Incorporating methods and findings from neuroscience to better understand placebo and nocebo effects in sport

Christopher Beedie[1,2], Fabrizio Benedetti[3,4], Diletta Barbiani[4], Eleanora Camerone[5], Jacob Lindheimer[6,7], Bart Roelands[8]

[1]School of Psychology, University of Kent, Canterbury, UK

[2]CHX Performance, London, UK

[3]Medicine and Physiology of Hypoxia, Plateau Rosà, Italy/Switzerland

[4]University of Turin Medical School, Neuroscience Dept, Turin, Italy

[5]Department of Neuroscience, University of Genoa, Italy

[6]Department of Veterans Affairs, William S. Middleton Veterans Memorial Hospital, Madison, WI, USA*

[7]Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, USA

[8]Department of Human Physiology, Vije Universiteit Brussels, Belgium

Corresponding author. Professor Chris Beedie, School of Psychology, University of Kent, Canterbury, UK. Email christopher.j.beedie@gmail.com

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ABSTRACT

Placebo and nocebo effects are a factor in sports performance. However, the majority of published studies in sport science are descriptive and speculative regarding mechanisms. It is therefore not unreasonable for the sceptic to argue that placebo and nocebo effects in sport are illusory, and might be better explained by variations in phenomena such as motivation. It is likely that, in sport at least, placebo and nocebo effects will remain in this empirical grey area until researchers provide stronger mechanistic evidence. Recent research in neuroscience has identified a number of consistent, discrete and interacting neurobiological and physiological pathways associated with placebo and nocebo effects, with many studies reporting data of potential interest to sport scientists, for example relating to pain, fatigue and motor control. Findings suggest that placebos and nocebos result in activity of the opioid, endocannabinoid and dopamine neurotransmitter systems, brain regions including the motor cortex and striatum, and measureable effects on the autonomic nervous system. Many studies have demonstrated that placebo and nocebo effects associated with a treatment, for example an inert treatment presented as an analgesic or stimulant, exhibit mechanisms similar or identical to the verum or true treatment. Such findings suggest the possibility of a wide range of distinct placebo and nocebo mechanisms that might influence sports performance. In the present paper we present some of the findings

from neuroscience. Focussing on fatigue as an outcome and caffeine as vehicle, we propose three approaches that researchers in sport might incorporate in their studies in order to better elucidate mechanisms of placebo/nocebo effects on performance.

Key words

Neurobiology; nocebo effects, fatigue, caffeine, research methods, experimental design

1. INTRODUCTION

Placebo and nocebo effects have been demonstrated in sports performance research (Beedie & Foad, 2009; Hurst et al., 2019). However, whilst much work in sport describes positive and negative effects on performance following the administration of a placebo or nocebo treatment respectively, such studies, especially those that report few directly measured variables, leave the door open for numerous alternative explanations. For example, what was reported as a placebo effect was simply the result of the participants having adopted a less conservative and more optimal pacing strategy following the administration of what they believed was an active treatment. In this context, most research designs do not allow the authors to reliably exclude such possibilities. Whilst the findings of many placebo and nocebo studies are intuitively compelling and resonate with the experience of many athletes, coaches and sports scientists, it is easy to offer alternative explanations.

Previous research on placebo and nocebo effects in sport has reported variation in the magnitude of outcome measures when researchers manipulated the 'dose' of placebo (Beedie, Stuart, Coleman, & Foad, 2006) and the direction (positive and negative) of the information presented with the placebo treatment (Beedie, Coleman, & Foad, 2007). Whilst such findings suggest that the treatment caused the effects observed, they do not however reveal the physiological and/or neurobiological processes that underlie these effects. Recent research in neuroscience has identified consistent neurobiological mechanisms associated with placebo and nocebo effects, many in relation to sport phenomena such as pain, fatigue and motor control. In this paper we report some of these findings, and whilst we do not infer that these effects – often reported in contexts very different to sport - stand as evidence for the placebo and nocebo effects in sport *per se*, we believe that they should at the very least encourage researchers in sport to adopt more robust research designs.

We will not provide a comprehensive review of placebo effects in sport or in neuroscience; the former can be found elsewhere (Hurst et al., 2019), the latter in numerous sources (Benedetti, 2013; Benedetti & Dogue, 2015; Tracey, 2010; Wager & Atlas, 2015). Neither will we evaluate the findings of the small number of papers described. However, we will highlight the potential usefulness of the respective methodologies of these papers to sports scientists. In this context, we aim to present sufficient evidence and methodological suggestions to encourage sports scientists to consider placebo and nocebo effects, as well as associated mechanisms, in their research.

2. HOW AND WHY ARE PLACEBO AND NOCEBO EFFECTS RELEVANT TO SPORTS PERFORMANCE?

In the context of placebos and nocebos, there is some confusion between the terms 'response' and 'effect'. A recent consensus statement (Evers et al., 2018) defined placebo and nocebo responses as all health changes that result after administration of an inactive treatment, including those that may occur from natural history and regression to the mean. These responses are commonly observed in the control arm of clinical trials. On the other hand, placebo and nocebo effects were defined as the changes specifically attributable to the

administration of an inert treatment, and therefore to placebo and nocebo mechanisms, including the neurobiological and psychological mechanisms of expectancies. These definitions were adapted to sport in a recent consensus statement, in which placebo and nocebo effects were defined as a desirable or undesirable outcome resulting from a person's expected and/or learned response to a treatment or situation (Beedie et al., 2018).

Placebo effects appear to enhance sports performance. A recent systematic review identified 34 studies of the placebo and/or nocebo effect in sport involving 1,555 participants (Hurst et al., 2019). It reported small to moderate placebo effects for nutritional (d = 0.35) and mechanical (d = 0.47) ergogenic aids. Larger placebo effects were found when participants were led to believe they were given banned performance enhancing ergogenic aids (anabolic steroids d = 1.44; EPO, d = 0.87), whilst moderate effects were found in studies investigating placebo effects of caffeine (d = 0.40) and amino acids (d = 0.36).

Nocebo effects appear to inhibit sports performance. Five studies have explicitly examined the nocebo effect on sports performance, that is an explicit negative expectancy protocol was used (Andani, Tinazzi, Corsi, & Fiorio, 2015; Beedie et al., 2007; Bottoms, Buscombe, & Nicholettos, 2014; Hurst, Foad, Coleman, & Beedie, 2017; Pollo, Carlino, Vase, & Benedetti, 2012). A recent systematic review estimated the overall effect size associated with these studies as d = 0.37 (Hurst et al., 2019). Nocebo effects on sports performance can also be inferred in data from several more studies, in which athletes appeared to set up their own negative expectations (Beedie et al., 2006; Foad, Beedie, & Coleman, 2008). These data collectively suggest that negative expectations can adversely affect sports performance.

Placebo effects might augment effects of real treatments. It has been demonstrated that both active/biological and placebo/psychological factors interact to contribute to the overall effect of legitimate treatments, for example caffeine (Foad et al., 2008). It has also been demonstrated that treatments administered without the knowledge of the patient, in which case zero expectation of benefit would theoretically exclude the possibility of a placebo component of the treatment, are less effective that those administered with patient knowledge (Benedetti, 2013). Placebo effects therefore appear to augment the biological effects of treatments. A placebo effect can be experienced in response to a placebo treatment and in response to a real treatment (Beedie et al., 2017).

Placebo effects might help explain variability in response to real treatments. There is much interest currently in variability in response to sports treatments (Atkinson, Williamson, & Batterham, 2019). Experimental evidence indicates that inter-individual variation in performance following the administration of a placebo treatment is greater than at baseline, which in turn suggests that not all people respond in the same way to a placebo (Beedie & Foad, 2009). Given that placebo effects interact with biological effects to determine overall treatment effect, variation in placebo responsiveness might be a factor in determining variability to real treatments. In short, variability to a treatment could be a function of i) the individual response to the biologically active component of the treatment only, ii) the individual response to the placebo component of the treatment only, or iii) the individual response to both the biological and placebo component. This has

implications in both research and applied contexts (Beedie et al., 2018; Lindheimer, Szabó, Raglin, & Beedie, 2019).

Placebo effects might help us better understand the mind and performances of athletes. Over the last 20 years, there has been growing interest among sports physiologists in the brain. This is evident in empirical advances regarding the role of neurotransmitter systems in sports (Meeusen & Roelands, 2018), and of mental fatigue in physical performance (Van Cutsem et al., 2017), conceptual advances such as the central governor (St Clair Gibson, Swart, & Tucker, 2018), and potential applications of brain manipulation in performance (Angius, Hopker, & Mauger, 2017). Arguably such data brings sports physiology and sports psychology ever closer. In this context, the placebo effect represents a useful vehicle for interdisciplinary research. Recent examples include potential mechanistic overlap between placebo effects and sports psychological variables (Beedie, Foad, & Hurst, 2015; Szabó, Lindheimer, Raglin, & Beedie, In Press), and between placebo effects and social facilitation effects (Davis, Hettinga, & Beedie, 2019).

3. EVIDENCE FOR NEUROBIOLOGICAL AND PHYSIOLOGICAL MECHANISMS OF PLACEBO & NOCEBO EFFECTS

Placebo effects are evident in neurobiological pathways. Neurobiological mechanisms of placebo effects have been recognised for over 40 years (Levine, Gordon, & Fields, 1978). Placebo and nocebo effects are underpinned by numerous neurobiological pathways, therefore whilst common brain processes are implicated in many studies, the idea that there is a single overarching placebo and/or nocebo mechanism is not supported (Geuter, Koban, & Wager, 2017). Numerous neurotransmitter systems are in fact involved, with the four most documented candidates being the opioid, endocannabinoid, serotonin and dopamine systems (Colagiuri, Schenk, Kessler, Dorsey, & Colloca, 2015). The endogenous opioids (endorphins) are arguably the most researched neurotransmitter in this context, and are implicated in pain mechanisms (Amanzio & Benedetti, 1999) and respiratory depression (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 2008)[1]. The endocannabinoid system appears to play a pivotal role in placebo analgesia when the opioid system is not involved (Benedetti, Amanzio, Rosato, & Blanchard, 2011). The serotonin system has been cautiously implicated to play a role in placebo effects on anxiety (Benedetti, Carlino, & Pollo, 2011) and depression (Colagiuri et al., 2015). Dopamine has been examined, perhaps most notably in the context of Parkinson's Disease (de la Fuente-Fernández et al., 2001), but also in the context of motivation (Scott et al., 2008). Representations of future events are an important component of placebo effects, and dopamine is implicated in many future-focussed mental processes (Previc, 2009), including expectation (Enck, Benedetti, & Schedlowski, 2008).

Placebo effect pathways mimic drug pathways. In what is considered the first mechanistic study of the placebo effect (Levine et al., 1978), pain reduction resulting from administration of a placebo analgesic was blocked by the administration the opiate antagonist naloxone. The authors concluded that the placebo and real

[1] Whilst the potential for neurobiological processes to modulate pain is intuitively logical to many in sport, the effects on respiratory depression of the endogenous opioids, for a long time associated with the 'runner's high' (Boecker et al., 2008) is less intuitive. However, given that many neuroscience studies have demonstrated that placebo opioid drugs mimic the effects and pathways of real opioid drugs (Benedetti, Pollo, & Colloca, 2007), this not only makes sense, but has implications for performance in hypoxia.

effects of the analgesic operated, at least in part, via the same neurotransmitter system. Data has since demonstrated that not only do different placebo treatments appear to activate different pathways in different contexts (Benedetti & Dogue, 2015), but that the placebo treatment often activates the same pathway as the drug that it purports to be. For example, placebo effects following conditioning with opioids activate endogenous opioid pathways (Benedetti, Pollo, et al., 2007) whilst placebo effects following conditioning with non-steroidal anti-inflammatory drugs activate endocannabinoid pathways (Benedetti, Amanzio, et al., 2011).

Expectation and conditioning result in different placebo pathways. The majority of placebo effect research published in sport has used an expectancy design (expectancy is a conscious cognitive process often resulting from verbal instruction). In this design, participants naïve to a treatment, or who have been asked to cease use of that treatment ahead of and during that study, are administered a placebo with the associated verbal expectation that it is the real treatment. This design contrasts with those reported in many studies of placebo effects elsewhere that have used a conditioning paradigm. Conditioning can be either conscious or unconscious learning resulting from the repeated pairing of a stimulus treatment and a response. Interestingly, each method, expectancy and conditioning, might activate different neurobiological pathways. For example, in a study of both conditioning and expectancy, expectation of analgesia resulted in placebo responses that were completely blocked by the opioid antagonist naloxone, and expectation cues together with morphine conditioning also produced placebo responses that were completely blocked by naloxone, as did morphine conditioning alone (Amanzio & Benedetti, 1999). However, placebo analgesia following conditioning with ketorolac together with expectation cues elicited a placebo effect that was only partially blocked by naloxone, and ketorolac conditioning alone produced placebo responses that were entirely naloxone-insensitive (Amanzio & Benedetti, 1999).

Nocebo effects inhibit pathways activated by placebo effects. Nocebo effects, like placebo effects, are underpinned by numerous discrete neurobiological pathways (Tracey, 2010). Expectation of pain has been found to induce nocebo effects observed in the endogenous opioidergic system (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006) and the dopaminergic system (Scott et al., 2008). These nocebo effects involved opposite responses in neurotransmitter systems to responses observed with placebo effects; that is, deactivation of the opioid and dopamine systems. Nocebo effects are also observed in relation to emotional responses such as anxiety; negative verbal suggestions induce anticipatory anxiety, which is associated with the activation of cholecystokinin (CCK) which in turn, facilitates pain transmission (Benedetti, Lanotte, Lopiano, & Colloca, 2007). The implications of nocebo effects can be significant and long-lasting, with some studies reporting that just one experience of a nocebo effect can influence the efficacy of future treatments (Colloca & Miller, 2011).

Placebo effects regulate emotion. Anxiety is a critical factor in sports performance. In fact a wide range of emotion responses are significant in this context (Beedie, Terry, & Lane, 2000; McCarthy, 2011; Robazza, Pellizzari, & Hanin, 2004). Like emotions, placebo effects can be considered a regulator of the relationship between organism and environment. Placebo effects and emotion also influence one another. Lieberman

(2006) proposed that placebo effects, which are *unintentional,* are one of a broad range of otherwise largely *intentional* self-regulatory processes such as emotion regulation and self-control, all sharing common brain mechanisms. Ashar, Chang, and Wager (2017) extended this reasoning and proposed that the appraisals that result in placebo effects also engage the default mode network (Raichle, 2015). This network is responsible for numerous self-regulatory processes, including emotion, memory and prospection (i.e., thinking about future outcomes; prospection has an intuitive role in placebo and nocebo responses). Ashar et al. proposed that conceptual representations of future events influence decision making and the subsequent emotional value of these representations. These future-focussed emotional responses themselves elicit broad and organism-wide physiological changes in the autonomic nervous (ANS) and endocrine systems.

Placebo effects influence ANS physiology. Geuter et al. (2017) proposed three placebo-responsive descending modulatory systems influencing pain, ANS function and immune responses respectively. Of these, the modulation of ANS activity is perhaps most relevant to sport; many athletes are aware of how their *perception* of the environment modulates ANS physiology. Pre-competition anxiety, arguably a future focussed cognitive appraisal, directly modifies variables such as heart rate (HR), respiration rate, muscle tension, blood pressure (BP), and heart rate variability (HRV). Consistent with this idea, placebo effects on ANS function have been reported on HR, ventilation, BP, coronary diameter, and lung function (Meissner, 2011, 2014). We will describe recent research in physical performance and fatigue that reports such effects in more detail in section 5. (Benedetti, Barbiani, & Camerone, 2018).

4. USING RESEARCH FROM NEUROSCIENCE AS A MODEL FOR THE STUDY OF PLACEBO EFFECTS IN SPORT

In each of sections 5., 6., and 7. below, we describe one or more previously published research study from the neuroscience literature, and then offer an experimental design based on that study that could be used in sport. In doing so we suggest designs that assess performance, especially placebo-induced reduction in fatigue, and which might use caffeine as the placebo treatment.

Fatigue as a common currency in placebo effect research. Whilst direct effects of placebo administration on fatigue have been reported in relatively few studies (Benedetti, Durando, Giudetti, Pampallona, & Vighetti, 2015; Piedimonte, Benedetti, & Carlino, 2015; Pollo, Carlino, & Benedetti, 2008), a placebo-induced reduction in fatigue can be inferred from most studies of placebo effects in sport. In this context it can be proposed that fatigue is a common currency across placebo effect research in sport. It is however a complex phenomenon, with objective and subjective components (Völker, Kirchner, & Bock, 2016), and central/brain (Meeusen & Roelands, 2018) and peripheral/body components (Kirkendall, 1990). Whilst we recognise that the dichotomies are biologically and conceptually problematic (Enoka & Duchateau, 2016; St Clair Gibson et al., 2018), and whilst objective markers of fatigue observed in directly measured performance in some studies might be considered the gold standard, it has been demonstrated that subjective measures of fatigue (often used in placebo effects research) are also a reliable index (Micklewright, St Clair Gibson, Gladwell, & Al Salman, 2017).

Each of the neurotransmitter systems identified in the previous paragraph may play a role in fatigue. Whilst a link between pain and fatigue is intuitive (Mauger, 2013) thereby implicating the opioid and endocannabinoid systems, the serotonin system has been most consistently linked with fatigue in sport (Davis, Alderson, & Welsh, 2000; Davis & Bailey, 1997; Meeusen & Roelands, 2018; Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2007; Roelands & Meeusen, 2010). A role for dopamine has also emerged, although this role is far from clear; while the capacity of dopamine to exert ergogenic effects and override inhibitory signals from the central nervous system is recognised (Meeusen & Roelands, 2010), it is not entirely clear why this effect is more evident at high temperatures. However there are many mechanisms by which dopamine could impact on fatigue: improved muscle activation via increased arousal, motivation and coordination (Abbiss & Laursen, 2005), enhanced information processing (Gibson et al., 2003), efficient thermoregulation (Meeusen & Roelands, 2018), increased glucose availability (Haltia Lauri et al., 2007), and enhanced reward processing (Pollo, Carlino, & Benedetti, 2011). Conversely, a reduction of dopamine could impair activation of the basal ganglia and reduce stimulation of the motor cortex leading to central fatigue (Foley & Fleshner, 2008), as well as disruption of sensory inputs (Millet, 2011). Recently a role for histamine in both physical and cognitive fatigue has also been demonstrated (Loy & O'Connor, 2016).

Caffeine as a useful model for placebo effect research in sport. Caffeine reduces fatigue in sport (Grgic et al., 2019). On this basis, caffeine has been widely studied by sport scientists, with 21 meta-analyses published to date (Grgic et al., 2019). The effects of caffeine are consistent with a neural as well as a metabolic explanation (Meeusen, Roelands, & Spriet, 2013). Caffeine is an adenosine receptor antagonist. Adenosine, a product of the breakdown of adenosine triphosphate, in turn has an antagonistic interaction with dopamine (Wisor, 2018). Therefore caffeine enhances dopamine signalling by antagonizing adenosine receptors (Volkow et al., 2015).

The placebo effects of caffeine on sports performance have likewise been widely reported (Beedie, 2010; Beedie & Foad, 2009; Beedie et al., 2006; Duncan, 2010; Foad et al., 2008; Pollo et al., 2008). Further, the relative 'real' and placebo contribution to the effects of caffeine on performance have been elucidated using the balanced placebo design (Foad et al., 2008). A number of brain processes might be implicated in the placebo response to caffeine, but given evidence that placebo pathways might mimic those of the verum or true treatment (Benedetti, Amanzio, et al., 2011; Benedetti & Dogue, 2015; Levine et al., 1978), we might expect the same pathways activated by real caffeine to be activated by the administration of placebo caffeine, adenosine and dopamine.

5. PHYSIOLOGICAL RESPONSES TO A PLACEBO.

5.1 An example of previous neuroscience research. Whilst much research in sport describes positive effects on performance following a placebo treatment, most studies do not identify mechanisms. We may for example be

confident given research findings that placebo caffeine might result in a 1-3% increase in endurance performance (Beedie & Foad, 2009; Hurst et al., 2019), but unsure as to precisely what physiological changes have facilitated that effect. Benedetti and co-workers (Benedetti et al., 2018) reported a series of studies investigating the effects of placebo oxygen (O_2) on cardiorespiratory, subjective and performance variables at high altitude. Assessing the effects of positive verbal suggestion (expectation) and conditioning, they reported placebo effects on a range of cardiovascular and performance variables. These findings are consistent with a proposed modulatory role for the brain in hypoxic conditions (Siebenmann et al., 2011). Illustrative of the research designs used was a 2015 study (Benedetti et al., 2015). In this study, 35 healthy participants were randomly subdivided into 5 groups prior to completing four performance trials of 3000 steps at a pace of 2 steps per second, T1 (baseline) at sea level and T2-T4 at 3,500m altitude. Groups were:

A. No-treatment (NT): Received NT in T1-T4
B. Oxygen: Received NT in T1-T3 and 100% O2 (7 L/min) in T4. Participants informed they would receive either real or placebo O2 double-blind. Assesses the effects of real O_2;
C. Placebo: Received NT in T1-T3 and placebo O2 in T4. The same double-blind paradigm was used. Assesses the effects of placebo O2;
D. O2 Conditioning: Received NT in T1, 100% O2 in T2 and T3, and placebo O2 in T4. Assesses a role for conditioning in placebo effects;
E. Conditioning Control: Received NT in T1, 100% O2 in T2 and T3, and NT in T4. Assesses any carryover effect of conditioning in the absence of a placebo O2 treatment.

Direct measures were HR and oxygen saturation (SO_2). Subjective fatigue was assessed every 8 minutes and at the end of the task on a 0-10 scale, as was high altitude headache pain. A saliva sample (1 mL) was taken before and following exercise for prostaglandin (PGE2) measurement. Subjects breathed through a mask connected to an O2 canister that, in turn, was connected to a larger O2 supply. Room temperature was 18°C. The authors reported no change in SO2 following administration of placebo O2, indicating that placebo O2 did not affect oxygenation. However, a similar hypoventilation effect to that reported by (Benedetti et al., 2008) was elicited by a placebo after O2 pre-conditioning, suggesting that the compensatory hyperventilation of high altitude that is inhibited by O2 was also inhibited by placebo O2. The effect was not limited to ventilation itself, but extended to blood pH; hyperventilation at high altitude is accompanied by an increase in pH (alkalosis), with O2 reducing both hyperventilation and pH. Placebo O2 after O2 pre-conditioning produced the same effect. Regarding circulation, Benedetti et al. reported that similar bradycardic effects as those reported by (Pollo, Vighetti, Rainero, & Benedetti, 2003) were elicited by a placebo O2 following O2 pre-conditioning. In short, the inhibition of compensatory tachycardia by O2 was mimicked by placebo O2. This was also the case with perfusion, where the typical PGE2 increase at high altitude that is blocked by O2 was also blocked by placebo O2. The authors indicated that on the basis that SO2 increased after O2 administration, but not after placebo administration, these effects were not due to SO2, but to a SO2-independent learning mechanism. Beyond directly measured physiological responses, Benedetti et al. also reported that placebo O2 reduced high

altitude headache, suggesting that in the same way as PGE2 can be considered an indirect measure of cerebral vasodilation, so headache can be considered the clinical expression of cerebral vasodilation. Placebos only reduced headache after O2 pre-conditioning, thus supporting the findings for PGE2.

Most saliently perhaps in the context of the present paper, placebo effects on fatigue did not require O2 pre-conditioning (Benedetti et al., 2018). Whilst total performance time increased from sea level to high altitude, it returned to that of sea level following both O2 and placebo O2 treatments. In other words, a placebo given for the first time along with positive verbal suggestions of fatigue reduction and performance improvement, was sufficient to reduce fatigue. The effect of placebo alone, without any O2 pre-conditioning, was so powerful that it was also present with an O2 reduction of 50% compared to sea level.

How might we study physiological effects of placebos in sport? Unlike much placebo effect research in sport, Benedetti et al. (2015) identified physiological processes hypothetically directly influenced by the administration of a placebo, and in two conditions, conditioning and expectancy. They reported discrete effects of each. Using Benedetti et al.'s study as a model, and hypothesising that placebo mechanisms mimic real mechanisms, in this case significant increases in HR, blood lactate, and blood glucose but no changes in O2 uptake, respiratory exchange ratio or RPE[2] (Glaister, 2018), we might undertake a study of the placebo effects of caffeine by measuring these variables in the below design:

A. No-treatment (NT): Receives NT in T1-T4
B. Caffeine: Received NT in T1-T3. Receives caffeine in T4. Assesses effects of caffeine;
C. Placebo: Received NT in T1-T3. Receives placebo caffeine T4. Assesses effects of placebo caffeine;
D. Conditioning: Receives NT in T1, caffeine in T2 and T3, and placebo caffeine in T4. Assesses a role for conditioning in placebo effects;
E. Conditioning Control: Receives NT in T1, caffeine in T2 and T3, and NT in T4. Assess any residual effect of caffeine conditioning.

It is important that the study is sufficiently powered to identify the variables that did and did not change in response to a placebo treatment, which has arguably not been the case in many placebo effect studies in sport. Further, in light of recent interest in understanding how variability in placebo responses can be explained by genetics (Hall, Loscalzo, & Kaptchuk, 2015), investigators might also consider genotyping participants for the Adenosine A_{2A} receptor subtype, as preliminary evidence suggests that the ergogenic effects of caffeine are greater for homozygous carriers of the T allele (Loy, O'Connor, Lindheimer, & Covert, 2015). It would be interesting to observe any relationship with responses to placebo caffeine in this context.

6. NEUROBIOLOGICAL RESPONSES TO A PLACEBO

[2] We recognize that RPE responses vary, caffeine/placebo caffeine might produce a reduction in RPE at the same power output or no change in RPE at increased power output.

An example of previous neuroscience research. The first neuroscience study of placebo effects used pharmacological blockade to demonstrate a neurotransmitters system involved in placebo analgesia (Levine et al., 1978). Geuter at al. (2017) indicated that the identification of neurobiological pathways and structures involved in the placebo effect in one setting, for example pain, and speculating that these same processes might at least partially explain placebo responses in another, is a legitimate approach, certainly in the absence of any conflicting evidence. On this basis, we propose that it is likewise legitimate to propose several neurobiological processes of placebo effects evident in the neurobiology literature, align these with neurobiological mechanisms related to fatigue in sport, and argue that they might contribute significantly to placebo effects in fatigue.

A model for this type of research can be found in a study of conditioned and expectation responses to real and placebo morphine in hand-grip muscle performance (Benedetti, Pollo, et al., 2007). Participants were randomly allocated to one of four groups: During a two week training phase, Groups A and B were given no morphine, whilst Groups C and D received intramuscular morphine one hour before each training session at a dose of 0.14 mg/kg. Groups C and D were also informed that an increase in pain tolerance was expected. In the training trials, ischemic arm pain was experimentally induced via a tourniquet technique in concert with a hand grip task. The authors argued that this type of ischemic pain increases over time very quickly, and the pain becomes unbearable after around 14 min. Following the training phase, and on what was termed to 'competition day', treatments administered to participants were as follows:

A. NT during training phase: no-treatment (NT) on competition day. Assessed natural history;
B. NT during training phase: Placebo saline solution via intramuscular injection plus verbal suggestion of morphine on competition day. Assessed effects of expectancy;
C. Morphine 0.14 mg/kg via intramuscular injection during training phase: Placebo saline solution via intramuscular injection plus verbal suggestion of morphine on competition day. Assessed effects of conditioning;
D. Morphine 0.14 mg/kg via intramuscular injection during training phase: Opiate antagonist naloxone by injection on competition day plus verbal suggestion of morphine. Assessed opioid mechanisms of placebo effects.

Benedetti, Pollo, et al. (2007) reported that mean pain tolerance on the 'competition day' for C was 20.8 minutes versus 16.7 for B, 15.7 for A, and 15.4 min for D. Placebo administration resulted in increased pain tolerance in B and C, but this effect was greater in C who had received morphine pre-conditioning than B who had received expectancy only. The conditioned placebo effect observed in C was inhibited by the administration of naloxone in D, indicating the activation of endogenous opioids after placebo administration. Tolerance times returned to pre-competition baseline in all cases at follow-up.

In this study, not only were placebo effects on performance observed, which of course is not unusual, but these effects were inhibited by blockade of the hypothesised placebo mechanism, in this case the endogenous opioid system. This inhibition was precognitive, that is it was not a conscious reduction in motivation or fatigue tolerance on the part of the participants, because those participants were not aware that they had been administered naloxone[3]. The study addresses a muscle task at the interface of pain and fatigue (the overlap between the two, whilst neurobiologically distinct, is perhaps semantically and experientially less so (Mauger, 2013).

How might we study neurobiological mechanisms of placebo effects in sport? Several neurotransmitter systems implicated in placebo are also associated with fatigue in sport. Hypothetically therefore, one or more of these might present a vehicle for blockade studies. We have highlighted the effects of caffeine on adenosine and dopamine; the effects of placebo caffeine have been observed on dopamine pathways of the thalamus (Kaasinen, Aalto, Någren, & Rinne Juha, 2004) and the striatum (Kaasinen, Aalto, Nagren, & Rinne, 2004). Theoretically therefore, positive effects on performance resulting from dopamine signalling following placebo caffeine administration could be blocked by use of a dopamine antagonist. A design in which to investigate the effects of placebo caffeine on fatigue might adopt one similar to (Benedetti, Pollo, et al., 2007), using the same 'training phase' and 'competition day' model as did those authors:

1. Control condition: NT during training phase; NT on competition day. Assesses natural history;
2. Expectancy condition: NT during training phase; placebo with verbal suggestion of caffeine on competition day. Assesses expectancy;
3. Conditioning condition: Caffeine during training phase; placebo with verbal suggestions of caffeine on competition day. Assesses conditioning;
4. Blockade condition: Caffeine during training phase; dopamine antagonist with verbal suggestions of caffeine on competition day. Investigates hypothesised neurobiological mechanisms of placebo effects.

Adding a condition that assesses effects of blockade on an expectation only treatment (i.e., condition 2), would also allow researchers to investigate whether expectancy and conditioning mechanisms are similar. Ecological validity of the design would be enhanced by using a fixed-distance performance measure, perhaps 40km (Foad et al., 2008), with measures of all relevant physiological variables as per the previous section including blood glucose, HR, blood lactate, O2 uptake, respiratory exchange ratio and ratings of perceived exertion (Glaister, 2018), as well perceptions of pain and fatigue.

7. BRAIN REGIONS INVOLVED IN PLACEBO EFFECTS.

[3] The authors discussed findings in the context of the ethics of sports competition, indicating that these raised important questions as to whether conditioned placebo responses to illegal treatments have to be considered a doping procedure.

Examples of previous neuroscience and related sports science research. Whilst the approaches described above allow investigators to identify which physiological processes are modulated by placebos and which neurotransmitter systems might be responsible, neither informs us, beyond inference, as to which brain regions and/or structures are involved (blockade, whilst targeting a single neurotransmitter system, might do so in a large number of brain structures and regions to which that system projects but which are uninvolved in the placebo effect).

There has been recent interest in identifying brain region responsible for placebo effects on motor performance. For example, Piedemonte et al (2015) reported that placebo caffeine reduced fatigue by acting at the central level on the preparatory/anticipatory phase of movement in the supplementary motor area, emphasizing the important role of the central nervous system in the generation of fatigue (Piedimonte et al., 2015). Fiorio et al (2015) applied transcranial magnetic stimulation (TMS) over the primary motor cortex to investigate whether a placebo modulation of force could change the excitability of the corticospinal system, and reported cognitive enhancement of corticospinal excitability as a neural signature of placebo modulation of motor performance (Fiorio, Emadi Andani, Marotta, Classen, & Tinazzi, 2014). Broelz et al (2019) investigated whether receiving an ergogenic placebo increased frontal alpha asymmetry (FAA). They reported a significant difference in change from baseline to intervention in FAA during cycling, and concluded that administering a placebo ergogenic aid significantly influenced FAA during maximum effort cycling (Broelz et al., 2019).

Brain imaging studies have shed considerable light on the regions involved in placebo responses (Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004). Whilst the imaging of brain activity via for example electroencephalogram (EEG) and functional near infrared spectroscopy (fNIRS) have been reported in sports studies, data are often problematic as the result of movement artefacts and noise (Perrey & Besson, 2018). The physical and mechanical constraints of more reliable imaging techniques such as functional magnetic resonance imagery (fMRI) in relation to anything but very small range movements are however evident. fMRI studies of real time brain activity during performance, for example, that by Fontes et al. (2013) who used a modified functional magnetic resonance imagery (fMRI) protocol to examine brain activity during cycling, are therefore rare. fMRI techniques have however been used in studies of anticipated (Wright, Bishop, Jackson, & Abernethy, 2010) and recalled sports scenarios (Davis IV et al., 2008).

There is a role for fMR imaging in placebo effects in sports performance. Once a placebo effect of a specific substance is reliably observed in a group or subgroup in a performance study, brain mechanisms of that effect are amenable to investigation. An example of this type of approach is to be found in glucose rinsing. Rinsing is a nutritional strategy that involves the rinsing of substrates within the mouth for 5–20 seconds without ingesting the solution. Improvements in performance ranging from 1.50% to 11.59% have been observed in moderate- to high-intensity exercise (Silva et al., 2014). Glucose rinsing also modulates cognitive processes. Jeukendrup and co-workers summarised several of the pathways and mechanisms involved, suggesting that taste receptor

cells provide the first analysis of potentially ingestible food, and that this information passes via the medulla and thalamus to the primary and secondary taste cortices. These in turn have projections to regions such as the dorsolateral prefrontal cortex, anterior cingulate cortex and ventral striatum, which might provide the link between the taste and emotional, cognitive and behavioural responses (Jeukendrup, 2013; Jeukendrup, Rollo, & Carter, 2013). These findings are consistent with those reported elsewhere relating to 'sweet induced analgesia' (Jain, Mukherjee, & Singh, 2004)

Rinsing studies tell us much about the way in which the brain modulates and arguably anticipates the relationship between an environmental cue and the body, a function also attributed to placebo effects (Ashar et al., 2017; Lieberman, 2006). Rinsing effects can be understood in terms of the body responding to a predictable cue – detecting glucose or caffeine in the mouth normally indicates that it will soon be available in the intestine – by regulating subsequent resource allocation (Harvey & Beedie, 2017). Whether placebo effect or not, rinsing offers an elegant example of how well the brain subconsciously regulates the relationship between environment and physiology, and how regulatory processes might be 'deceived' by cues such as glucose that enters the mouth but not the body. Or a pill that appears to contain caffeine but does not.

How we might identify brain regions involved in placebo effects in sport? We are not proposing that by studying rinsing effects we might elucidate placebo mechanisms, although the link between the two has been made previously (Jeukendrup, 2004). We are however suggesting that methods used in glucose rinsing research represent an interesting and potentially productive model by which to study brain mechanisms of placebo effects. Whilst to our knowledge the effects of rinsing on physical performance *and* directly imaged brain processes are yet to be concurrently examined in any one study, once a rinsing effect was identified on performance, subsequent studies sought to identify the brain mechanisms of what was conceived of a counter-intuitive phenomenon. We could adopt exactly this approach in studying placebo effects. A template for an analogous study in placebo effects of caffeine on fatigue would be:

1. Conduct a standard experimental trial such as Beedie et al. (2006), aimed at identifying participants who respond to a placebo in that context. Such placebo run-in trials are commonly used by drugs companies ahead of full clinical trials (Sedgwick, 2012).
2. Identify participants in the trial who experienced a positive effect of the placebo treatment on performance. Beedie, Foad & Coleman (2008) identified 'responders' and 'non-responders' to placebo caffeine in an earlier study of caffeine and placebo caffeine on 40km cycling performance (Foad et al., 2008). If that number is larger than can be accommodated at the imaging stage, identify those participants who experienced the largest and most reliable effects. Progress only these participants to the imaging stage of the study (imaging is both expensive and time consuming).
3. In an imaging lab, administer the same placebo treatment in conditions as close as possible to those of the placebo run-in trial. At this point the researcher has two options:
    a. Use fMRI or similar imaging technique whilst giving the participant the *expectation* that they

will subsequently complete the same performance trial as in 1. following the scan. However terminate data collection at the end of the scan and debrief the participants.

b. Use fMRI or similar imaging technique followed by an identical performance trial as that completed in 1. This allows greater triangulation and greater validity stage 2 than does 3a, but requires greater resources.

This model could be extended to examining a role for cognition. Most research relating to placebo effects in physical performance assumes placebo effects in the brain that activate peripheral physiological mechanisms. Placebo effects can however be manifest in cognitive performance (Turi et al., 2018), that could also benefit performance. It would be interesting to examine how such effects might cascade to improved performance in sport. Participants habituated to caffeine could be randomly assigned to receive no-treatment, placebo or caffeine. All groups would be told that taking caffeine prior to physically challenging activities can preserve mental performance. Participants would be asked to complete a physically challenging task standardized across groups, prior to fMRI during which they would undertake a cognitively challenging task. Manipulation checks such as the measurement of perceived fatigue after physical and mental challenges could be used to confirm no differences between placebo and caffeine groups (ensuring that the placebo group believe they received caffeine). Assuming that the manipulation check supports the integrity of the treatments, and that cognitive performance is similar between the placebo and caffeine groups (but better than no-treatment), the brain areas that are shown to be similarly active in the placebo and caffeine groups may be indicative of caffeine related placebo pathways.

8. SUMMARY

Mechanistic research into placebo and nocebo effects in sport is important from three perspectives. First, it will help explain variability to treatments, and in doing so will allow researchers to better understand the conditions in which treatments are likely to be most effective (Beedie et al., 2015; Beedie et al., 2017). Second, it will augment the growing database of research that examines neurobiological mechanisms in a range of sports phenomena (Fargier, Collet, Moran, & Massarelli, 2017; Meeusen & Roelands, 2018). Third, it will extend the existing neuroscience database beyond sport, complementing existing research on placebo effects and movement (Benedetti, Pollo, et al., 2007; Pollo et al., 2008). Collectively, this could lead to greater integration of psychology and physiology within sports science, contribute to the development of neuropsychological performance interventions (Maerlender, 2017), and allow sports scientists greater interdisciplinary opportunities beyond sport (for example, there is much interest among neuroscientists in sports-related phenomenon).

We recognise that placebo effect research is resource intensive, and can present significant research ethics challenges. Also, especially in the case of imaging, some of the technology required is relatively scarce in sports science laboratories. However, imaging technology is developing quickly, and it is likely that over the coming years advances will be made rendering these techniques even more informative, especially in relation to the

study of brain during processes of movement (Boto et al., 2018). We encourage sport scientists to consider the placebo effect in their future studies, not only to investigate the mechanisms of placebo effects per se, but for the novel insights it might provide in relation to athletes' brains and minds during performance; this is an interesting and ambitious goal.

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