Facemasks and face recognition: Potential impact on synaptic plasticity

Chiara Ferrari\textsuperscript{a,b}, Tomaso Vecchi\textsuperscript{a,b}, Giuseppe Sciamanna\textsuperscript{c}, Fabio Blandini\textsuperscript{a,b}, Antonio Pisani\textsuperscript{a,b,*}, Silvia Natoli\textsuperscript{d}

\textsuperscript{a} Department of Brain and Behavioral Sciences, University of Pavia, Italy
\textsuperscript{b} IRCCS Mondino Foundation, Pavia, Italy
\textsuperscript{c} IRCCS Santa Lucia Foundation, Rome, Italy
\textsuperscript{d} Department of Clinical Science and Translational Medicine, University of Rome Tor Vergata, Rome, Italy

1. Introduction

The novel Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) is responsible for the ongoing COVID-19 pandemic, with nearly 95 million confirmed cases and over two million deaths, as of January 19, 2021, https://covid19.who.int/. Although the lungs remain the main target of SARS-CoV-2, COVID-19 can involve virtually all body organs including the brain, with resulting neurological and psychiatric complications whose pathogenesis is still elusive (Moro et al., 2020; Qiu et al., 2020; Wang et al., 2020). Indeed, contrary to DNA viruses such as the JC virus, which persist in the human nervous system and whose neurotropism is established, the potential of the SARS-CoV-2 RNA virus to invade the human brain is still debated (for rev. see Natoli et al., 2020). Massive inflammatory reaction with activated microglia and infiltration by CD8\textsuperscript{+} T lymphocytes, mainly involving the brainstem, has been reported, without clear signs of encephalitis or parenchymal destruction (Matschke et al., 2020). However, both viral RNA and proteins were detected in brain specimens, confirming the neurotropism of SARS-CoV-2, although this was not associated to the severity of the clinical phenotype (Matschke et al., 2020). More recently, olfactory transmucosal SARS-CoV-2 invasion of the brain has been demonstrated in COVID-19 patients (Meinhardt et al., 2021). The potentially long-term impact determined either by the viral invasion or by the neuroimmune response remains to be established (for revs. Perlman and Dandekar, 2005; Bergmann et al., 2006), but a number of post-COVID-19 conditions have already been described, in a middle- to long-term follow-up, including depression, psychosis, obsessive-compulsive disorders (Qiu et al., 2020; Wang et al., 2020).

The impact of COVID-19 on higher brain functions may expand beyond the direct consequences of brain invasion by SARS-CoV-2. The ongoing pandemics is causing a pervasive social distress and behavioral effects (Cerami et al., 2020; Galandra et al., 2020) that are further enhanced by two major defensive measures adopted by national and international institutions, i.e. social distancing and wearing of facemasks. In particular, facemasks represent an evident obstacle to recognizing other people by their facial appearance, with possible consequences for establishing and maintaining effective interpersonal social interactions. Indeed, faces convey multiple cues that govern our social interactions. Indeed, faces convey multiple cues that govern our social interactions. Compelling experimental evidence indicates that face conveys plenty of information that are fundamental for humans to interact. These are encoded at neural level in specific cortical and subcortical brain regions through activity- and experience-dependent synaptic plasticity processes. The current pandemic, due to the spread of SARS-CoV-2 infection, is causing relevant social and psychological detrimental effects. The institutional recommendations on physical distancing, namely social distancing and wearing of facemasks are effective in reducing the rate of viral spread. However, by impacting social interaction, facemasks might impair the neural responses to recognition of facial cues that are overall critical to our behaviors.

In this survey, we briefly review the current knowledge on the neurobiological substrate of facial recognition and discuss how the lack of salient stimuli might impact the ability to retain and consolidate learning and memory phenomena underlying face recognition. Such an “abnormal” visual experience raises the intriguing possibility of a “reset” mechanism, a renewed ability of adult brain to undergo synaptic plasticity adaptations.
social behavior and are critical for human interactions. When a person wears a facemask, the amount of social information that an observer can use to successfully interact with that person is dramatically reduced. From the cognitive perspective (for reviews see, Rossion, 2014; Rapcsak, 2019), face recognition consists of a first stage of visual analysis of facial features, a process that relies on the integration of multiple face parts into a unified perceptual representation. This fine-grade visual processing allows discrimination among (also similar) faces. Then, the memory representation of the previously encountered (or familiar) face is activated and matched with the face perception. A recent study demonstrates that facemasks have a large detrimental effect on human face matching performance (Carragher and Hancock, 2020). Specifically, participants were presented with pairs of faces with facemask (one or both faces of the pair could wear a facemask) or without facemask (control condition) and indicated whether the faces showed the same person or two different people (identity matching task). Their findings show that compared to the control condition, the ability to process face identity was impaired when at least one face of the pair wore the facemask. Using a different paradigm (the Cambridge Face Memory Test), Freud et al. (2020) further corroborate these findings by showing a similar decrease in the ability of processing faces wearing the facemask compared to control stimuli. Furthermore, this study showed that holistic processing, the perceptual hallmark of face perception, is largely reduced with masked faces, suggesting that the processing of unmasked and masked faces might rely on qualitatively different perceptual mechanisms. We hypothesize that such impairment relies on changes at the physiological level linked to basic, synaptic plasticity phenomena.

Here, we briefly analyze the neuroanatomical and neurophysiological underpinnings of face recognition. We specifically discuss the possible effects of facemasks on the physiological processes underlying the recognition of other faces, with a particular emphasis on synaptic plasticity mechanisms. We further consider a particular case of facial recognition that is the recognition of others’ facial emotional expressions. We explore the possibility that facemasks affect the emotion recognition from faces at the cognitive and neural level with consequences on empathic responses and social behaviors.

### 2. Neural basis of face recognition

It is certainly beyond the scope of this brief survey to discuss each aspect of a complex issue such as the neurophysiology of face recognition, for which we refer the reader to other specific and exhaustive reviews (Behrmann et al., 2016; Grill-Spector et al., 2017; Visconti di Oleggio Castello et al., 2017). This section aims to provide a general framework to interpret the core hypothesis of the present paper.

Face recognition undoubtedly relies upon the perception of visual stimuli, but the process is intriguingly more complex than the simple visual recognition of an object. By viewing a face, one gathers information about a person’s identity, as well as gender, age, mental and emotional states. Identity, gender, and age are data that can be extracted from the analysis of invariant face features (e.g., the shape of the eyes). In turn, others’ emotions and intentions can be inferred using qualitatively different face cues, such as changeable face features (e.g., facial expressions) (Haxby et al., 2000). Thus, it is intuitive that facial perception activates a neural network, which is dynamic and widely distributed across brain areas. Of note, face-selective activations of brain areas involved in facial processing occur within 200 ms after stimuli (for rev., see Yovel, 2016). Studies using high temporal resolution demonstrated that the first brain area to be activated in perception of facial features resides in the inferior occipital gyrus and is called OFA (Occipital Face Area, Pitcher et al., 2011). This region is involved in the discrimination of faces differing by single components, such as the shape of the eyes or the mouth (Fig. 1) (Pitcher et al., 2011). From OFA, information is transferred to the posterior Superior Temporal Sulcus (pSTS) and to the lateral fusiform gyrus (Fusiform Face Area = FFA), both located in the temporal cortex. Connections between the OFA and FFA, and pSTS represent a Core System of processing the visual appearance of faces. The pSTS is involved in the perception of facial features that are changed by movements such as gaze, emotional expressions and speech-related facial movements. Indeed, delivering transcranial magnetic stimulation (TMS) over pSTS affects the ability to discriminate facial emotional expressions (Pitcher, 2014; Sliwinska and Pitcher, 2018) and judge face expressiveness (Ferrari et al., 2018a, 2018b). In turn, FFA is dedicated to detect invariant aspects of faces that drive unique identity perception (Haxby et al., 2000). Nevertheless, the distinction between areas is not univocal. Indeed both, FFA and pSTS show adaptation to repeated identity in fMRI studies (Winston et al., 2020).
interaction with people wearing facemasks changes the way we recognize facial emotion recognition, either from a biological or a psychological point of view, and in particular prosocial behavior (Christov-Moore and Iacoboni, 2016). Thus, interacting with people that wear a facemask might reduce to some extent empathic responses to specific emotional states of others, possibly influencing our motivation to (prosocially) behave towards them. Still, the link between mask-related difficulties in emotion recognition and the quality of the social interactions has never been systematically investigated, and therefore this hypothesis remains on the speculative level.

4. Synaptic plasticity and maladaptive rearrangements

During memory acquisition, activity-dependent changes in synaptic efficacy occur between neurons. The pioneering assumption that “neurons that fire together wire together” recapitulates Hebb’s fundamental intuition (Hebb, 1949), indicating that synaptic strengthening occurs only if both pre- and postsynaptic sites are simultaneously activated. The first report of a long-term potentiation (LTP) of synaptic transmission at hippocampal synapses (Bliss and Lomo, 1973) was then followed by multiple observations of similar changes in synaptic strength in different brain regions (Ito, 1989; Lynch and Baudry, 1984; Kuba and Kumamoto, 1990; Madison et al., 1991). It is now widely accepted that sustained changes of synaptic efficacy, through LTP and LTD processes, may indeed represent the fundamental mechanism for the acquisition and consolidation of memory engrams. Depending on the experimental protocol and on the intrinsic properties of the neural subtypes involved, a high-frequency stimulation protocol of an excitatory afferent pathway produces either a long-lasting increase or an enduring decrease of synaptic efficacy, LTP, or LTD, respectively. Synapses also retain the ability to return to a resting state following low-frequency stimulation, a phenomenon termed synaptic depotentiation, which is believed to represent the physiological mechanism through which unnecessary information are eliminated (Chen et al., 2001). Besides frequency stimulation, timing of pre- and postsynaptic firing is another critical factor, delineating “spike-timing-dependent plasticity” (STDP) (Markram et al., 1997). Of note, the modulation of gene expression and protein synthesis during plasticity induction are well-known mechanisms underlying the formation of new and elimination of old synapses, therefore leading to structural plasticity adaptations (Holtmaat and Svoboda, 2009).

Both experimental and clinical neurophysiology studies demonstrate maladaptive shifts of synaptic plasticity as a fundamental pathophysiological event in multiple neurological and psychiatric disorders, including neurodegenerative diseases (Calabresi et al., 2016; Skaper et al., 2017), ischemia (Calabresi et al., 2009), pain (Woolf and Salter, 2000), schizophrenia (Crabtree and Gogos, 2014), addiction (Kauer and Malenka, 2007), as well as neurodevelopmental disorders, such as autism (Golarai et al., 2006; Gilbert and Man, 2017; Trobiani et al., 2020). Similarly, exposure to persistent psychophysical stress is also able to induce, to different extent and magnitude, structural and functional plasticity modifications. Morphological, electrophysiological,
pharmacological and behavioral studies enabled a detailed analysis of the effect of stressful stimuli on plasticity, revealing distinct patterns of alterations in the hippocampus, amygdala and medial prefrontal cortex (Popoli et al., 2011).

Face recognition can be considered one of the most refined visual perceptual abilities. As such, this process relies on the complex, concerted activity of multiple cortical and subcortical regions (as described above, Fig. 1). LTP and LTD are the natural candidates for the cellular and molecular mechanisms of these activity-dependent memory processes, which have been extensively characterized independently in multiple regions, including hippocampus, visual cortex, but also in the amygdala involved in the behavioral/emotional component.

Thus, it appears objectively difficult to connect these multiple levels of description at cellular and behavioral/system level. On the other hand, it is meaningful to assume that a number of conditions that impair the experience-dependent process of face recognition will be mirrored, at cellular level, by changes in synaptic strength. An exemplificative case is represented by synaptic plasticity in the visual cortex. Indeed, Hebb identified the primary visual cortex (V1) as the ideal region to represent his theory on long-term plasticity (Hebb, 1949).

In visual cortex, distinct forms of plasticity have been described including LTP, LTD, STDP, whose appearance depends on both the developmental stage and the network recruited (excitatory neurons or inhibitory interneurons), as well as on the ionotropic glutamate receptors involved (Artola and Singer, 1987; Bear et al., 1992; Kirkwood et al., 1995). These plastic changes were demonstrated in vitro and then confirmed in vivo, supporting their functional relevance (see Hofer et al., 2006; Karmarkar and Dan, 2006; Cooke and Bear, 2013). Of interest, long-lasting changes of visual responses evoked by paradigms utilized to elicit in vitro LTP/LTD, have also been demonstrated in humans (Teyler et al., 2005; Beste et al., 2011).

Experimental protocols causing deprivation of sensory visual inputs, such as light deprivation, retinal damage or eyelid suture, have been shown to induce dramatic shifts in plasticity, either by silencing the corresponding cortical receptive areas, or subsequently expanding towards nearby visual receptive fields (Darian-Smith and Gilbert, 1995; Karmarkar and Dan, 2006; Cooke and Bear, 2013). Pioneering work on non-human primates allowed unravel the basis of binocular vision and the plastic consequences of visual deprivation on the architecture and function of visual cortex (Hubel and Wiesel, 1977). Similarly, the first evidence of segregation of face-responsive areas derives from single-unit recordings in the macaque cortex, showing a different location of neurons tuned to variations in face identity compared to those activated by variations in face expression (Hasselmo et al., 1989).

In vitro, visual deprivation from birth either as “dark exposure” or “dark rearing” amplified NMDA-dependent LTP in visual cortex (Kirkwood et al., 1996; Guo et al., 2012). Mechanistically, induction of LTP and LTD depends on calcium entry via postsynaptic NMDA receptors, whereas their expression relies on the long-lasting, clathrin-dependent, insertion or removal, respectively, of AMPA receptors at the post-synaptic membrane (Huganir and Nicoll, 2013). Yet, changes in NMDA receptor subunit composition exert a crucial role in shaping the direction of synaptic plasticity. Visual input deprivation was shown to modify, in a relatively short time period, the NR2A/NR2B ratio, with down-regulation of the NR2A subunit favoring the induction of LTP over LTD. This is consistent with the evidence that a prevalence of the NR2B subunit prolongs the duration of synaptic currents, causing a higher intracellular calcium rise. Contrarily, an increase in NR2A subunit over NR2B, by shortening the duration of NMDA currents promoted LTD instead of LTP (Quinlan et al., 1999), further demonstrating the dynamic and bidirectional nature of experience-dependent plasticity. Coherently with the direction of long-term synaptic modifications, the different amount of intracellular calcium elevation is also expected to activate distinct calcium-dependent kinases and phosphatases. In particular, NR2B-containing NMDA receptors interact with calcium-calmodulin kinase (CaMKII) in promoting LTP, whereas the lower rise in postsynaptic calcium through NR2A-containing NMDA receptors would preferentially activate the calcineurin pathway, for LTD induction (Yashiro and Philpot, 2008; Cooke and Bear, 2013). Additional signalling pathways, downstream the activation of enzymes and other transcriptional regulators, including Erk kinase, CREB response element binding protein (CREB) and changes in gene expression, contribute to the shifts in plasticity. Lastly, in layer 5 of visual cortex, LTD involves also endocannabinoid signalling and presynaptic NR2B-containing NMDA receptors (Hofer et al., 2006; Massey and Bashir, 2007).

It should be acknowledged that we provided a brief summary of the main molecular mechanisms underlying visual cortical plasticity, and we refer to other comprehensive reviews for further readings (Hofer et al., 2006; Yashiro and Philpot, 2008; Cooke and Bear, 2013).

Alterations in cortical plasticity have been proposed also for prosopagnosia, a neurological deficit consisting in the inability to recognize
faces, often caused by acute lesions involving the occipitotemporal cortex (Hecaen and Angelergues, 1962). However, prosopagnosia can occur also in other pathological conditions such as developmental disorders, in the absence of overt structural lesions, but caused by an altered connectivity (Zhao et al., 2018; Cohen et al., 2019). In these conditions, the idea of an underlying loss of synaptic connection among the different nodes at circuit level has been proposed, consistent with our hypothesis that partial deprivation of visual inputs caused by wearing facemasks, might ultimately modify plasticity in the face core neural system (Fig. 2). Reminiscent of input deprivation, it is likely that such changes may occur at cellular level, in turn leading cortical neurons to express a shift in plasticity towards an enhanced, adaptive form of LTP (Fig 2), which is known to depend on NR2B-containing NMDA receptor activation and on calcium-dependent post-receptor mechanisms, primarily involving CaMKII (Bear et al., 1992; Cooke & Bear, 2013; Kirkwood et al., 1995; Quinlan et al., 1999).

5. Perspectives and conclusions

Our considerations, as well as their implications, remain speculative, and future studies involving large cohorts of subjects are mandatory to confirm these hypotheses and eventually identify the neural substrates for such changes. However, in line with recent evidence suggesting that facemasks dramatically affect people’s ability to recognize others’ identity and emotional states (Carbon, 2020; Carragher and Hancock, 2020; Freud et al., 2020), we hypothesize that the persistent and long-term use of facemasks will alter experience-dependent synaptic plasticity on which facial identity and emotions recognition ability rely. These cellular-based modifications may be critical and lead to detrimental effects in the first years of life when the ability to recognize faces develops (Nelson, 1987) and in clinical populations affected by social and emotional impairment. For instance, autistic individuals show abnormal activity in the face core neural system (and the amygdala) associated with abnormal (neutral and emotional) face processing, in particular, of the eye region (Golarai et al., 2006). Therefore, for autistic individuals dealing with people wearing a facemask that leaves the eye regions as the only source of information might further complicate already difficult interactions. As a consequence, as long as the COVID-19 pandemic requires it, we encourage the adoption of transparent facemask that may be particularly suitable to prevent such possible alterations in face perception. Moreover, emphasizing alternative communicative channels in social communication (i.e., the body and the voice), sufficient information might be provided for effective social interactions.

Declaration of Competing Interest

None.

Acknowledgements

This research was supported by funding from the Italian Ministry of Research (PRIN 2017 no Visconti di Oleggio Castello, 20175SKFE) to TV, from the Italian Ministry of Health (Mondino Ricerca Corrente 2020) to CF, TV and AP and from the Regional Directorate for Economic Development and Productive Activities of Lazio (POR FESR Lazio 2014-2020, Det. N G0100061, 3.8.18) to SN. The work has not received any specific support from funding agencies in the commercial sector.

References

Artola, A., Singer, W., 1987. Long-term potentiation and NMDA receptors in rat visual cortex. Nature. 330 (6149), 649–652. https://doi.org/10.1038/330649a0.

Atkinson, A.P., Adolphs, R., 2011. The neuropsychology of face perception: beyond simple dissociations and functional selectivity. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 366 (1571), 1726–1736. https://doi.org/10.1098/rstb.2010.0349.
Grill-Spector, K., Weiner, K.S., Kay, K., et al., 2017. The functional Neuroanatomy of human face perception. Annu. Rev. Vis. Sci. 3, 167–196. https://doi.org/10.1146/annurev-vision-062416-010109.
Guo, Y., Huang, S., de Pasquale, R., et al., 2012. Dark exposure extends the integration window for spike-timing dependent plasticity. J. Neurosci. 32, 15027–15035. https://doi.org/10.1523/jneurosci.2694-12.2012.
Hussted, M.E., Rolls, E.T., Buck, G.C., 1989. The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. Behav. Brain Res. 32 (3), 203–218. https://doi.org/10.1016/0166-2236(89)90054-5.
Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. Trends Cogn. Sci. 4, 223–233. https://doi.org/10.1016/s1364-6613(00)01482-0.
Hebb, D.O., 1949. The Organization of Behavior: A Neuropsychological Theory. Wiley, New York.
Heckenlively, B., Konig, F., 2015. Agnosia for faces (prosopagnosia). Arch. Neurol. 7, 92–100. https://doi.org/10.1001/archneur.1962.04210021004002.
Hofer, S.B., Meric-Fegel, T.D., Bonhoeffer, T., et al., 2006. Lifelong learning: ocular dominance plasticity in mouse visual cortex. Curr. Opin. Neurobiol. 16 (4), 451–459. https://doi.org/10.1016/j.conb.2006.06.007.
Holtmaat, A., Svoboda, K., 2009. Experience-dependent structural synaptic plasticity in the mammalian brain. Nat. Rev. Neurosci. 10 (9), 647–658. https://doi.org/10.1038/nrn2699.
Hubel, D.H., Wiesel, T.N., 1977. Ferrier lecture. Functional architecture of macaque monkey visual cortex. Proc. Roy. Soc. Lond. B Biol. Sci. 198 (1130), 1–59. https://doi.org/10.1098/rspb.1977.0085.
Huganir, R.L., Nicoll, R.A., 2013. AMPARs and synaptic plasticity: the last 25 years. Neuron 80, 704–717.
Ito, M., 1989. Long-term depression. Annu Rev Neurosci. 12, 85–102. https://doi.org/10.1146/annurev.ne.12.030189.000555.
Karmarkar, U.R., Dan, Y., 2006. Experience-dependent plasticity in adult visual cortex. Neuron 52 (4), 577–585. https://doi.org/10.1016/j.neuron.2006.11.001.
Kauer, J.A., Malenka, R.C., 2007. Synaptic plasticity and addiction. Nat. Rev. Neurosci. 8 (11), 844–850. https://doi.org/10.1038/nrn2334.
Kirkwood, A., Lee, H.K., Bear, M.F., 1995. Co-regulation of long-term potentiation and LTD. Neuron 15 (3), 549–556. https://doi.org/10.1016/0896-6273(95)90021-3.
Kirkwood, A., Rioult, M.C., Bear, M.F., 1996. Experience-dependent modification of cascades with common subprocesses. Prog. Neurobiol. 34 (3), 197–216. https://doi.org/10.1016/0301-0082(94)90002-0.
Kirkwood, A., Liu, H.K., Bear, M.F., 1995. Co-regulation of long-term potentiation and LTD. Neuron 15 (3), 549–556. https://doi.org/10.1016/0896-6273(95)90021-3.
Klauck, S., Berthoz, A., Schadidfi, S., Ghez, C., 2012. Plasticity in the human brain cortex during postnatal development. Proc. Natl. Acad. Sci. USA. 109 (34), 13457–13457. https://doi.org/10.1073/pnas.1202919109.
Krug, T., Shilton, T., 2005. Immunopathogenesis of coronavirus infections: lessons from SARS and MERS. Curr. Opin. Immunol. 17 (5), 544–550. https://doi.org/10.1016/j.coi.2005.06.007.
Krug, T., Shilton, T., 2005. Immunopathogenesis of coronavirus infections: lessons from SARS and MERS. Curr. Opin. Immunol. 17 (5), 544–550. https://doi.org/10.1016/j.coi.2005.06.007.
Krug, T., Shilton, T., 2005. Immunopathogenesis of coronavirus infections: lessons from SARS and MERS. Curr. Opin. Immunol. 17 (5), 544–550. https://doi.org/10.1016/j.coi.2005.06.007.
Krug, T., Shilton, T., 2005. Immunopathogenesis of coronavirus infections: lessons from SARS and MERS. Curr. Opin. Immunol. 17 (5), 544–550. https://doi.org/10.1016/j.coi.2005.06.007.
Krug, T., Shilton, T., 2005. Immunopathogenesis of coronavirus infections: lessons from SARS and MERS. Curr. Opin. Immunol. 17 (5), 544–550. https://doi.org/10.1016/j.coi.2005.06.007.