The reward for placebos: mechanisms underpinning placebo-induced effects on motor performance

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Abbreviations

ACC – Anterior cingulate cortex

GABA – Gamma-aminobutyric acid

NAcc – Nucleus accumbens

NMDA - N-methyl-D-aspartate

OFC – Orbitofrontal cortex

PCC – Posterior cingulate cortex

PFC – Prefrontal cortex

PMC – Primary motor cortex

VTA – Ventral tegmental area

Abstract

Different from the most popular thinking, the placebo effect is not a purely psychological phenomenon. A body of knowledge from multidisciplinary fields has shown that the expectation of a potential benefit when receiving a treatment induces a cascade of neurochemical-electrophysiological alterations in brain reward areas, including motor-related ones. Alterations in the dopamine, opioid, and glutamate metabolism are the neural representation converting reward-derived declarative forms into an attractive and wanted behavior, thereby changing the activation in reward subcortical and cortical structures involved in motor planning, motor execution, and emotional-cognitive attributes of decision-making. We propose that the expectation of receiving a treatment that is beneficial to motor performance triggers a cascade of activations in brain reward areas that travels from motor planning and motor command areas, passing through corticospinal pathways until driving the skeletal muscles, therefore facilitating the motor performance. Although alternative explanations cannot be totally ruled out, this mechanistic route is robust in explaining the results of placebo-induced effects on motor performance and could lead to novel insights and applications in the exercise sciences. Factors such as sex differences in reward-related mechanisms and aversion-induced nocebo effects should also be addressed.

Keywords

Fatigue, nocebo effect, exercise performance, neurotransmitter, neuroimaging.

Introduction

Imagine you are an athlete willing to break your record. Then, imagine that your coach tells you there is a pill ready to improve your performance while relieving exercise-induced aversive sensations such as pain and fatigue. Your coach is a reputed sports professional and gives you a verbal suggestion that this ergogenic aid is powerful. The psychological clues of this scenario such as the trust in your coach and the social learning regarding the ergogenic aid make you believe in a positive performance outcome as a reward for ingesting the pill (Davis et al. 2020). Thus, after getting the pill you perform the trial, experience relief in exercise-induced aversive sensations, and do the best performance ever. However, you got a pharmacologically inert pill and you have just experienced the so-called placebo effect. But you were not surprised, were you?

The placebo effect can be defined as an improvement in a specific outcome usually induced by conditioning or the expectation of a potential benefit in receiving a given treatment or intervention (Colloca et al. 2008). Different from the most popular thinking, placebo effects are not a purely psychological phenomenon. The expectation-derived placebo effects trigger neurochemical routes of the reward cerebral system that facilitate motor performance. Evidence from multidisciplinary fields supports the notion that wanted target-driven behavior leads to a discharge in dopamine, opioid, and glutamate neurons in subcortical and cortical structures involved in reward, initiating a cascade of activations in motor planning and motor command areas, traveling through corticospinal pathways (de la Fuente-Fernández et al. 2001; de la Fuente-Fernández 2009; Cohen et al. 2012; Tachibana and Hikosaka 2012; Benedetti et al. 2022). However, the potential role of the brain reward system in responding to placebos has been unexplored to explain how the placebo effect improves motor performance in sport and exercise scenarios, as theoretical studies have focused on the performance responses to placebo rather than its underpinning mechanisms (Beedie et al. 2018). A few reviews have organized evidence regarding the role of reward on placebo responses (Benedetti et al. 2011; Frisaldi et al. 2020), however they focused on placebo effects found in medical outcomes of conditions such as depression, Parkinson, and pain, limiting the translation to motor performance

in exercise scenarios. For example, brain structures mostly involved in pain were addressed, so cerebral areas and medullar pathways of motor planning and motor command have yet to be addressed into the reward-placebo model. Furthermore, dopamine has been highlighted as the main neurotransmission pathway in brain structures involved in reward paradigms, but less has been made to include opioid and glutamate as a neural signature of the reward-induced placebo effects (Lidstone et al. 2005). Studies addressing the mechanisms underlying the placebo effects on cerebral motor areas and motor performance outcomes are crucial to understanding the interaction between exercise and clinical or pharmacological interventions, as well as to exploring the exercise performance from a behavioral perspective. For example, while the effectiveness of the pharmacological effects of analgesics or nutritional supplements in improving the motor output may be confounded with the performance improvements derived from the expectation of their beneficial effects (i.e. placebo effect), the mechanisms underlying the exercise tolerance may be well explored within a placebo paradigm.

In this review, we discuss neurochemical and electrophysiological mechanisms underpinning reward-induced placebo effects on cerebral motor areas and motor performance. Potential sex differences and mechanisms of the negative expectation-derived harmful response in motor performance, the nocebo effect, are also addressed. To incorporate these mechanisms into the exercise performance perspective, we discuss how the expectation for reward triggers neurochemical alterations in areas involved in motor output modulation and present insights from neuroimaging studies to inform future designs of placebo studies in exercise scenarios.

Psychological triggers: conditioning or expectation of reward

We have depicted an example that could be easily found in real-world scenarios of sport and exercise, highlighting the role of the individual's expectation in eliciting a true placebo effect (Benedetti et al. 2011; Davis et al. 2020). This example may fit a

variety of motor performance contexts in which expectations affect exercise-related behavior.

There is broad evidence that the expectation is the main psychological trigger of a neurophysiological cascade of events that results in wanted behavior and altered perceptual responses. However, first, it is important to differentiate the placebo effect derived from expectation and conditioning. The placebo effect following expectation is a conscious process related to the belief that the future will follow the premises built with the environment-derived clues, influenced by prior experiences and social learning (Colloca et al. 2008; Colloca and Benedetti 2009). The classical Pavlovian conditioning effect refers to the unconscious conditionate response following a neutral stimulus due to the repeated association between the neutral stimulus and the true unconditioned treatment (Voudouris et al. 1989; Finniss et al. 2010). Despite being conceptually different, both constructs are intrinsically connected given that conditioning processes also create expectancy. For example, although simple verbal cues can drive (positively or negatively) the expectation of an individual, prior experiences derived from conditioning processes may strengthen this expectation-driven response. Indeed, while simple verbal cues about the potential of caffeine as ergogenic elicited a powerful placebo effect on endurance performance (Beedie et al. 2006; Brietzke et al. 2017), patients with chronic pain experienced a robust analgesic placebo effect when the expectation was combined with prior therapeutic experiences (Colloca et al. 2020). Therefore, although the expectations about the future do not necessarily depend on conditioning processes, the expectation-derived placebo effects may be potentiated if combined with conditioning (Fiorio et al. 2014; Colloca et al. 2020).

Changes in expectation have been suggested to be associated with alterations in brain reward areas through dopaminergic, opioidergic, and glutamatergic projections (Berridge and Robinson 1998; You et al. 2001; De la Fuente-Fernández et al. 2002). It is assumed that the expectancy codifies a future event through explicit representations of its sensory and rewarding features, bringing up information to guide the individual's action (Berridge and Robinson 1998). Declarative forms of expectation such as imagery, and symbolic or semantic representations serve to build up

inferences about the future through reward neural signatures mediated by neurotransmitters, changing the individual's attention toward an attractive and wanted behavior (Fields and Margolis 2015). Studies have supported this neural signature hypothesis, as they reported activation of dopamine neurons in the brain reward areas during the incentive phase, in anticipation to reward (Dubol et al. 2017). Studies have also shown that opioid activity in reward-related areas was associated with expectation-driven behavior (Wager et al. 2007; Scott et al. 2008), being this response present in anticipation to reward (Korb et al. 2020). Accordingly, recent results demonstrated that alterations in different brain reward areas were associated with glutamatergic activity during the incentive phase of a reward (Bossong et al. 2018; Malvaez et al. 2019). Hence, rather than in isolation, these neural substrates play a role together in assigning the reward responses.

From the exercise sciences perspective, the reward-driven behavior mediated through dopamine, opioid, and glutamate constitutes a robust route for the placebo-derived improvements in motor performance, given the connectivity between brain reward and motor-related areas (Adkins and Lee 2021). The expectation-induced neurochemical alterations in areas of the reward system are the first step in initiating cerebral electrophysiological changes that ultimately facilitate the motor output.

Neurochemical routes of reward-related placebo effects on motor performance

During exercise, a cascade of information must travel from sensory afferents to high-level cortical areas such as the prefrontal cortex (PFC) and associative cortex to plan the motor schema necessary to perform the physical task. This neurological planning is then finalized when the planned motor command travels from the primary motor cortex (PMC) to skeletal muscles through the corticospinal pathways (Codol et al. 2020). Results from independent studies suggest that placebos may influence reward neural substrates involved in this stream of information.

Studies with different reward-placebo paradigms have shown that expectations induce a change in the metabolism of subcortical and cortical structures involved in motor planning, motor execution, and emotional-cognitive attributes of decision-making (Petrovic et al. 2002; Bush et al. 2002; Bingel et al. 2006; Vachon-Presseau et al. 2018). It has been shown that brain reward structures such as the ventral tegmental area (VTA), nucleus accumbens (NAcc), dorsal striatum, insula, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), PFC, and PMC have a large population of dopaminergic, opioidergic and glutamatergic neurons (Berridge and Robinson 1998; Scott et al. 2008; Le Merrer et al. 2009). The increase in dopamine, opioid, and glutamate metabolism over these areas has been suggested to be involved in predicting past experience-based future outcomes, thus guiding current actions (Dickinson 1988). Therefore, neural representations of placebo-induced expectations containing objective or subjective declarative forms are thought to be mediated through the neurotransmission that alters the neurophysiological activity of these areas (Scott et al. 2008).

Changes in neural substrates are the first step in converting placebo-induced expectation changes into attractive and wanted target-driven behavior (Berridge and Robinson 1998; Le Merrer et al. 2009). Dopamine has been traditionally pointed out as one of the main neurotransmission currencies of rewards (Baik 2013). For example, assessing the baseline raclopride binding potential values (a D2/D3 dopamine receptor competitor) in Parkinsonian patients, de la Fuente-Fernández et al., (2002) observed that the expectation of receiving a dopamine agonist (apomorphine) increased the dopamine release in the NAcc. Accordingly, Scott et al., (2008) showed that the expectation of receiving analgesic intervention in a pain paradigm also increased the D2/D3 dopamine neurotransmission, as observed by the reduced binding potential by 10-16% in the bilateral NAcc, and by 9% and 10% in the ventral caudate and putamen, respectively. However, other neural substrates also play a role in signing the placebo effects on brain reward areas.

It has also been suggested that opioids are a neural substrate for most cerebral reward-placebo structures (Zubieta and Stohler 2009). Studies by Petrovic et al. (2002) and Zubieta et al. (2006) found altered μ-opioid receptors activity in the NAcc,

ACC, OFC, and PFC in healthy participants submitted to analgesic placebos in different pain paradigms. These results agreed with several pieces of evidence for increased activity in μ-opioid receptors in the NAcc, insula, ACC, OFC, and PFC (Zubieta and Stohler 2009), showing overlap with the activation mediated by dopamine neurons. Importantly, glutamate has also been described as a neural substrate of reward responses. A study by Bossong et al., (2018) observed that healthy participants submitted to a monetary reward paradigm showed increased activation of the NAcc during the reward anticipation phase, and such a response was associated with glutamate levels in the hippocampus area. These results agreed with recent results obtained in mice, as glutamate neurons increased the activity in the VTA due to reward-predicting cues (McGovern et al. 2021). Hence, neural representations of reward use an interplay between the metabolism of dopamine, opioid, and glutamate (Jocham et al. 2014; Qi et al. 2014; Korb et al. 2020).

Changes in neural substrate metabolism codify the electrophysiological signature of reward in subcortical and cortical-related motor areas, likely facilitating the motor output (Bundt et al. 2016; Galaro et al. 2019; Codol et al. 2020; Swanson et al. 2021). For example, using neuroimaging analysis assessed by PET scan (Positron Emission Tomography) with a specific radiotracer technique, Wager et al., (2007) observed activation induced by μ-opioid in periaqueductal gray matter, amygdala, OFC, insula, rostral ACC, and lateral PFC in healthy individuals submitted to a pain paradigm treated with placebo. Using a similar methodology and pain-placebo paradigm, Scott et al., (2008) found increased activity of the reward circuity due to the increased dopamine and opioid projections in the VTA, nigrostriatal, NAcc, insula, ACC, OFC, PFC, and amygdala. Furthermore, independent *f*MRI studies observed comparable results in glutamate projections. For example, while Jochan et al., (2014) found that changes in activation of the NAcc, putamen, caudate, and ACC in the presence of NMDA glutamate receptor antagonist were correlated with predicted reward in a reinforcement learning task, Bossong et al., (2018) found higher activation in the NAcc due to glutamate projection in the hippocampus during a monetary task-induced reward.

Alterations in neural substrates of reward-placebo paradigms are the basis for the improved activation and excitability in motor-related regions, including the corticospinal pathways. Indeed, while it was observed that different reward paradigms improved the excitability of motor cortex areas such as PFC, and PMC (Galaro et al. 2019; Codol et al. 2020; Adkins and Lee 2021; Swanson et al. 2021), others observed increased excitability in corticospinal pathways (Klein et al. 2012; Bundt et al. 2019). The reward-induced alterations in electrophysiological properties of motor-related areas may be ultimately beneficial to motor performance and perceptual responses to exercise.

Perspectives for mechanistic studies investigating placebo effects in exercise performance scenarios

Subcortical reward structures project directly to cortex areas involved in motor planning and execution as well as in emotional-cognitive appraisals such as ACC, PFC, and PMC so that the activation of these reward areas may modulate the motor drive to skeletal muscles and reduce the exercise-derived sensations as suggested elsewhere (Pires and Pinheiro 2016; Robertson and Marino 2016). Results of a neuroimaging study reinforced the role of the connectivity between reward and motor-related areas in facilitating the motor performance in large muscle mass exercise, as the improved 1-h cycling time trial performance with carbohydrate mouth with rinses was likely associated with the greater activation in reward-related areas such as the insula, caudate, OFC, ACC and dorsolateral PFC (Chambers et al. 2009). Participants of that study also reported a comparable perceived exertion despite the higher motor output in the experimental trial, thus hypothesizing a relationship between reward circuitry, motor performance, and perceptual responses to exercise. Results of independent neuroimaging studies investigating different placebo paradigms in a variety of fine and gross motor tasks suggested the same.

Studies from multidisciplinary fields have found a placebo-induced modulation in the PFC and PMC activation or increased corticospinal excitability during exercise (Fiorio et al. 2014; Pires et al. 2018; Codol et al. 2020). For example, we demonstrated

that caffeine and placebo-perceived-as-caffeine induced comparable changes in PFC oxygenation and PMC activity, improving cycling performance when compared with a baseline trial (Brietzke et al. 2017; Pires et al. 2018). In contrast, we recently observed that mouth rinses of carbohydrate and placebo perceived as carbohydrate induced a higher activation of PFC and PMC areas when compared with a baseline trial, regardless of changes in exercise performance and perceived exertion (Brietzke et al. 2020). One may suggest that these results are controversial, given that motor performance was unchanged despite the placebo-induced motor cortex activation. However, other areas sensitive to placebos that may explain these results were not assessed in these studies. For example, an earlier study by Fiorio et al., (2014) found enhanced corticospinal excitability and improved motor performance in a placebo of transcutaneous electric nerve stimulation treatment, indicating that future placebo studies should make efforts to assess different electrophysiological responses such as activation and excitability, in a variety of motor-related areas such as the PFC, PMC and corticospinal pathways (Brietzke et al. 2020).

Importantly, the placebo-induced facilitation in motor performance is somehow associated with attenuated exercise-induced aversive sensations. In this regard, we found that participants elicited a lowered perceived exertion in the placebo-perceived-as-caffeine trial, even though the higher cycling power output when compared with the baseline trial (Brietzke et al. 2017). Furthermore, Pollo et al., (2008) found a reduced muscle fatigue perception when individuals ingested a placebo perceived as caffeine, as individuals increased the total muscle work mainly if the verbal suggestions were combined with conditioning procedures to induce a positive placebo-related expectation. Accordingly, while Bottoms et al. (2014) found that the placebo of an energetic sports drink increased the power output and reduced the perceived exertion in a maximal arm crank exercise, Piedimonte et al. (2015) reported that participants perceiving the placebo as caffeine reduced the perceived exertion, attenuating the exercise-derived fatigue sensation and improving the performance during repeated flexions of a fine exercise task.

We argue that results from multidisciplinary neuroimaging studies investigating different placebo paradigms show that placebo-derived changes in brain reward areas

trigger a cascade of neurophysiological alterations that modulate the motor cortex and corticospinal pathways, facilitating motor output and alleviating the exercise-related aversive sensations, as depicted in figure 1. This suggestion is supported by the fact that ACC, PFC, and PMC play a role in the exercise decision-making, as these areas are involved in driving the motor command to skeletal muscles (Pires et al. 2018; Brietzke et al. 2020; Codol et al. 2020) and converting aversive sensations into messages emotionally relevant to exercise (Robertson and Marino 2016; Ramkumar et al. 2016; Pires et al. 2018). Therefore, the placebo ergogenic effects reported in different exercise types (Hurst et al. 2019) may be related to a placebo-reward hypothesis. Future mechanistic studies are necessary to advance the knowledge of this hypothesis, designing creative and straightforward methodologies to assess neuroimaging responses in motor-related areas, mainly in large muscle mass exercises. The assessment of activation and excitability parameters over motor-related areas responding to placebo paradigms is fundamental to cover this gap.

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Including sex and nocebo in mechanistic studies

Sex differences in brain reward responses

Despite the controversy involving the role of sex in placebo-induced changes in reward cerebral structures (Scott et al. 2007; Rivera-Garcia et al. 2020), a body of literature is consistent in showing sex differences in stress-induced cerebral neurophysiological response over reward structures (Enck and Klosterhalfen 2019).

Animal studies have shown that male rats elicit a higher number of dopamine neurons in the substantia nigra than females, but not in the VTA (Dewing et al. 2006; McArthur et al. 2007). Furthermore, it has been reported a higher dopamine release and reuptake in the striatum of female than male rats (Walker et al. 2000). Recently, Lefner et al., (2022) found sex differences in dopamine release in NAcc of rats submitted to the Pavlovian paradigm, as females showed a smaller reward-evoked dopamine release than males. Such sex differences in dopaminergic metabolism have been associated with the role played by the estradiol in homosynaptic and

heterosynaptic regulation of dopamine release through D2R receptors (dopamine type 2 auto-receptors), GABA, and kapa opioid receptors, respectively (Zachry et al. 2020). Importantly, there is theoretical and empiric support to also propose sex differences in dopaminergic pathways over the mesocorticolimbic pathways of humans, being such differences likely associated with altered decision-making responses in behavioral tasks such as exercise (Douma and de Kloet 2020).

Studies have found important differences in reward neural substrates between women and men. A study reported a higher magnitude of μ-opioid system activity in men than women, mainly in the anterior thalamus, ventral basal ganglia, NAcc, and amygdala, thereby indicating sex differences in cerebral activation (Zubieta et al. 2002). Indeed, using an analgesic-induced placebo, Shi et al., (2021) observed that men showed higher brain functional connectivity in the ventromedial PFC, posterior cingulate cortex, and OFC than women, although the decreased functional connectivity between rostral ACC and thalamus, insular cortex, and supplementary motor area. Interestingly, the same study used a hyperalgesia-induced nocebo paradigm and observed that men elicited higher functional connectivity than women in the rostral ACC, OFC, ventromedial PFC, dorsolateral PFC, and supplementary motor area, but not in the posterior cingulate cortex and insular cortex (Shi et al. 2021). Also, an earlier study by Dodd et al., (2017) suggested a sex difference in placebo-induced activation of ACC and PFC. Together, these results show that sex may impact the placebo-induced activation in reward structures, thereby being a confounding factor of placebo effects on motor-related areas and motor performance. Future investigations are necessary to explore whether placebos also affect motor performance differently in women and men.

Aversion-induced nocebo effects

Nocebo effects have been poorly investigated in exercise scenarios, as studies from exercise fields have been oriented to find performance boosters rather than performance reductors. Consequently, this has been also poorly comprehended from the motor performance perspective (Kong and Benedetti 2014). Separate analgesia

studies have shown that placebo and nocebo share similar motor-related areas, although inducing different responses in reward structures (Kong et al. 2008; Frisaldi et al. 2020). A study by Scott et al. (2008) showed that a nocebo-driven response copied placebo responses in a mirrored fashion, as the nocebo-induced hyperalgesia led to a 2-25% increase in the binding potential of μ-opioid receptors in VTA, NAcc, insula, striatum, ACC, OFC, and PFC, thus resulting in reduced opioid-mediated neurotransmission. Accordingly, it was observed a 6-8% increase in the binding potential of dopaminergic D2/D3 receptors in the same reward areas, reducing the dopamine-mediated neurotransmission (Scott et al. 2008).

The few available studies using a motor performance paradigm suggested a complex response to nocebo, as the expectancy of an undesirable impairment in motor performance may lead to a varied response in reward areas and performance outcomes. A study by Andani et al., (2015) observed that healthy participants conditioned to expect detrimental effects from transcutaneous electrical nerve stimulation, shortened the cortical silent period assessed in the PMC during a fine motor task performed with the right index finger. Interestingly, although the unchanged motor evoked potentials, the motor performance as measured as peak force was reduced in the nocebo session. Recently, the same research team found similar results in a factorial design combining negative and positive verbal suggestions with positive and negative conditioning (Corsi et al. 2019), evidencing that nocebo intervention may elicit a reduced inhibitory activation in the PMC comparable to placebo, although inducing oppositive motor performance outcomes. Results of different nocebo paradigms (Scott et al. 2008) may suggest that the nocebo-induced alterations in dopamine and opioid neurotransmission modulate the motor-related areas in a complex way rather than simply mimicking the placebo fashion. Consequently, the potential of the nocebo effects on exercise performance may be more challenging than placebos, as the suggestion of a performance reductor intervention may not necessarily result in performance impairments. For example, Bottoms et al. (2014) observed no arm crank exercise performance reduction when participants ingested a sports drink suggested as a performance reductor, although the higher perceived exertion.

We are unaware of studies assessing motor-related areas such as ACC, PFC, and PMC, together with corticospinal pathways during exercises in nocebo paradigms, so future studies are necessary to pave the avenue of the nocebo effects on motor performance.

Considerations for using the reward system to understand the placebo effects on motor performance

The suggestion of reward-driven placebo effects through dopamine, opioid, and glutamate metabolism does not exclude the participation of neural substrates eventually dismissed here. For example, an earlier study had suggested that GABA metabolism influenced the running speed of rats submitted to a food reward during different strategies of reinforcement (Hawkins et al. 1988), thus indicating that other substrates could mediate the neural signature of reward. Here, we have focused on the most consolidated and consensual evidence from multidisciplinary fields, so addressing all possible neural substrates of reward would be beyond the scope of this review. Furthermore, we have used evidence derived from different reward paradigms such as analgesia, food, monetary, etc. thus one may challenge the similarities between reward neural signatures of motor performance and those manipulations. We have noted a consistency in the reward-mediated placebo effects on motor output through different placebo paradigms, thus this review may offer a theoretically sound model to advance the understanding of how placebos boost motor performance in a variety of exercise scenarios, serving to drive hypotheses and designs of future studies of placebos in exercise sciences fields.

Conclusions

We propose that placebo-induced changes in reward cerebral structures may be beneficial for improving motor performance in a variety of exercises. Placebo-induced discharges of dopamine, opioid, and glutamate neurons trigger a cascade of neurophysiological alterations in motor planning, motor execution, and corticospinal

pathways that may facilitate motor performance and reduce exercise-related aversive sensations. Creative and straightforward designs are necessary to advance this hypothesis in exercise scenarios.

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Figure's caption

Fig. 1. Illustrative representation of the reward-related structures involved in the placebo ergogenic effects on motor performance. AMY = amygdala, ACC = anterior cingulate cortex, HYP = hypothalamus, IC = insular cortex, NAcc = nucleus accumbens, OFC = orbitofrontal cortex, PAGm = periaquedutal gray matter, PCC = posterior cingulate cortex, PFC = prefrontal cortex, PMC = primary motor cortex, THS = thalamus, VTA = ventral tegmentar area. Venus and Mars symbols were used to indicate potential sex differences in placebo and nocebo paradigms. Created with BioRender.com.