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ABSTRACT

Although the great increase in interest in the placebo phenomenon was spurred by the clinical implications of its use, the progressive elucidation of the neurobiological and pharmacological mechanisms underlying the placebo effect also helps cast new light on the relationship between mind (and brain) and body, a topic of foremost philosophical importance but also a major medical issue in light of the complex interactions between the brain on one side and body functions on the other.

While the concept of placebo can be a general one, with a broad definition generally applicable to many different contexts, the description of the cerebral processes called into action in specific situations can vary widely. In this paper, examples will be given where physiological or pathological conditions are altered following the administration of an inert substance or verbal instructions tailored to induce expectation of a change, and explanations will be offered with details on neurotransmitter changes and neural pathways activated. As an instance of how placebo effects can extend beyond the clinical setting, data in the physical performance domain and implications for sport competitions will also be presented and discussed.

Keywords: placebo, nocebo, expectation, conditioning, pain, physical performance

INTRODUCTION

The best known mechanisms underlying the placebo effect have been illustrated for pain and Parkinson's disease. In placebo analgesia, the activation of the descending pain modulating network from the cerebral cortex to the brainstem and spinal cord has been described, with the involvement of opioids, cholecystokinin, and dopamine. In Parkinson’s

disease, the modulation of the basal ganglia and thalamic circuit has been proposed, with the involvement of dopamine. Other medical conditions, like depression, anxiety, hormone secretion, immune functions, addiction, are less understood, although some of the underlying mechanisms have been identified as well.

The recent increase in interest in the placebo phenomenon has been without doubt spurred by the clinical implications of its use, i.e. by the ethical controversy about its possible exploitation in medical practice and by the search of better-designed clinical trials to test new drugs and treatments. However, placebo effects are the consequence of a general interaction between an organism and its environment, and as such they extend beyond the healing context. One example is offered by placebo effects in physical performance, during training or in competition, where it can be shown that under placebo suggestions an athlete can extend performance limits and/or diminish fatigue perception.

In both clinical and performance settings, the neurobiological changes involved can be triggered by a variety of psychological mechanisms, such as conditioning, expectations, reward, anxiety reduction, and can be modulated by desire, motivation and memory. Many of these factors fall under the concept of learning, in different forms such as conscious, associative or social. Initial genetic studies are beginning to identify genetic variants associated with enhanced responsiveness to placebo treatments, at least in a few conditions. On the other hand, the experimental or clinical loss of executive prefrontal control mechanisms is coupled to the failure of placebo responses. Thus, we are slowly improving our understanding of how procedural interventions can bring the placebo response under control, in order to deliberately maximize it to the patient's advantage in clinical practice, and minimize it in clinical trials for the evaluation of active principles.

This review focuses on the many psychological and neurobiological mechanisms which have been delineated across different medical conditions, stressing the multiplicity of placebo

responses, which more and more appear as a multifaceted manifestation of the complex interactions between the brain on one side and body functions on the other, effected through the endocrine, immune, and autonomic nervous systems.

A number of recent reviews and books address these topics in great detail [1-7]. Here we attempt to give a concise updated summary of the advances in the field, emphasizing how placebo effects can be relevant not only in pathological conditions but also in physiological contexts outside medical practice.

THREE NEUROTRANSMITTERS HAVE BEEN IDENTIFIED IN PLACEBO ANALGESIA

The placebo analgesic response is the reduction in pain experienced by an individual after one or more events in the environment have induced in him/her the expectation and anticipation that the pain will decrease. No established pharmacological or physical treatment is associated with these events, and indeed, there is no reason for the pain to subside other than what is set in motion in the patient's brain. Confounding factors such as spontaneous remission, patient or medical staff bias, regression to the mean or effect of unidentified co-interventions must have been ruled out (these are factors frequently contributing to the magnitude of the placebo effect observed in the placebo arm of a clinical trial; see [8, 9] for a detailed description). What the experimenter analyzes is thus only the psychobiological phenomenon in isolation.

1- The opioid system

The first evidence of the involvement of a neurotransmitter system in placebo analgesia came from a clinical study on post-operative pain in patients undergoing third molar tooth extraction. Levine et al. observed that the opioid antagonist naloxone interfered with placebo analgesia and suggested that this action was due to its tampering with the endogenous opioid

system [10].This is a top-down regulatory system extending from cognitive and affective cortical brain regions to the brainstem and spinal cord dorsal horns, with the ability to negatively modulate the incoming nociceptive signals [11, 12]. Although the study by Levine et al. lacked the necessary controls, it is considered a seminal work, as it opened up a new line of research. With an experimental ischaemic arm pain model, Benedetti et al. showed that naloxone could antagonize placebo analgesia induced with both verbal suggestions alone, or verbal suggestions coupled with a preconditioning procedure - whereby the subject's belief in the treatment efficacy (the expectation of analgesia) was reinforced by having him experience the analgesic effect of the real drug [13]. Further support for the role of endogenous opioids came from the demonstration of higher concentrations of endorphins in the cerebrospinal fluid of placebo-responders compared to non-responders [14], from the appearance of naloxone-sensitive typical opioid side-effects (respiratory depression) during the placebo response [15], from naloxone-sensitive reduced β-adrenergic activity of the heart accompanying the placebo response [16], and from naloxone-reversibility of somatotopically activated opioid systems [17].

A number of neuroimaging studies elegantly built on this knowledge, contributing information on the location and timing of endogenous opioids release [18, 19]. In the first of such works, Petrovic et al. showed by positron emission tomography (PET) that during placebo analgesia or after the exogenous administration of an opiate (the μ-opioid agonist remifentanil) the patterns of brain activation largely overlapped (but see important differences in [20]), involving in both cases the rostral anterior cingulate cortex (rACC) and the orbitofrontal cortex [21]. While these results were stimulating, they did not yet establish a causality link. Shortly afterwards, Zubieta et al. provided in another PET study a direct demonstration of endogenous opioid release in the course of an experimental pain protocol with placebo manipulation in healthy volunteers. They employed a molecular imaging

technique, whereby [^{11}C] carfentanil, a μ-opioid receptor-selective radiotracer, binds to in vivo available μ-opioid receptors. The activation of opioid neurotransmission is revealed as a reduction of binding. After placebo, decreased binding was observed in pregenual rACC, insula, nucleus accumbens and dorsolateral prefrontal cortex (DLPFC); in all areas except DLPFC, this decrease was correlated with placebo reduction of pain intensity reports [22]. In a fMRI study with subsequent connectivity analysis, activity in rACC upon placebo administration was suggested to be strictly correlated with the activation of the subcortical antinociceptive network (periaqueductal gray (PAG) and bilateral amygdalae) [23]. In a recent paper, the same authors also showed strict opioid-specificity of this coupling, which was abolished by naloxone administration [24]. Similar conclusions were reached by Wager et al. in a PET study with in vivo receptor binding. [25].

Data have been provided regarding also the distal part of the antinocicepive system, namely the spinal cord. Earlier studies had already pointed to a modulation by placebo of spinal activity, with smaller dimensions of skin areas displaying heat-induced mechanical hyperalgesia in placebo relative to control [26], and with expectations of reduced pain resulting in diminished spinal (withdrawal) reflexes and brain evoked-potentials after sural nerve stimulation [27]. Recently, direct evidence has been supplied that fMRI responses related to painful heat stimulation can be reduced in the ipsilateral dorsal horn under placebo analgesia [28]. Also of note, permanent [29] or transitory [30] impairment of prefrontal cognitive functions results in the disruption of placebo analgesia.

2- Cholecystokinin

The second neurotransmitter identified in placebo analgesia was in fact one mediating an antagonizing effect. In 1995, Benedetti et al. showed that proglumide, a cholecystokinin (CCK)-antagonist, potentiated the placebo analgesic response in a model of experimental ischemic pain as well as in postoperative pain [31. 32], consistent with the anti-opioid action

of CCK, the receptors of which largely overlap in brain distribution with those of opioids [33]. Thus, CCK appears to play an inhibitory role in placebo analgesia which is likely to be exerted in the same areas involved in opioid transmission, although unfortunately no imaging data are at present available.

Interestingly, CCK also modulates the counterpart of placebo analgesia, i.e. nocebo hyperalgesia. This can be defined as the increase in pain experienced by an individual led by environmental clues to expect a negative outcome, in the absence of an effective cause of symptom worsening [34]. In this case, by antagonizing the pronociceptive effect of CCK, proglumide produces the inhibition of the nocebo response [35]. Nocebo suggestions act by triggering anticipatory anxiety, and in fact both nocebo hyperalgesia and the concomitant hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis can be blocked by benzodiazepines. However, the CCK system activation is involved specifically in the generation of hyperalgesia, as proglumide has no effect on ACTH and cortisol plasma levels [36].

Taken together, all these results suggest that the pain inhibiting endogenous opioids system promotes placebo analgesia, while the pronociceptive endogenous CCK system antagonizes placebo analgesia and facilitates nocebo hyperalgesia. No data are as yet available on a possible role of opioids on nocebo hyperalgesia. It can be speculated that the placebo-nocebo phenomenon is a continuum, with opioid and CCK-ergic systems acting as the mediators of opposing effects. Opposing effects of these two systems are well documented also for mood disorders [37] and have been described also in the emotional modulation of other external signals, like visual input [38].

3- Dopamine

Dopamine was first implicated in placebo research in investigations on Parkinson's disease (PD, see below). It was noted that the motor placebo response in Parkinsonian

patients was associated not only with dopamine release in the dorsal striatum, consistent with the role of this structure in motor control, but also in the ventral striatum, which is part of the reward circuit, an ensemble of brain structures crucial for reinforcement learning and decision-making [39].

In an attempt to investigate the possible role of reward mechanisms in placebo responses different than motor improvement in PD, Scott et al. performed a brain imaging study with fMRI and PET with the radiotracer raclopride, a dopamine D2/D3 agonist, on healthy subjects. Each subject underwent both a placebo analgesia protocol and a monetary task testing reward. It was possible to establish a correlation between the release of dopamine as measured by in vivo receptor binding after the placebo procedure, and the fMRI response in the nucleus accumbens (receiving dopaminergic input from the ventral tegmental area in the brainstem) after the monetary task. In other words, the greater the efficiency of reward mechanisms, the greater the placebo responsiveness [40]. In a subsequent study, the same investigators probed both endogenous opioid and dopaminergic systems, under placebo or nocebo pain challenges. Using PET with [11C] carfentanil and [11C] raclopride respectively, they showed placebo-associated opioid (in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter) and dopaminergic (in the ventral basal ganglia, namely in the nucleus accumbens) activation on the one hand, and nocebo-associated deactivations of both systems in the same areas [41]. Thus, as for CCK and opioids, it appears that also for dopamine bidirectional changes in neurotransmitter release can be involved in the shift between responses to positive and negative suggestions.

An important difference between the opioid and the dopaminergic systems is that only the second has the potential to be part of placebo responses in medical conditions different from pain, as its expectation-related mechanism (reward) can be generalized to any condition susceptible to the placebo effect. For example, following expectation of caffeine ingestion

changes in the brain dopaminergic system, as assessed with PET and [11C]raclopride binding, were observed in the thalamus and putamen of habitual coffee drinkers [42].

DOPAMINE AND NEURONAL FIRING CHANGES UNDER PLACEBO SUGGESTIONS IN PARKINSON'S DISEASE

While for placebo analgesia a complex and varied neurochemical picture has been gradually outlined, the running portrayal of placebo effects in PD is still quite straightforward, involving only dopamine. At the core of PD pathophysiology is the degeneration of the dopaminergic nigro-striatal pathway, with ensuing disruption of its modulation of the striatal motor functions. The pharmacological treatment attempts to restore normal levels of dopamine by the administration of dopamine precursors or agonists. The surgical treatment is represented by deep-brain stimulation (DBS), and it is aimed at restoring normal function in the hyperactive subthalamic nucleus (STN) [43]. A placebo procedure is best carried out by the administration of an inert substance that the patient believes to be an effective anti-Parkinsonian drug, but can also effectively be achieved by the manipulation of DBS electrodes. Outcome measures can include one or more symptoms (bradykinesia and rigidity being the most sensitive), or a complete evaluation of motor performance improvement by the Unified Parkinson's Disease Rating Scale (UPDRS).

The first evidence that endogenous dopamine was released in the striatum after pharmacological placebo administration was produced in a PET study employing the D2-D3 dopamine receptor antagonist [11C]raclopride as a radiotracer. In the simulation of a classic clinical trial, patients in the placebo arm, aware of a 50% chance of receiving apomorphine (a dopamine agonist), exhibited a calculated extracellular dopamine increase of more than 200%, comparable to the response to amphetamine in healthy subjects [44]. This finding was later confirmed by Strafella et al., who evaluated repetitive transcranial magnetic stimulation

(rTMS) as a PD alternative treatment. They reported that the application of sham- (placebo-) rTMS induced changes in striatal [11C]raclopride binding. In this case as well, changes involved both dorsal and ventral striatum, confirming the possible role of reward in the generation of placebo responses [45]. Thus, in PD the same neurotransmitter can mediate both the clinical benefit in a brain region and the more general expectation of the clinical benefit (as seen for placebo analgesia) in another.

DBS has provided a unique opportunity in placebo research, allowing for a privileged window on human neuronal firing activity and the possibility to observe its modification directly, during a placebo procedure. In an initial study, PD patients with implanted electrodes in the STN underwent bradykinesia evaluation with a specifically-designed movement analyzer, while expecting good or bad motor performance. By manipulating the stimulator settings within 20 and 100% of optimal values, and correctly or deceptively informing the patient about the stimulator condition, the experimenters observed better performance (i.e., faster movements) associated with positive expectation, thus validating DBS as an efficient tool to induce immediate motor placebo effects [46]. This knowledge was exploited in a subsequent work, taking advantage of the intraoperative need to ascertain the precise electrode localization by recording STN single-neuron electrical activity during implantation in awake patients. Drawing on the notion that apomorphine induces lowering of the hyperactive STN firing rate [47], Benedetti et al. [48] searched for changes associated to placebo administration (a saline subcutaneous injection believed to be apomorhine) after preoperative conditioning with the same drug. Only those patients showing decreased arm rigidity at the wrist and reporting subjective improvement of well-being (i.e., the placebo-responders) also exhibited decreased firing rate and change from a bursting to a non-bursting pattern of activity. Although not directly demonstrated, it is tempting to speculate that these changes could be brought about by dopamine released in the striatum upon placebo

administration, through disinhibition of the external globus pallidus which negatively modulates STN neurons. Consistent with this hypothesis are also the decrease of the firing rate in the substantia nigra pars reticulata and the increase in the ventral anterior and ventral anterior lateral thalamus recorded in placebo-responders but not in placebo non-responders [49] under the same protocol as in [48].

PLACEBO RESPONSES CAN EMPLOY BRAIN-BODY PATHWAYS

Placebo analgesia and motor functions improvement in PD are examples of placebo responses which are generated in the nervous system and in the nervous system terminate their action, impacting on perception or motor output. Their substrate is represented, as we have seen, by neurotransmitters and neural activity. There are however other placebo responses, which make use of the bi-directional brain-body pathways mediating reciprocal influence through the endocrine, the immune, and the autonomic nervous systems. Here, also hormones and immune factors can play a role, affecting a variety of end organ functioning. Contrary to pain or PD, where expectations are crucial, in the endocrine and immune systems the placebo effect generally takes the form of a conditioned response, as characterized in Pavlovian classical conditioning. A few examples will follow.

Endocrine responses – In healthy volunteers, after repeated administration of sumatriptan, a 5-$HT_{1B/1D}$ receptor agonist which stimulates growth hormone and inhibits cortisol secretion, placebo modulation of these hormones levels could be obtained by a saline solution. Interestingly, this modulation could not be observed in the absence of the conditioning procedure, that is, by the use of verbal suggestions alone inducing expectation of hormone level change. And verbal suggestions going in the direction opposite to the conditioning were similarly ineffective [50]. In Pavlovian conditioning, a conditioned stimulus elicits the effect (the conditioned response) by virtue of its previous coupling with

the unconditioned stimulus, which induces the unconditioned response. Here, the conditioned stimulus is presumably the injection act, or more generally the context surrounding drug (and placebo) administration.

Conditioned responses have been observed in humans also for insulin and blood glucose levels [51] and for dexamethasone and cortisol levels [52].

Immune responses – Similar to endocrine responses, also many immunomodulatory effects can undergo behavioural conditioning and be conceptualized as placebo (or nocebo) effects (for a review, see [53, 54]). For instance, both in multiple sclerosis patients [55] and healthy subjects [56], immunosuppression after placebo could be induced after conditioning with immunosuppressive drugs, possibly by calcineurin inhibition [57]. In an attempt to elucidate the nervous structures involved in central processing of conditioned immunosuppression, Pacheco-López et al. carried out selective excitotoxic lesions of rat brain, highlighting a role for the amygdala and the insular cortex in the acquisition phase, and for the insular cortex and the ventromedial nucleus of the hypothalamus in the evocation phase [58]. All these data should be interpreted in the light of psychoneuroimmunological research, where recent findings have identified neural circuits that operate reflexively, with an afferent branch bringing to the CNS information about injury and infection, and an efferent branch operating through cholinergic and catecholaminergic output in the autonomic nervous system, the most prominent example being perhaps the cholinergic anti-inflammatory pathway. The stress response is also part of this regulation, acting on immune endpoints through the HPA axis [59, 60]. This reflex activity could conceivably be modulated by neocortical activity, and indeed a neocortical-immune axis has been described [61, 62]. A key point for future research is the evaluation of the possible role of cognitive factors, such as expectations and beliefs, in placebo immunological responses so far confined to the unconscious domain.

Autonomic responses – Besides playing a part in the above described hormonal and immunological responses, the autonomic nervous systems also appears to be implicated in other aspects of the placebo response. Autonomic responses can be induced in PD patients by stimulation of the subthalamic region, with ensuing increases in heart rate, blood pressure and respiratory rate [48]. Taking advantage of the open/hidden protocol (whereby no placebo is given, but the context action is inferred from the difference in outcome between the two conditions, i.e., with or without the patient's awareness of the stimulation application), a stronger stimulation had to be applied in order to obtain the same autonomic responses in the hidden with respect to the open condition. Interestingly, this discrepancy was found only in the ventral part of the subthalamic nucleus, which is implicated in associative limbic functions. Thus, this suggests that expectation (the context) might increase the excitability of limbic structures [63]. Many other studies have highlighted placebo effects targeting autonomic functions of the respiratory, gastrointestinal and cardiovascular systems (see ***ref***., this issue).

The examples so far illustrated demonstrate how the context can impact on body performance, affecting perception and movement through CNS circuits and motor nerves, or end organ functioning through autonomic, immune and hormonal loops. In such a comprehensive depiction, encompassing the organism as a whole, it seems rational to wonder whether placebo effects are effective also outside the strictly medical domain, influencing aspects of our life different from recovery from illness.

IN SEARCH FOR EXCELLENCE: HOW TO PERFORM BETTER THAN WE CAN

As for drug development, also in the assessment of efficacy of the many substances revolving around the sport world there is a gray zone where placebos (and nocebos) can exert their influence. Here too, chemicals such as vitamins, ergogenic aids or diet supplements are

handed out, or physical treatments and manipulations of different kinds are delivered, and expectations about their effects are set in motion in the athlete's brain. And here too, care must be taken to distinguish between the psychobiological phenomenon and the overall improvement in the control arm of trials, which in spite of being called "placebo effect" is contaminated and amplified by other factors [8, 9]. Thus, only very recently and only few works have been published, focusing on placebo mechanisms in physical performance.

The role of expectation in physical performance

Attention to improvement in the control group in studies with ergogenic aids was called almost forty years ago, in a paper on the effects of anabolic steroids. Weightlifters receiving a placebo were reported to improve on average about 10% with respect to a baseline condition in different exercise tasks, an increase significantly greater than that recorded in a pre-placebo phase of the study. However, no appropriate natural history group was employed, a bias that prevents real placebo effect assessment [64]. Thirty years later, smaller but better controlled placebo effects were again obtained by deceptive administration of a placebo believed to be a fast-acting anabolic steroid in competing weightlifters. After baseline measurements, all subjects received the presumed steroid (actually a placebo), and performed significantly better in a first evaluation trial, with average values around 4%. A few days later, after reporting improvements in the ongoing training performance, they underwent a second evaluation trial, during which the real protocol was disclosed to a subset of participants. While the deceived athletes maintained their improved maximal weight lifted, in those informed of the deception the performance fell back to around the baseline levels [65]. This return to baseline highlights the role of expectation as the main factor involved in the improvement, pointing to the presence of cognitive mechanisms in the generation of the placebo effect. Similar results with an almost identical protocol including a control group

and follow-up interviews to chart subjects expectations were obtained in a bigger trial on college students [66].

An experimental design which is well-suited to study placebo effects in the laboratory setting is the balanced placebo design (also known as Latin square design). It includes two conditions, in which active treatment or placebo are delivered. Each condition is further subdivided according to what participating subjects are told about the treatment they receive (again, active treatment or placebo). Thus, a two-by-two matrix is generated, allowing the estimate of natural history (told placebo, get placebo) and placebo effects (told active treatment, get placebo) on the one hand, and treatment effect in isolation (told placebo, get active treatment) or treatment plus placebo effects (told active treatment, get active treatment) on the other [67]. By applying this design to the evaluation of carbohydrate supplementation in an endurance cycling performance, Clark et al. [68] reported a net measurable placebo effect of 3.8% enhancement of mean power output over baseline. However, while no significant isolated effect of carbohydrate supplementation was found, little or no increase in mean power output was detected also in the told carbohydrate/get carbohydrate group, which would have been expected to yield a placebo component. Interestingly, in this study also a "not told" group was included, in which the subjects knew that they had a 50% chance of receiving carbohydrate or placebo. In this group also, no improvement was observed, irrespective of the treatment received. This could be interpreted as a strong influence of uncertainty in weakening the subject's expectations, although it must be noted that in other contexts an intermediate effect was found for similar levels of uncertainty [69, 70]. Another way of modulating the subject expectation is by suggesting a variable strength of the placebo. For example, in a double-blind administration of placebo caffeine to competitive cyclists, Beedie et al. [71] instructed the subjects that over three experimental trials they would be given placebo or two different doses of caffeine, and subsequently questioned them about

their beliefs and expectation in each trial. They reported a dose-response relationship, with graded improvements of mean power output ranging from -1.4% with respect to baseline for the 10-km run believed to be the placebo trial, to 1.3 and 3.1% in the runs believed to be the moderate- and high-dose caffeine trials, respectively.

Specifically addressing the relative contribution of expectations and sodium bicarbonate (known to improve performance during short-term maximal exercise, by delaying the onset of metabolic acidosis [72]), McClung et al [73] again used the Latin square design in trained endurance athletes. In a within-subject protocol, each subject run one 1000-m time trial per condition, in random order. Time and rate of perceived exertion (RPE) were recorded. Subsequent ANOVA for both performance and perceptions yielded a significant main effect for Told, but not for Given or for the interaction Told x Given, suggesting that what made the difference was the subject's expectation, while the improvement observed when expecting the drug without receiving it was not much different than that observed when receiving the drug without knowing it. A similar design was applied to the study of caffeine ingestion on power output during endurance cycling, with somewhat different results [74]. Here, the improvement after placebo (i.e., told caffeine/given placebo) was not significant with respect to baseline, but it was significant with respect to the told placebo/given placebo condition, where in fact performance worsening was observed. Also, in a subsequent paper the same authors suggested that the majority of participants in that study were placebo non-responders, on the basis of the individual performance evaluated against a quantitative model for placebo responsiveness. The performance of the few selected placebo-responders produced in fact a robust placebo effect [75].

When expectations about a forthcoming event are negative, what ensues is a nocebo effect [34]. Thus, if an athlete holds a negative belief about the ergogenic aid just received, the following performance might as well drop below baseline levels. Evaluating precisely this

effect of contrasting expectations, Beedie et al [76] had two groups of sport athletes repeatedly perform 30-m sprints, under opposite suggestions. After three baseline sprints showing a progressively diminishing speed, a placebo was given and three more sprints were again carried out. While the positive belief group displayed increasing speed, thus reversing the negative trend, the negative belief group continued to perform ever worse.

In spite of very different experimental conditions, ranging from short anaerobic sprints to long aerobic endurance cycling, and across many different outcome measures, such as mean power output, time, speed, weight lifted, or RPE, all the above described data strongly indicate context factors and athletes expectations as important factors in physical performance, to be taken into account in training strategies.

Pre-conditioning adds to expectation: could it be doping?

One question which might be relevant to the development of training strategies incorporating knowledge of placebo research is whether pharmacological or non-pharmacological conditioning is effective in shaping the placebo response in the sport context, acting like classical conditioning and/or reinforcing conscious expectations. In a laboratory simulation of a team competition [77], four groups of volunteers had to compete against one another in a test of pain endurance, whereby arm ischemic pain was induced by means of the submaximal effort tourniquet technique [13]. After baseline evaluation, each team underwent a different "training program", with two sessions prior to the "competition day": team A and B without any treatment, team C and D with morphine preconditioning, i.e., with the administration of morphine accompanied by the suggestion of increased pain endurance. On the competition day, team A received no treatment (natural history), team B and C received a placebo with the instruction that it was again morphine, team D the same placebo plus naloxone. Both team B and C performed significantly better on the competition day than in control conditions, but team C did significantly better than team B. The

pharmacological preconditioning added on to the verbally-induced expectation, providing team C with the winning edge. It must be considered that morphine is a drug prohibited by the World Anti-Doping Agency during competition, but not in training, and that team D performed as poorly as team A, indicating that naloxone blocked the effect of endogenously released opioids. Should these opioids be considered illegal? Should more drugs be banned also during training?

Similar results, that is additive effects of expectation and conditioning, were obtained also by applying a non-pharmacological conditioning procedure [78], without administering any drug. Studying the effect of placebo caffeine on the quadriceps muscle work and fatigue during volitional maximal exercise, Pollo et al. [79] applied a surreptitious reduction of the load to lift, in order to reinforce by personal testing the verbal suggestion given about the facilitatory effects of caffeine on muscle performance. In the subsequent evaluation phase, while muscle work, but not fatigue, increased after suggestion, both objective and subjective parameters increased with more robust effects when the preconditioning procedure was associated. Clearly, learning underpins all these responses, but it is unclear whether it takes the form of classical conditioning or only that of conscious reinforcement of expectation [80]. Future studies should try to implement new training strategies, addressing the issue of the legal vs. illegal exploitation of psychological mechanisms in sport competition.

The central governor of fatigue

Contrary to other areas of placebo research, in physical performance knowledge about underlying mechanisms is still scant. Apart from a role for endogenous opioids in placebo pain endurance [77] and a conceivable role of the general dopamine reward mechanism (see above), not much is known at present. In many of the above reported studies, athletes were asked to perform at their limit, in an all-out effort. Placebos apparently acted by pushing this limit forward. It can be speculated that they could impact on a central governor of fatigue,

which although not identified, has been proposed as a brain centre integrating peripheral signals (such as heart and respiratory rate, lactate, carbohydrate availability and mechanical strain) and central control processes, so as to continuously regulate exercise performance avoiding to reach maximal physiological capacity. This would provide protection against damage on one side, and constant availability of a reserve capacity on the other [81, 82]. By altering expectations, placebos could then represent a psychological means to signal the central governor to release the brake, allowing an increase in performance in a manner not dissimilar from that achieved by pharmacological means (for example, by amphetamines decreasing perceived fatigue). While this awaits experimental evidence, it is intriguing to consider that it could represent but another example of the way the context can act on the same membrane receptors targeted by drugs and neurotransmitters [4].

CONCLUSIONS

We are witnessing an epochal passage, when purely theoretical entities like "suggestibility" and "power of the mind" are finally being replaced by biological accuracy and molecular certainty, with rituals and context interpreted in terms of specific brain regions and biochemical pathways activated. The capacity of the mind to affect the body can now become visible and mechanistically understandable in circuits of the prefrontal cortex calling into action the endogenous antinociceptive system, or in the subthalamic nucleus shifting its firing properties, resulting in changes in perception or movement in response to a placebo.

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