

Schwartz, B. L., Mastropaolo, J., Rosse, R. B., Mathis, G., & Deutsch, S. I. (2006). Imitation of facial expressions in schizophrenia. *Psychiatry Research*, *145*(2-3), 87-94.

Schmidtmann, G., Logan, A. J., Carbon, C. C., Loong, J. T., & Gold, I. (2020). In the blink of an eye: Reading mental states from briefly presented eye regions. *i-Perception*, *11*(5), 2041669520961116.

Schultz, J., & Pilz, K. S. (2009). Natural facial motion enhances cortical responses to faces. *Experimental brain research*, *194*(3), 465-475.

Sejnowski, T. J. (1999). The book of Hebb. *Neuron*, *24*(4), 773-776.

Sel, A., Verhagen, L., Angerer, K., David, R., Klein-Flügge, M. C., & Rushworth, M. F. (2021). Increasing and decreasing interregional brain coupling increases and decreases oscillatory activity in the human brain. *Proceedings of the National Academy of Sciences*, *118*(37).

Serino, A., Canzoneri, E., & Avenanti, A. (2011). Fronto-parietal areas necessary for a multisensory representation of peripersonal space in humans: an rTMS study. *Journal of cognitive neuroscience*, *23*(10), 2956-2967.

Shaham, G., Mortillaro, M., & Aviezer, H. (2020). Automatic facial reactions to facial, body, and vocal expressions: A stimulus-response compatibility study. *Psychophysiology*, *57*(12), e13684.

Shamay-Tsoory, S. G. (2011). The neural bases for empathy. *The Neuroscientist*, *17*(1), 18-24.

Silvanto, J. (2015). Why is “blindsight” blind? A new perspective on primary visual cortex, recurrent activity and visual awareness. *Consciousness and cognition*, *32*, 15-32.

Silvanto, J., Lavie, N., & Walsh, V. (2005). Double dissociation of V1 and V5/MT activity in visual awareness. *Cerebral cortex*, *15*(11), 1736-1741.

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in cognitive sciences*, *12*(12), 447-454.

Sjöström, P. J., & Häusser, M. (2006). A cooperative switch determines the sign of synaptic plasticity in distal dendrites of neocortical pyramidal neurons. *Neuron*, *51*(2), 227-238.

Sjöström, P. J., Turrigiano, G. G., & Nelson, S. B. (2001). Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron*, *32*(6), 1149-1164.

Smith, M. L., Cottrell, G. W., Gosselin, F., & Schyns, P. G. (2005). Transmitting and decoding facial expressions. *Psychological science*, *16*(3), 184-189.

Sommer, M., Norden, C., Schmack, L., Rothkegel, H., Lang, N., & Paulus, W. (2013). Opposite optimal current flow directions for induction of neuroplasticity and excitation threshold in the human motor cortex. *Brain stimulation*, *6*(3), 363-370.

Stefan, K., Kunesch, E., Benecke, R., Cohen, L. G., & Classen, J. (2002). Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *The Journal of physiology*, *543*(2), 699-708.

Stefan, K., Wycislo, M., & Classen, J. (2004). Modulation of associative human motor cortical plasticity by attention. *Journal of neurophysiology*, *92*(1), 66-72.

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*, *123*(3), 572-584.

Stefanacci, L., & Amaral, D. G. (2000). Topographic organization of cortical inputs to the lateral nucleus of the macaque monkey amygdala: a retrograde tracing study. *Journal of Comparative Neurology*, *421*(1), 52-79.

Subramaniam, K., Luks, T. L., Fisher, M., Simpson, G. V., Nagarajan, S., & Vinogradov, S. (2012). Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. *Neuron*, *73*(4), 842-853.

Surcinelli, P., Codispoti, M., Montebarocci, O., Rossi, N., & Baldaro, B. (2006). Facial emotion recognition in trait anxiety. *Journal of anxiety disorders*, *20*(1), 110-117.

Stel, M., Van Baaren, R. B., & Vonk, R. (2008). Effects of mimicking: Acting prosocially by being emotionally moved. *European journal of social psychology*, *38*(6), 965-976.

Suppa, A., Quartarone, A., Siebner, H., Chen, R., Di Lazzaro, V., Del Giudice, P., ... & Classen, J. (2017). The associative brain at work: evidence from paired associative stimulation studies in humans. *Clinical Neurophysiology*, *128*(11), 2140-2164.

Sweeny, T. D., Grabowecky, M., Suzuki, S., & Paller, K. A. (2009). Long-lasting effects of subliminal affective priming from facial expressions. *Consciousness and cognition*, *18*(4), 929-938.

Thickbroom, G. W., Byrnes, M. L., Edwards, D. J., & Mastaglia, F. L. (2006). Repetitive paired-pulse TMS at I-wave periodicity markedly increases corticospinal excitability: a new technique for modulating synaptic plasticity. *Clinical neurophysiology*, *117*(1), 61-66.

Thomas, L. A., De Bellis, M. D., Graham, R., & LaBar, K. S. (2007). Development of emotional facial recognition in late childhood and adolescence. *Developmental science*, *10*(5), 547-558.

Tiffin, J., & Asher, E. J. (1948). The Purdue Pegboard: norms and studies of reliability and validity. *Journal of applied psychology*, *32*(3), 234.

Tong, G., Malenka, R. C., & Nicoll, R. A. (1996). Long-term potentiation in cultures of single hippocampal granule cells: a presynaptic form of plasticity. *Neuron*, *16*(6), 1147-1157.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., ... & Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry research*, *168*(3), 242-249.

Tramacere, A., & Ferrari, P. F. (2016). Faces in the mirror, from the neuroscience of mimicry to the emergence of mentalizing. *Journal of Anthropological Sciences*, *94*(1-14).

Tübing, J., Gigla, B., Brandt, V. C., Verrel, J., Weissbach, A., Beste, C., ... & Bäumer, T. (2018). Associative plasticity in supplementary motor area-motor cortex pathways in Tourette syndrome. *Scientific reports*, *8*(1), 1-8.

Urgesi, C., Calvo-Merino, B., Haggard, P., & Aglioti, S. M. (2007a). Transcranial magnetic stimulation reveals two cortical pathways for visual body processing. *Journal of Neuroscience*, *27*(30), 8023-8030.

Urgesi, C., Candidi, M., Ionta, S., & Aglioti, S. M. (2007b). Representation of body identity and body actions in extrastriate body area and ventral premotor cortex. *Nature neuroscience*, *10*(1), 30-31.

Vallence, A. M., & Ridding, M. C. (2014). Non-invasive induction of plasticity in the human cortex: uses and limitations. *Cortex*, *58*, 261-271.

Van Honk, J., Schutter, D. J., d'Alfonso, A. A., Kessels, R. P., & de Haan, E. H. (2002). 1 hz rTMS over the right prefrontal cortex reduces vigilant attention to unmasked but not to masked fearful faces. *Biological psychiatry*, *52*(4), 312-317.

Vaportzis, E., Giatsi Clausen, M., & Gow, A. J. (2017). Older adults perceptions of technology and barriers to interacting with tablet computers: a focus group study. *Frontiers in psychology*, *8*, 1687.

Varela, F., Lachaux, J. P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nature reviews neuroscience*, *2*(4), 229-239.

Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. *Human brain mapping*, *30*(3), 829-858.

Veniero, D., Ponzo, V., & Koch, G. (2013). Paired associative stimulation enforces the communication between interconnected areas. *Journal of Neuroscience, 33*(34), 13773-13783.

Vetter, P., Grosbras, M. H., & Muckli, L. (2015). TMS over V5 disrupts motion prediction. *Cerebral cortex*, *25*(4), 1052-1059.

Vitale, J., Williams, M. A., Johnston, B., & Boccignone, G. (2014). Affective facial expression processing via simulation: A probabilistic model. *Biologically Inspired Cognitive Architectures*, *10,* 30-41.

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia, 45*(1), 174-194.

Walsh, V., Ellison, A., Battelli, L., & Cowey, A. (1998). Task–specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *265*(1395), 537-543.

Walsh, V., & Pascual-Leone, A. (2003). *Transcranial magnetic stimulation: a neurochronometrics of mind*. MIT press.

Wan, C. Y., & Schlaug, G. (2010). Music making as a tool for promoting brain plasticity across the life span. *The Neuroscientist*, *16*(5), 566-577.

Wang, K., Liang, M., Wang, L., Tian, L., Zhang, X., Li, K., & Jiang, T. (2007). Altered functional connectivity in early Alzheimer's disease: A resting-state fMRI study. *Human brain mapping*, *28*(10), 967-978.

Wang, J. X., Rogers, L. M., Gross, E. Z., Ryals, A. J., Dokucu, M. E., Brandstatt, K. L., ... & Voss, J. L. (2014). Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science*, *345*(6200), 1054-1057.

Warren, G., Schertler, E., & Bull, P. (2009). Detecting deception from emotional and unemotional cues. *Journal of Nonverbal Behavior, 33*(1), 59-69.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(1), 1-16.

Wegrzyn, M., Vogt, M., Kireclioglu, B., Schneider, J., & Kissler, J. (2017). Mapping the emotional face. How individual face parts contribute to successful emotion recognition. *PloS one*, *12*(5), e0177239.

Winston, J. S., Henson, R. N. A., Fine-Goulden, M. R., & Dolan, R. J. (2004). fMRI-adaptation reveals dissociable neural representations of identity and expression in face perception. *Journal of neurophysiology*, *92*(3), 1830-1839.

Wolters, A., Sandbrink, F., Schlottmann, A., Kunesch, E., Stefan, K., Cohen, L. G., ... & Classen, J. (2003). A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *Journal of neurophysiology*, *89*(5), 2339-2345.

Wolters, A., Schmidt, A., Schramm, A., Zeller, D., Naumann, M., Kunesch, E., ... & Classen, J. (2005). Timing-dependent plasticity in human primary somatosensory cortex. *The Journal of physiology*, *565*(3), 1039-1052.

Wood, A., Rychlowska, M., Korb, S., & Niedenthal, P. (2016). Fashioning the face: sensorimotor simulation contributes to facial expression recognition. *Trends in cognitive sciences*, *20*(3), 227-240.

Wyatte, D., Jilk, D. J., & O'Reilly, R. C. (2014). Early recurrent feedback facilitates visual object recognition under challenging conditions. *Frontiers in psychology*, *5*, 674.

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry*, *168*(5), 472-485.

Yang, J., Xu, X., Du, X., Shi, C., & Fang, F. (2011). Effects of unconscious processing on implicit memory for fearful faces. *PloS one*, *6*(2), e14641.

Xerri, C. (2012). Plasticity of cortical maps: multiple triggers for adaptive reorganization following brain damage and spinal cord injury. *The Neuroscientist*, *18*(2), 133-148.

Zhou, Q., & Poo, M. M. (2004). Reversal and consolidation of activity-induced synaptic modifications. *Trends in neurosciences*, *27*(7), 378-383.

Zibman, S., Daniel, E., Alyagon, U., Etkin, A., & Zangen, A. (2019). Interhemispheric cortico-cortical paired associative stimulation of the prefrontal cortex jointly modulates frontal asymmetry and emotional reactivity. *Brain stimulation*, *12*(1), 139-147.

Ziemann, U., Iliać, T. V., Pauli, C., Meintzschel, F., & Ruge, D. (2004). Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *Journal of Neuroscience*, *24*(7), 1666-1672.