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Enacting the mind/body connection: the role of self-induced placebo mechanisms

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Placebo effects are beneficial mind-body outcomes derived from beliefs or expectations, not explainable as the consequence of active medical treatments. These phenomena have long been considered a result of external manipulation, generally obtained with deceptive strategies (e.g., fake pills) or suggestions. Open-label placebos showed promising results, but even in that case, the individual has a passive role: they are not actively engaged in promoting the effect. We propose a framework to investigate the potential for individuals to self-induce placebo effects through conscious and deliberate psychological mechanisms, such as mental imagery, somatic focusing, and perceived control. These mechanisms may be tested in combination with open-label placebos and active treatments, as well as standalone strategies. The framework may push the boundaries of current mind-body research and have the potential to place these self-induced mechanisms alongside expectations and learning as key players in the placebo effect, ultimately elevating the individual's active role in shaping their health.

Understanding how individuals can be actively involved in enhancing their health outcomes is a critical area of research. Decades of studies on mind/body interactions, including placebo and nocebo effects, support the possibility that a person's psychological states can impact their physical health. While research has greatly increased our understanding of these phenomena, it has mostly focused on a 'passive' role of the individual. This paper tries to suggest a different perspective, in an attempt to tackle three questions: are self-induced placebo effects possible? How can a person be actively engaged in promoting a placebo response (and prevent a nocebo response) in their body? And are there mechanisms that can improve one's health conditions, further boost active medical treatments, or as a stand-alone strategy?

Placebo and nocebo effects

Placebo and nocebo effects are psychobiological phenomena induced by words, rituals, symbols, and meanings (Benedetti, 2021). Placebo effects generate favorable outcomes, while nocebo effects are associated with negative ones (Colloca and Barsky, 2020; Grosso et al. 2024b). These

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phenomena can affect patient-reported changes, as well as physiological and biological parameters (Petrie and Rief, 2019), and can substantially influence the effects of medical interventions in an array of symptoms and conditions (Evers et al. 2021). Ample evidence demonstrates there is not just one single placebo effect but many, with different mechanisms across different disorders and conditions (Benedetti, 2021). The most fruitful models to understand the psychobiology of the placebo effect are those studying pain (Colloca, 2019), fatigue and physical performance (Shaibani et al. 2017), the gastrointestinal system (Elsenbruch and Enck, 2015), the respiratory system (Vlemincx et al. 2021), and the immune system (Smits et al. 2018). Across these and other domains, placebo administration significantly affects outcomes with remarkable changes in biochemical, neurophysiological, and behavioral parameters (Benedetti et al. 2016; Vits et al. 2011). For example, fake cough syrups showed an effect of up to 85% of symptom reductions due to a placebo effect (Eccles, 2020); in the trials testing the COVID-19 vaccine, about 35% of participants in the placebo group experienced side effects (Haas et al. 2022); in sports contexts, runners believing to have ingested caffeine improve performance to the same magnitude as those receiving caffeine (Hurst et al. 2019).

While the "classical" placebo effect is studied following the administration of an inert substance, there are many types of mind-body interactions that are similar to placebo/nocebo effects, which happen without the administration of inert treatments (Benedetti, 2021). Psycho-social factors, including the patient-physician relationship (Howe et al. 2017) and personal expectations (Pagnini, 2019) can produce placebo/nocebo effects without the need for an external primer, such as a pill or another fake treatment. For example, we conducted a study on people with type-II diabetes (Park et al. 2016) in which we manipulated their perception of time, leading them to believe that more or less time had passed than the actual time. Remarkably, these patients' blood glucose levels followed *perceived* time rather than *actual* time. Even though the chronological time was the same for everybody, participants who thought more time had passed had a significantly greater decrease in blood glucose levels as compared to those who believed less time had passed. Placebo and nocebo effects can also modulate the efficacy of medical and psychological treatments (Evers et al. 2021; Petrie and Rief, 2019). It is therefore important to note that every medical and psychological intervention includes placebo/nocebo components that could enhance (or hinder) their effects (Bingel et al. 2011; Enck et al. 2013), such as verbal suggestions from the clinicians, implicit/explicit features of the patient-clinician relationship (e.g., clinicians' attitude and behavior), and treatment and contextual cues (Bartels et al. 2017; Howe et al. 2017; Meissner and Linde, 2018).

Placebo/nocebo mechanisms

As placebo research has gained momentum in the scientific literature (Weimer et al. 2022), several contributions have highlighted the mechanisms that can explain these effects (Bagarić et al. 2022; Fiorio et al. 2022; Frisaldi et al. 2023). Expectations, which are specific future-oriented cognitions (Pagnini, 2019; Rief et al. 2015), seem to exert a central role in promoting placebo/nocebo effects, acting as self-fulfilling prophecies (Petrie and Rief, 2019). They can develop through learning, social observation, and information received from health professionals or other sources and can be activated by cues within the clinical setting (Petrie and Rief, 2019). Sometimes expectations are distinguished from classic conditioning (Stewart-Williams and Podd, 2004), especially in the case of hidden procedures (Bąbel, 2019). Through conditioning, for example, placebos have been used as "dose-extenders", exploiting the conditioned association between a placebo characteristic and the drug effects to continue providing the effects without the drug assumption (Colloca et al. 2016). Conditioning is often considered a required mechanism for long-term placebo effects (Evers, 2017), with a systematical re-exposure to the conditioning stimulus (e.g., the drug) (Doering and Rief, 2012). Indeed, a lack of "preserved" placebo effects in the absence of re-exposure can be explained by extinction, especially in the case of physiological processes, such as immune function (Tekampe et al. 2017).

Bayesian brain and placebo/nocebo effects

An emerging interpretation of placebo and nocebo effects is offered by the Bayesian brain hypothesis (Friston, 2009). In this model, *priors* (e.g., expectations and beliefs) are integrated or updated with new information (i.e., the *likelihood*), resulting in an outcome (i.e., the *posterior* = the *new prior*) in a continuous process of belief updating. According to this view, both the priors and the likelihood are represented by probability distributions with their own expected values and variances. The model states, in analogy with Bayes' Theorem, that the new prior has a new probability distribution that is "conditioned" by the probability distribution of the likelihood (see Fig. 1). In this process of belief updating, the brain tries to minimize the "surprise" (i.e., the prediction error), creating a more stable and foreseeable representation of the world (Holmes and Nolte, 2019). To achieve this goal, the brain can either directly intervene on the beliefs, by "re-adjusting" and updating them (i.e., through perceptual inference, Limanowski and Friston, 2018), or also act upon the world (e.g., the body), modifying it so that sensory inputs are more consistent with the prior beliefs. This latter mechanism, which allows predictions to become self-fulfilling prophecies and avoid surprises, is defined as active inference (Friston, 2009). Following this model, placebo/nocebo effects can be interpreted as the result of active inference processes (see Fig. 1) aimed to reduce the prediction error, self-fulfilling the "mental images" that substantiate the predictions (*priors*). Psychological factors such as expectations and conditioning may play the role of priors and shape the process of reducing prediction errors given a perceptual stimulus.

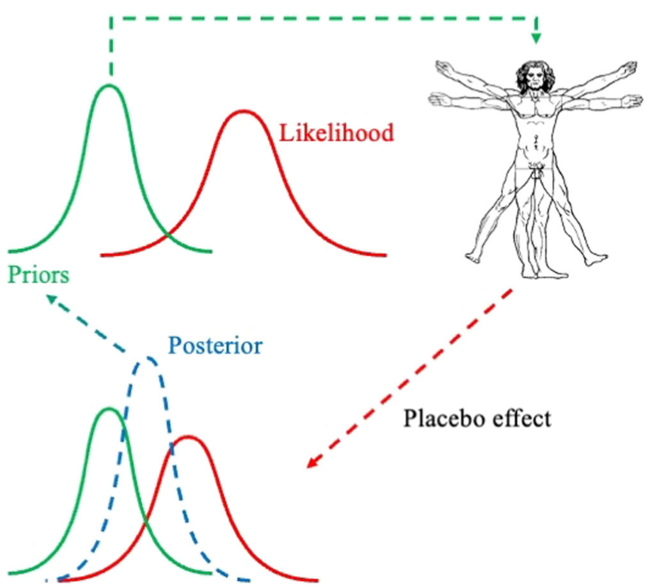

Fig. 1 Active inference in placebo effects. To minimize prediction error, psychobiological changes are implemented (placebo effect) to be consistent with beliefs and expectations (priors), providing, through a change in the likelihood, an updated belief (posterior), in a continual cycle.

One example focuses on symptom relief following placebo administration: the placebo triggers the brain to analyze small interoceptive changes in the body as a hallmark of the healing process rather than mere "noise", resulting in the revision of the ingrained maladaptive hypothesis of being chronically ill (Ongaro and Kaptchuk, 2019). This mechanism might be influenced by both higher-order priors (pre-existing models of reality involving beliefs, learning, expectations, memories, etc.), as well by the somatosensorial information received, in continuous top-down/bottom-up cycles (Pagnini et al. 2023). The idea of applying a Bayesian explanatory framework to placebo mechanisms has been suggested by prominent scholars in the field (Kaptchuk et al. 2020; Ongaro and Kaptchuk, 2019) and successfully used to explain, among other phenomena, placebo hypoalgesia (Büchel et al. 2014; Grahl et al. 2018). This latter can be interpreted as an endogenous modulation of the nociceptive activity, based on the weight of prediction errors resulting in a mitigation of the sensory data and being influenced by factors such as anxiety and stress, which change the salience of the pain expectations (Milde et al. 2023). This is consistent with recent models on painful conditions such as migraine, which have explained the symptoms as an attempt to resolve prediction errors (Sedley et al. 2024). The parallel between placebo responses and the Bayesian brain hypothesis is supported by some shared neural mechanisms (Knill and Pouget, 2004), including the prefrontal cortex as a critical hub for both placebo responsiveness (Ashar et al. 2017; Zunhammer et al. 2021) and prediction processing and integration with incoming sensory information (Geuter et al. 2017).

Deceptive placebo effects and open-label placebo

While the placebo effect can be beneficial for patients, it also comes with ethical challenges, especially when it involves deception (Bliamptis and Barnhill, 2022). For this reason, a recent expert consensus emphasized the importance of providing truthful information to the patient, and to prefer, if possible, forms of "honest" placebos (Evers et al. 2018; Evers et al. 2021). Nevertheless, most placebo research has externally manipulated expectations and learning mechanisms, through inert medical treatments, verbal instructions, or deceptive strategies aimed to create specific beliefs, either explicitly or implicitly (Colloca and Howick, 2018). In fact, despite its usefulness, placebo research has mainly investigated *externally induced* placebo effects, whereby the placebo means was often something foreign to the mind and body of the recipient. Evidence is lacking on how an individual may actively engage in self-inducing a placebo effect, leveraging internal cognitive and psychological resources. Arguably, open-label placebos (OLP) (Kaptchuk, 2018) are the closest available concept for this scenario, as "patients can experience symptom relief from taking pills that they know lack any medication" (Kaptchuk and Miller, 2018). The act of taking a placebo knowingly while being aware of its inert properties implies a greater level of consciousness in the process of its effects, differently from when this same act is grounded on deception. In fact, the existence of robust open-label placebo effects suggests the possibility of fostering placebo effects with no deceptive practice. While the psychological mechanisms underlying these effects are still unclear, the current discussion focused on the role of implicit mechanisms, such as self-conditioning and rituals-based implicit expectations (Leibowitz et al. 2019; Schaefer et al. 2022). Nonetheless, even with an honest prescription of these inert treatments, the subject is not purposefully, consciously engaged in the process of promoting a placebo effect. They are, in fact, a surprised and passive spectator of these mind/body processes (Kaptchuk and Miller, 2018). Therefore, the question of how a conscious mind can deliberately modulate or create a placebo/nocebo effect is still open.

The role of the individual in placebo responses

To date, when research has browsed potential scenarios for an individual's contribution to the placebo response, it mainly refers to personality traits and other psychological characteristics. These factors can explain individual differences in placebo responding (e.g., to identify placebo responders and non-responders), as well as individuals' greater susceptibility to experiencing placebo or nocebo effects. For example, optimism (Kern et al. 2020) and other personality traits (Frisaldi et al. 2018) are related to placebo effects, while anxiety and stress are some of the moderating factors for the nocebo effects (Maroli et al. 2022; Roderigo et al. 2017). Therefore, individual characteristics and their role in placebo/nocebo effects have been mainly considered in terms of differences in mental or personality *traits*, but much less work has been done to consider the role of mental *states*, at least that can be deliberately controlled by the person. In most placebo research, mental states are passively guided by external influences, such as a primer (e.g., a fake pill), suggestions, or conditioning mechanisms. Placebo research has been mostly driven by external stimuli, sometimes even working against the "active" role of the participants and reinforcing the idea that placebo effects can only be exogenously driven. The capability of activating specific mental states, however, may also arise from within, without a strict reliance on external agents. These spontaneously activated mental states, in turn, may leave space for placebo effects to take root.

Are self-induced placebo effects possible?

We advance the hypothesis that conscious and deliberate processes involving self-generated beliefs, mental images, and spontaneous attention may play a role in engendering or modulating placebo effects, with similar mechanisms hypothesized to reduce nocebo effects. Placebo effects could also be interpreted as a form of meaning response (Hutchinson and Moerman, 2018), referring not just to expectations, but also to the interpretation, significance, and relevance that some personal and contextual cues represent for the person. This meaning effect is particularly relevant in the self-healing literature, even though the methodological standards for these studies have not always been particularly solid (Hutchinson and Moerman, 2018). With the current proposal, we aim to suggest a new framework, rooted in the current interpretation of placebo and nocebo effects, to investigate these mind-body phenomena with an evidence-based approach. Even though the idea of self-inducing placebo effects has been speculated before (e.g., Brody and Brody, 2000), no study to date has directly tackled this issue, with individuals' active role and self-determination being mostly left out of the "placebo spotlights". This hypothesis aims to bridge this knowledge gap.

Guided by the active inference interpretation of the placebo phenomena, at least three conscious and deliberate mechanisms may have the potential to modulate or generate a placebo effect. First, at a meta-cognitive level, fantasy and mental imagery may target pre-existing schemas about the body, overturning dysfunctional priors to foster renewed and more adaptive top-down processes. Second, at both a cognitive and sensorial level, attention-driven somatic focus may shape the precision (i.e., salience) of sensory information from the body, modulating perception accordingly and prompting new bottom-up feedback. Third, the feeling of being actively engaged in a certain process requires some degree of perceived control (Pagnini et al. 2016), acting as a catalyst for further enhancing the effects of the other two mechanisms.

Mental imagery. With regards to mental imagery techniques (Deroy and Rappe, 2022), people can intentionally visualize possible worlds in their minds, reducing the rigidity of their perceptive and cognitive structures, and challenging them with more adaptive ones, as happens for psychedelic treatments (Timmermann et al. 2022; Villiger, 2022). Imagery can impact emotions with a stronger intensity than verbal instructions (Pile et al. 2021) and it can shape new cognitive biases, which may be purposefully guided toward desirable outcomes, such as increasing positive emotions (Blackwell et al. 2015). The idea is often used in cognitive-behavioral therapy, to change mental states (Blackwell, 2021), and, when deeply absorbed, is part of self-hypnosis protocols (Eason and Parris, 2019). It can be argued that placebo effects may require some form of mental imagery manipulation (Gukasyan and Nayak, 2022), and research has demonstrated the efficacy of these techniques in the promotion of placebo-like expectancy effects on pain (Peerdeman et al. 2016). In pain research, specific response imagery (i.e., imagining reduced pain) proved successful in promoting analgesia (Peerdeman et al. 2017), while another study using a more generalized imagery task (i.e., imagining one's best possible health), in combination with a placebo pill, did not obtain an effect on pain, itch, or fatigue (Peerdeman et al. 2015). Despite promising results, many studies on mental imagery used heterogeneous methods, often with protocols that excluded an active engagement of participants, who needed to be externally "guided" (Kaur et al. 2019). Aside from mental health and pain reduction, mental imagery techniques facilitate physical performance in sports activities (Lindsay et al. 2021) and in clinical settings in which movement has been impaired (López et al. 2019; Zach et al. 2018). For example, as reported in a recent study with volleyball players (Grosso et al. 2024a), simply imagining the act of flying for a few minutes greatly impacted their jumping performances. In sum, research evidence suggests that including vivid images in one's mind can not only change their psychological state but it can be reflected in the bodily states as well. Mental imagery ability varies among people, with individual differences being influenced by background experiences, such as sports and music expertise (Floridou et al. 2022), and associated with different psychological aspects, including mindfulness traits (Kharlas and Frewen, 2016). The use of mental imagery ascribes increased salience to specific aspects of the priors about psychophysiological responses (e.g., pain attenuation, wound healing, or fatigue recovery), improving their precision and making them more "influential" to the resulting posteriors.

Somatic focusing. With respect to the second mechanism, attentive mechanisms can sample the information received from the somatosensorial channels, actively changing the precision of different components of the likelihood. As recently described (Pagnini et al. 2023), somatic focusing has the potential to modulate the placebo effect. Only a few studies have explored this possibility, with promising results, suggesting that paying selective attention to specific somatic perceptions could result in an increased magnitude of these inputs (Barbiani et al. 2024; Geers et al. 2006; Rossettini et al. 2018). From an active inference perspective, somatic focusing allows to increase the salience of specific somatosensorial information, integrating it with that of the priors, resulting in a modification/re-adaptation of the whole system. For example, while taking an energy drink, a person can focus on the specific experience of being 'energetic,' paying attention to the somatosensory data that are consistent with that, and thus reducing the salience of other contrasting information, resulting in a more 'energetic' overall perception. One of the main individual characteristics that may influence somatic focusing is interoception (Gibson, 2019), which is a complex construct related to the internal perception that includes sensing, interpretation, and integration of bodily signals (Khalsa et al. 2018). There are many approaches to defining its components, and the scientific community is currently working on delineating its processes and measurement techniques (Suksasilp and Garfinkel, 2022). People vary in their levels of interoceptive accuracy (i.e., the ability to accurately detect bodily signals), which can be objectively observed (Garfinkel et al. 2015), and in their interoceptive beliefs and metacognition (Suksasilp and Garfinkel, 2022), which is accessible to declarative knowledge. Interestingly, interoception seems to be related to OLP mechanisms: in a recent study (Ballou et al. 2022), visceral sensitivity was found to be a predictor of response to OLP in people with Irritable Bowel Syndrome, supporting the hypothesis that somatic focusing-related mechanisms may be involved in the process.

Perceived control. Both imagery and attention may be deliberately controlled and enable targeting the main components of the Bayesian brain placebo model. Therefore, they represent optimal candidate mechanisms for self-modulating and promoting placebo effects. A conscious engagement in these two processes, however, implies some degree of perceived control (e.g., one's capacity to successfully activate and modulate these processes), which is the third mechanism (Gallagher, 2012). In particular, being actively "present" during these processes goes hand in hand with the feeling of being the agent of them (Arandia and Di Paolo, 2021; Pagnini et al. 2016). When control is perceived, self-attributive cognitive styles are fostered, which are grounded on the belief that the course of external events may be molded by one's efforts (Stolz et al. 2020). In other words, the person may need a certain perceived control over the procedure to be able to "act out the placebo", as an outcome of one's efforts and actions (Pan et al. 2022). As suggested by the self-validation theory (Briñol and Petty, 2022; Tormala et al. 2007), thoughts are more consequential as the perceived validity is increased, which is related to the control one feels to exert – leading to "high thought expectations" that make these beliefs more salient and are associated with higher placebo effects (Geers et al. 2019). In terms of the Bayesian brain hypothesis, perceived control acts through higher levels of priors, fostering the precision of expectations that are consistent with the person's will, supposedly resulting in a more desirable outcome. For example, instrumental control was proven to enhance placebo analgesia (Tang et al. 2019). The mechanisms of perceiving oneself to be in control include several characteristics (Wang et al. 2021), all relevant to foster self-generated placebo effects: there is an affective component, related to choice-making and reinforcing feedback, that explains the eliciting of positive feelings and reward-related processing; a motivational attribute that suggests the importance of proper motivation, including knowledge and meaningfulness; perceived control also exerts a protective effect when dealing with threats and challenges, which highlights its importance in clinical conditions (Pagnini et al. 2016). A common way to promote perceived control is by offering the person the opportunity to **make choices**. Actively involving the patients in decisions about the treatment (e.g., choosing which treatment they prefer during a task) leads to more pronounced placebo effects (Brown et al. 2013; Geers and Rose, 2011; Geers et al. 2013). A recent meta-analysis (Tang et al. 2022) suggests that offering choices (e.g., allowing to decide the timing, or the type of treatment) facilitates the placebo effect, even though with a small effect size, and it concludes that methods that enhance the choice effect should be further investigated. In terms of the active inference framework, control states are important prior beliefs (Friston et al. 2013) that interact with other priors to define the sense of self, as being an embodied agent (Limanowski and Blankenburg, 2013), and

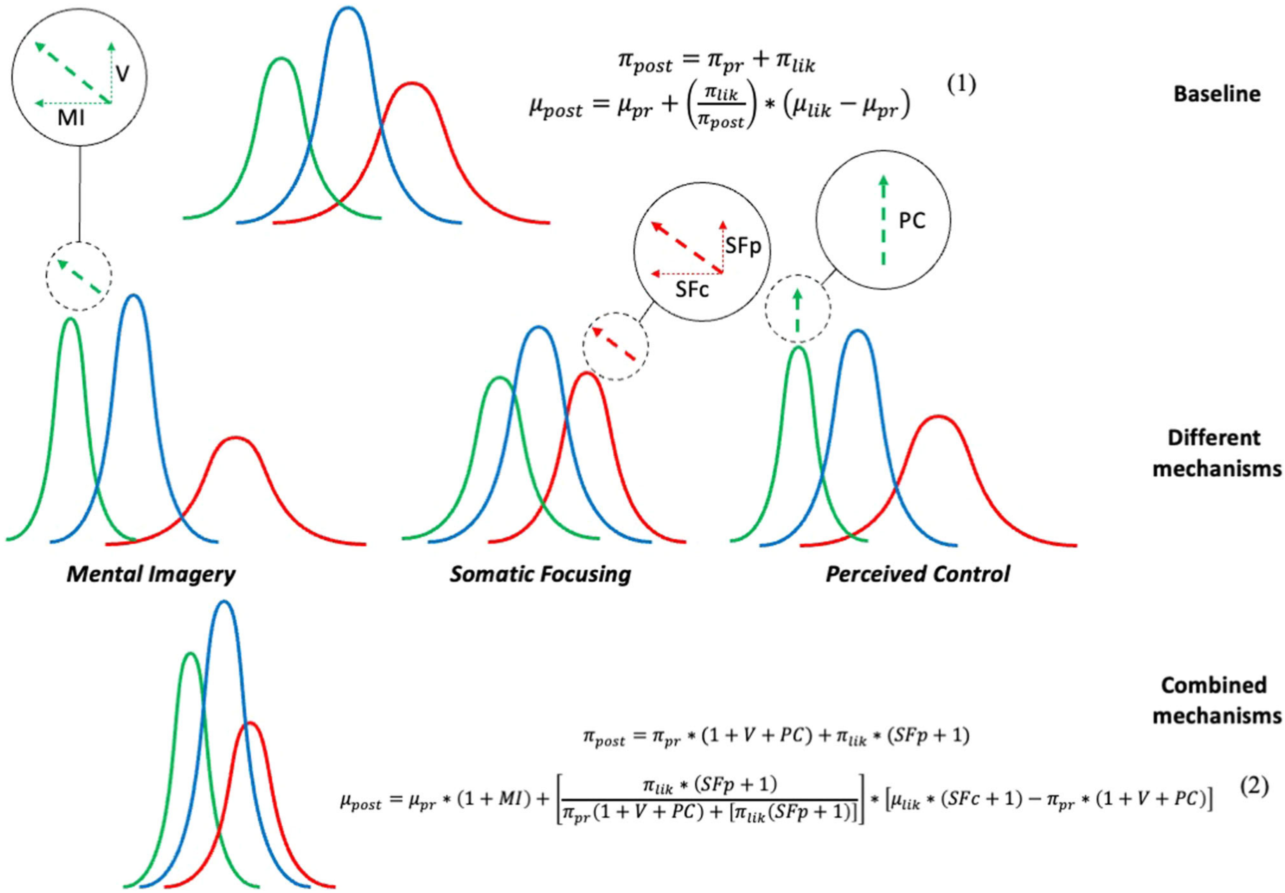

Fig. 2 Anticipated changes in the distributions after mechanisms are applied. Equation (1) describes expected baseline values, while equation (2) outlines the expected values with combined mechanisms applied (the individual mechanism contributions will be weighted based on the collected data). π precision, μ expected value, $_{pr}$ priors, $_{post}$ posterior, $_{lik}$ likelihood, MI mental imagery, V vividness, SFc somatic focusing contents, SFp somatic focusing precision, PC perceived control.

modulate information salience, emphasizing or downplaying it according to its direction. A recent study that used this framework suggests that agency additively enhanced the effects of positive expectations in pain treatment (Strube et al. 2023). While perceived control is something experienced on various degrees during a person's life, as it varies with each task, belief, and action, there are individual differences that can describe the disposition towards feeling more or less in control, such as the locus of control, sense of agency, and self-efficacy (Ajzen, 2002; Rotter, 1966). Fig. 2 depicts the expected changes at the Bayesian brain level.

Mental imagery abilities, interoceptive skills, and dispositional sense of agency are among the individual characteristics that could directly impact the execution of the supposed mechanisms. Other psychological dispositions, among those that influence the placebo/nocebo effects, can moderate the efficacy of these mechanisms. The concept of mindfulness, the process of actively noticing new things as a way to be in the present (Pagnini and Philips, 2015), which has not received much attention in placebo research, is individually related to each of the identified mechanisms. Mindfulness, both as a trait and as a result of mindfulness meditation, is associated with imagery vividness (Kharlas and Frewen, 2016); it has been associated with metacognitive interoception (Bornemann et al. 2015; Hanley et al. 2017; Khoury et al. 2017), though the correlation with interoceptive accuracy provided mixed results (Verdonk et al. 2021); and it can foster perceived control (Pagnini et al. 2016). Furthermore, mindful attention, a specific form of attention in which a person is aware of thoughts and experiences and can observe them as transient mental events (Papies et al. 2015), is particularly relevant to the application of this framework: priors are mindless insofar as they shape experience based on previous schemas without regard to current contextual cues; in a mindful attention state, the individual focuses on the present moment, decentered from previous schemas. Thus, these schemas will have a limited impact on predicting current experiences. In Bayesian terms, the precision of the priors reduces while the salience of the likelihood increases (Manjaly and Iglesias, 2020; Pagnini et al. 2023). Mindful attention is also effective in reducing emotional reactivity and in the improvement of emotional regulation (Pagnini and Langer, 2015). As emotional aspects are important factors in placebo/nocebo effects (Geers et al. 2021), mindfulness can facilitate the exploration of the embodied cognitive effect, by reducing the emotional activation and increasing the ability to self-regulate it -even under highly stressful conditions (Grosso et al. 2023; Pagnini et al. 2024). Therefore, mindful attention has the potential to "set the stage" to apply conscious placebo mechanisms. The role that mindful attention can play in the mitigation of nocebo effects, as well as in the promotion of "mindful" placebo effects, can be a key component in developing future approaches.

Implicit mechanisms can also be considered, to be mindfully exploited. Associative memories can be triggered by both conscious and unconscious mechanisms (Tal et al. 2024), with or without being aware of them. For instance, athletes may recognize that certain rituals or superstitions lack supernatural power. However, the placebo effect—attributable to both explicit and implicit mechanisms—often exerts a potent influence in these cases (Raglin et al. 2020), which involve conscious beliefs that certain behaviors or actions have a specific purpose or power to influence performance. This is not necessarily a self-promoted effect, as it refers to an external locus of control (e.g., beliefs in external entities that could explain the superstitions), and not to an internal control mechanism. In other words, similar rituals may share some mechanisms with OLPs, maybe without its meta-awareness, and likely with a prominent role of conditioning processes.

Alongside the "classic" psychological training, technological solutions can be developed to further increase both somatic focusing and mental imagery by manipulating the brain's predictive coding system (Di Lernia et al. 2023; Riva et al. 2021). For example, the former can be trained with biofeedback training (de Bruin et al. 2016), while the latter can be improved by stimulative technologies such as virtual reality (Riva et al. 2019). Interestingly, to be engaged in these simulated scenarios, people need to perceive some form of control (Jang and Park, 2019).

Potential applications of this model

The overall hypothesis of the model is that people can deliberately and consciously modulate or induce a placebo effect by using mental imagery, somatic focusing, and promoting perceived control. While this hypothesis can be tested in multiple conditions and with different aims, we would like to describe how it can be applied in three different domains: respiratory function, immune responses, and ageing. These conditions are commonly encountered in the general population (e.g., Labaki and Han, 2020; OECD, 2022; Sah et al. 2019), and are all susceptible to placebo effects.

Respiratory function. Psychological outcomes and respiratory function feed off each other, as demonstrated by the effects that anxiety can have on breathing, and vice versa (Chen et al. 2017; Volpato et al. 2018; Volpato et al. 2021). The mind can also exert an effect on respiratory symptoms, such as breathlessness, and previous studies have demonstrated the potential for placebo interventions to reduce them (Currow et al. 2019). For example, the placebo/nocebo effects have been known for a long time to be relevant for people with asthma. A 1956 study suggested that simply showing an allergen sealed in a transparent container can stimulate a psychogenic asthma attack (Dekker and Groen, 1956). More recently, it was demonstrated that exposure to an odor that was described as "asthmogenic" elicited an asthma exacerbation (Jaén and Dalton, 2014). Furthermore, we recently demonstrated that expectations are important predictors of asthma symptoms over time (Pagnini et al. 2021; Pagnini et al. 2022). Despite limited knowledge about the underlying mechanisms, with the notable exception of respiratory depressant responses mediated by opioid receptors following a placebo induction (Benedetti et al. 1998), the field of respiratory conditions represents an excellent model for testing the self-induction of placebo effects. Moreover, respiratory function lends itself well to be investigated in light of the three proposed candidate mechanisms (i.e., mental imagery, somatic focus, and perceived control), as breathing can be successfully visualized and perceived (Nord and Garfinkel, 2022), and it can be easily subject to both interoceptive ability (Harrison et al. 2021) and voluntary control (Park et al. 2020).

Immune response. The immune system is a complex network of organs, cells, and molecules that defend the body against infections and other foreign substances (Delves and Roitt, 2000). The immune response uses various adaptive mechanisms to react against pathogenic microbes, including fever (Evans et al. 2015), but abnormalities in the immune system can lead to allergic diseases, immunodeficiencies, and autoimmune disorders (Marshall et al. 2018). The immune system is well known for its interactions with the brain and the psychological domain (Price et al. 2008), and immune system reactions can be provoked by placebo/nocebo responses (Benedetti, 2021), in particular following conditioning procedures (Smits et al. 2018). For example, subcutaneous injection of placebo enhances immunoreactivity in immunocompetent cells from healthy participants (Klein et al. 2008). Moreover, the development of common cold symptoms can be extensively influenced by psychological domains, as explored in the various Common Cold Projects (Cohen et al. 1991). In a pre-pandemic study, we found a strong association between the expectations of developing influenza-like symptoms and their actual development, over the wintertime, even when accounting for previous influenzas or general health (Pagnini et al. 2020). Mental imagery has been successfully used in the past to increase immune function within relaxation exercises (Miller and Cohen, 2001; Trakhtenberg, 2008), but its "pure" effects in terms of overturning maladaptive priors remain elusive. Attending the immune system may be challenging, as it is a source of various internal stimuli (Critchley and Harrison, 2013), with a slower and more controverted timescale than other stimuli, such as respiratory function (Nord and Garfinkel, 2022).

Ageing. The third considered area is ageing, which is typically deemed as a process of inevitable physiological and psychological decline (Levy, 2009). While most medical research has focused so far on its physiological mechanisms, there are important psychological predictors of the ageing process, suggesting its susceptibility to placebo/nocebo effects (Vailati Riboni and Pagnini, 2022; Vailati Riboni et al. 2022). Specifically, ageing stereotypes (i.e., the image describing one's perception of the aging process) proved to be optimal predictors of one's ageing trajectory (Levy, 2008; Vailati Riboni and Pagnini, 2022). These images, far from being just passive descriptors, often represent a self-fulfilling prophecy, as suggested by the stereotype embodiment theory (Levy, 2009). Negative aging stereotypes, which can be interpreted as priors in an active inference paradigm, can lead to reduced survival and increased risk of neurodegenerative disorders (Ng et al. 2016). The more rigid these stereotypes are, the more pervasive their impact is on the aging process (Levy, 2008), consistent with the hypothesis that priors with high precision may have a major effect. Negative ageing stereotypes are also associated with shorter telomere, a marker of accelerated cellular aging (Pietrzak et al. 2016). It is possible, however, to modify these perceptions. A study we conducted (Pagnini et al. 2019), based on the original counterclockwise study (Langer, 2009), experimentally demonstrates that groups of older adults living for a week *as if* they were 30 years younger (in a retrofitted 1989 environment), improve their physical function and look younger to independent raters when compared with both active and passive control groups. In this framework, ageing represents an excellent model for testing the project hypotheses and verifying the potential for psychological mechanisms to impact age-related physical issues. While the ability to imagine and visualize has been successfully used to improve performance in older adults (Nicholson et al. 2018), these skills tend to progressively decline as age advances (Kemps and Newson, 2005). Interoceptive skills may also be influenced by ageing, with a reduction of interoceptive accuracy (Khalsa et al. 2009; Murphy et al. 2018).

Potential Impact

The hypothesis that placebo-like effects can be deliberately modulated and induced by the conscious mind, through a proactive engagement of the individual requires multiple studies to be examined. Within these studies, multiple questions can be addressed:

1. Can open-label placebo effects be maximized by mental imagery, somatic focusing, and perceived control?
2. Can these mechanisms be leveraged to enhance the effects of active medical treatments, boosting their efficacy - and perhaps changing the dose/response efficacy?

   *E.g., some studies reported a placebo response for ibuprofen around 48% (*Yuan et al. 2021*). If the promotion of deliberate mental states can increase this response, that may mean that the same effect obtained with 800 mg could be obtained with 600 mg, or perhaps even less.*

3. Can these mechanisms be learned and applied without any external manipulation or intervention?

   In other words, can a person self-stimulate a placebo effect simply by learning these mechanisms, keeping the effect under their control?

4. Will these self-induced placebo effects endure over time?
5. And finally, can conscious and deliberate processes be used to reduce nocebo effects?

Placebo effects are important scientific and medical phenomena and hold significant potential for improving people's lives, but they have been rarely considered as something that patients "can do by themselves". This framework emphasizes the role of the individual, actively and autonomously engaged in the process of shaping their health. Should it be correct, it can therefore lead to a paradigm shift, with a novel way of thinking about placebo effects, free from hardly negligible ethical constraints. Demonstrating the potential for the conscious mind to modulate placebo effects can lead to the development of new protocols to further enhance active medical treatments. This knowledge could also be used to reduce the nocebo effect, or the nocebo side effects of active treatments, perhaps by mindfully addressing the negative expectations (Camparo et al. 2022; Pagnini et al. 2023) and purposefully substituting them with more adaptive priors. An entirely new field of study can emerge, aimed at matching conscious psychological mechanisms with specific medical interventions. The studies can approach these research questions using a Bayesian brain hypothesis, which, despite its early stage of development, holds significant promise for advancing our understanding of the placebo effects (Pagnini et al. 2023). The use of the mind to enhance drug efficacy is particularly relevant in situations where traditional methods may be problematic, such as when drug tolerance or residue occurs with repeated use. The potential role of technology, simulative scenarios, and even the metaverse, could be investigated. Non-clinical contexts could find this approach relevant. For example, placebo-nocebo effects related to rituals and superstitions used by athletes could benefit from the use of conscious mechanisms to increase their impact (Davis et al. 2020), while also making athletes more autonomous, allowing them to self-unleash their hidden potential. As reported by anthropological studies, placebo-like effects are often described as symbolic healing, stressing the role of culture and social meanings (Apud and Romaní, 2020).

Discoveries about mind-body interaction can impact both the medical and psychological fields. Should conscious mechanisms be modulators of placebo/nocebo effects, it would have several implications for clinical practice (e.g., in a doctor's recommendation) and research. While this would allow for increased engagement in their care, a potential ethical risk is related to possible misunderstandings, such as 'we can heal the body with our mind.' Scholars and clinicians should be mindful of this possibility, mitigating it with proper patient-doctor communication and being particularly careful not to overemphasize the effects found.

To the extent that the hypothesis is confirmed, it will lead to a novel way of thinking about the placebo effect, using innovative and ethically acceptable techniques to further boost it, especially in its "honestly prescribed" form. Imagery, attention, and perceived control may earn a place, joining expectations and learning, among the mechanisms capable of shaping placebo/nocebo responses. Furthermore, should these phenomena be as relevant as expected, future studies should consider incorporating them into their methods. Arguably, the most common implication of the placebo effect in science is the incorporation of placebos in randomized controlled trials. Perhaps an improved understanding of the modulatory effects that individuals can have would lead to consideration in new trial designs. For example, whether a certain dose-response may be associated with specific conscious activities or mindsets, and not with others.

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The authors declare no competing interests

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Additional information

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