The placebo and nocebo effects on peak minute power during incremental arm crank ergometry

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Running Title: Effect of Placebo and Nocebo on arm cranking

Abstract

This investigation aimed to explore the effects of inert sugar free drinks described as either 'performance enhancing' (placebo) or 'fatigue inducing' (nocebo) on peak minute power (PMP;W) during incremental arm crank ergometry (ACE). Twelve - healthy, non - specifically trained individuals volunteered to take part. A single blind randomized controlled trial with repeated measures was used to assess for differences in PMP;W and oxygen uptake, heart rate, minute ventilation, respiratory exchange ratio, and subjective reports of local (LRPE) and central (CRPE) ratings of perceived exertion, between three separate, but identical ACE tests. Participants were required to drink either 500ml of a 'sports performance' drink (placebo), a 'fatigue inducing' drink (nocebo), or water prior to exercise. The placebo caused a significant increase in PMP;W, and a significant decrease in LRPE compared to the nocebo (p=0.01; p=0.001) and water trials (p=0.01). No significant differences in PMP;W between the nocebo and water were found. However, the nocebo drink did cause a significant increase in LRPE (p=0.01). These results suggest that the time has come to broaden our understanding of the placebo and nocebo effect and their potential to impact sports performance.

Keywords: Placebo, Nocebo, upper body exercise

Introduction

The placebo effect in sport has only become a subject of regular research enquiry in the last 10 to 15 years. Despite this slow start, several studies have observed significant increases in endurance (Clark, Hopkins, Hawley and Burke, 2000) and strength performance (Maganaris, Collins and Sharp, 2000; Kalasountas, Reed and Fitzpatrick, 2007) as a result of ingesting a substance with no inherent ability to produce such a positive effect.

Despite suggestions of its existence in sports science, less is known about the nocebo effect (Beedie and Foad, 2009), defined as 'the undesirable effects an individual experiences after ingesting an inert substance'. However, it is axiomatic to propose that the nocebo effect may be just as relevant to sports performance (Maganaris *et al*., 2000; Kalasountas *et al*., 2007). For example, Maganaris *et al.* (2000) and Kalasountas *et al.* (2007) reported significant decreases in performance when subjects were told that their improvements in weightlifting were the result of a sham anabolic steroid. Such a suggestion assumes the nocebo effect is simply reversing a positive outcome, which may underestimate its true potential to negatively impact performance if studied in isolation.

Testing this hypothesis, Beedie, Coleman and Foad (2007) observed a trend towards reduced speed in consecutive sprint trials in a group that held a negative belief about an inert substance. In comparison they found a significant linear trend of greater speed with each successive experimental trial in a group that had been informed that the same substance enhanced performance. Compared to mainstream medicine an understanding of the placebo/nocebo remains in its infancy. However, a greater understanding of the placebo/nocebo effect, and their application to various sports and exercise modalities will supplement current understanding of these factors reportedly

influencing athletic performance. Prior research and theory from the pain sciences suggest that expectations influence the placebo/nocebo effect (Stewart-Williams and Podd, 2004; Pollo *et al.,* 2001; Fillmore and Vogel-Sprott, 1992). Illustrating this point, Clark *et al.* (2000) reported the greatest changes in power during a 40km cycle time trial, in a group that were told their performance would be increased by carbohydrate administration, regardless of whether they eventually received carbohydrate or placebo.

Contrary to this, ambiguity surrounding the proposed treatment may produce results that are incongruent with expectation (Foad, Beedie and Coleman, 2008). More specifically, Foad *et al*. (2008) reported that the effects of caffeine were greatest when participants believed that they had not ingested caffeine as opposed to when they believed they had. The mere presence of potential placebo and/or a placebo design made individuals question treatment allocation and thus had a contradictory effect on the anticipated outcome. Despite the link between expectation and the placebo effect, few studies have assessed this experimentally in the sports science domain (Pollo, Carlino and Benedetti, 2008). A better understanding here may help to clarify the relationship between the effect an individual expects to experience, and the actual experience itself. A meta-anlysis by Berdi, Koteles, Szabo, and Bardos (2011) has established that further research is needed to determine the importance of the placebo effect on sports performance and that a more balanced placebo design is required along with comparing a no treatment group. Therefore, the current investigation aimed to explore the effects of inert sugar free drinks described either as ‘performance enhancing’ (Sports performance drink - placebo) or ‘fatigue inducing’ (nocebo) or plain water on peak minute power (PMP;W) during an incremental arm crank

ergometry (ACE) test to volitional exhaustion. This dynamic has not been explored previously and as incremental tests are used extensively in applied and clinical settings it is a valid predictor of performance and health respectively (Bassett and Howley, 2000). It was hypothesised that the sports performance and fatigue inducing drink would significantly increase and decrease PMP;W respectively, compared to a comparison test using water.

Methods

Participants

Twelve, healthy, non-specifically trained, able-bodied male individuals volunteered to take part in the study (mean ±SD age: 25.3 ± 4.4 years; weight: 80.5 ± 16.9 kg; height: 178.8 ± 4.4 cm). Participants volunteered to take part on the basis that they would received the outcome of the study but no financial incentive was provided. Participants were injury free at the time of data collection and provided written informed consent. University Ethics Committee approval for the study's experimental procedures was obtained and followed the principles outlined in the Declaration of Helsinki.

Design:

Participants were required to perform three separate (one week apart), incremental tests using a Monark arm crank ergometer (Monark Inc, London UK) to determine PMP;W. Thirty minutes prior to each test, participants were required to drink either 500ml of water, or the same volume of a 'sports performance' (placebo) or 'fatigue inducing' drink (nocebo). These drinks were in fact identical commercial sugar - free drinks that had no known physiological effect on performance. The study was performed in a randomized cross over design and was single blinded.

Prior to the relevant test, a standardized written script was handed to the participant's. These highlighted how the drinks worked to increase (sports performance drink) or decrease (fatigue inducing drink) PMP;W. Participants were told that the water trial was being used as a comparison.

Procedures:

A ramp protocol was used whereby power output (watts) increased every two minutes (Price *et al*., 2011; Smith *et al*., 2001). Participants initially exercised for two minutes at 0W. After this, the workload increased to 50W, and then by 20W every two minutes. Participants were required to complete the test using a constant speed of 70 rev. min^{-1} until volitional exhaustion.

PMP;W was calculated using the value(s) of the workload experienced during the final minute of the test. If a participant performed their final workload at 150W for a minute, their PMP was 150W. However if a participant performed at different workloads, the calculation by Smith *et al*. (2004) was used to determine PMP;W.

Oxygen consumption ($VO_{2)}$ respiratory exchange ratio (RER), carbon dioxide production (VCO_2) and minute ventilation were analysed using an online breath-by-breath analysis system (Cosmed Quark b^2 metabolic analyse-gas analysis) and averaged over the final 15 seconds of each workload, and over the final 15 seconds of the test for peak responses. Heart rate (HR) was monitored using a heart rate monitor, and measured at the same intervals (Price, Bottoms, Smith and Nicholettos, 2011).

Fingertip blood samples were collected at volitional exhaustion and analysed for blood lactate concentration (Analox GM7, Surrey, UK). Ratings of perceived exertion for local working muscles (LRPE) and cardio-respiratory (CRPE) components of effort perception (Borg Scale) were recorded during the last 15 seconds of each exercise stage and at volitional exhaustion (Price *et al*., 2011).

After the third test, participants were asked to identify (using a Likert scale from 1 to 10) the degree to which they expected the sports performance drink would positively impact their performance (1 being not at all, 5 to some extent and 10 being very much so), and the degree to which they expected the nocebo drink would decrease their performance (1 being very much so, 5 to some extent and 10 being not at all). Following this, they were informed about the true nature of the experiment and why deception was a fundamental component.

Statistical analysis

All data was analysed using SPSS version 20.0. The Shapiro-Wilk statistic confirmed that the normal distribution assumption was met for all variables. Therefore, a repeated measures one-way ANOVA was used to assess differences in PMP:W between trials, post blood lactate values, and expectation scores (Likert scale). A two-way ANOVA for repeated measures was used to assess the main effect of time, group, and time - group interactions for physiological variables: heart rate, VO_2, VCO_2, RER, VE, and subjective ratings of central and local RPE values. Appropriate post-hoc analyses were conducted using a Bonferroni correction to control for type I error. Partial effect sizes were calculated using an η^2. Spearman's rank correlation co-efficients were used to explore the relationship between the extent to which the

participants expected (likert score) the two drinks would increase (placebo)/ decrease (nocebo) their performance, and how their PMP;W subsequently increased/ decreased compared to the water trial. Data are presented as mean ± standard deviation in tables and figures. Significance was set at $p<0.05$.

Results

PMP;W

Ten out of 12 participants improved on the placebo trial compared to the water trial (Table 1), whereas only 5 out of 12 participants produced a lower PMP;W on the nocebo trial compared to the water trial.

Table 1 near here

A significant difference in PMP;W was found between the three conditions ($F_{2, 22}$ =5.8: p= .001, η^2= .347, with the highest PMP;W values occurring in the placebo trial (Figure 1). Post - hoc analyses demonstrated a significant increase in PMP;W using the placebo compared to water (p= .013), and the nocebo (p= .044). No significant difference in PMP; W was found between the nocebo and water (p= 1.00).

Physiological measurements

A significant increase in LRPE with exercise intensity was observed (main effect of time ($F_{5, 30}$ =130.0: p <.001, η^2= .956). Furthermore, significant differences in LRPE values between the conditions (main effect of condition ($F_{2, 12}$ =4.81: p =.03, η^2= .445). Post - hoc analyses demonstrated significantly lower LRPE for placebo compared to water (p =.004), and significantly greater LRPE values for nocebo

compared to water (p = .01), and finally significantly higher values for nocebo compared to placebo (p = .001; Table 2). There was no significant interaction between condition and time ($F_{10, 60}$ =1.76: p = .09, η^2= .270).

HR, VO_2, VCO_2 RER and subjective scores of central ratings of perceived exertion increased significantly with exercise intensity as they all demonstrated significant main effects for time ($F_{5, 15}$ =39.0: p < .001, η^2= .929, $F_{5, 20}$ =33.4: p < .001, η^2= .893, $F_{5, 20}$ =9.5: p < .001, η^2= .759, $F_{5, 15}$ = 11.99: p < .001, η^2= .800 and $F_{5, 25}$ =60.4: p < .001, η^2= .930 respectively). However, no significant condition and time * condition interactions were found. Post blood lactate levels did not differ between the three conditions ($F_{2, 22}$ = 1.897: p = .174, η^2= .147; Table 2).

Table 2 near here

A significant difference between the three Likert scores (expectation) was found ($F_{2,22}$ = 14.2: p < .001, η^2= .563). Post hoc tests revealed significantly greater scores for placebo compared to water (p < .001), and for nocebo compared to water (p < .001), with no significant difference observed between the placebo and nocebo (p = .80).

Spearman's rank correlation co-efficients revealed a significant correlation (rho= 0.85 ; p < .001) between individuals who had the greatest increase in PMP;W (compared to water) and those who had the highest expectation of the placebo drink (Likert). Similarly, a significant weak correlation was found between individuals who had the largest decrease in performance (compared to water) and individuals with the highest expectation of the nocebo drink (Figures 1 and 2 respectively).

241 ***Figures 1 and 2 near here***

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Discussion

Consistent with the hypothesis, the current investigation demonstrated a significant increase in PMP;W when participants ingested a placebo drink compared to water. Furthermore, a significant decrease in LRPE compared to water and nocebo was observed. Consequently, participants increased their power output, whilst simultaneously reporting less discomfort in their arms.

These data add to an increasing number of studies that have reported improvements in performance as a result of ingesting a placebo aid. The percentage increases in performance here (6.3%; percentage increase in PMP;W compared to the water and nocebo trial) are both lower (Pollo *et al.*, 2008; Kalasountas *et al.*, 2007; Ariel and Saville, 1972) and higher than values previously recorded (Foad *et al.*, 2008; Beedie *et al.*, 2007; McClung and Collins, 2007; Beedie *et al*., 2006; Clark *et al.*, 2000; Maganaris *et al.*, 2000). However, methodological variances between the studies, including the mode of exercise and its outcome measure, and the duration of the study make direct comparisons difficult. The present study used a water trial as a no treatment group to more accurately assess the extent of the placebo effect as suggested by Berdi *et al*. (2011). The collective data do suggest that the placebo can exert its effect across several exercise modalities and protocols of different durations.

Contrary to the hypothesis the nocebo drink failed to cause a significant decrease in performance. This asymmetry between the placebo and nocebo may be due to discrepancies in the participant's appreciation of the two drinks. That is, participants better understood that a drink could increase, rather than decrease performance. Statistical tests suggested that there was no significant difference in the expectation assigned to the two drinks (Likert scale). This finding may highlight a possible

limitation of the Likert scale and it may not be sensitive enough to determine differences, compared to qualitative equivalents. In addition, the likert scale was given after the test and may therefore not completely reflect their expectation prior to the test. In future the scale should be presented prior to the test to more accurately measure the expectation of the drink. It may also be reasonable to suggest that a fatigue inducing drink may not be the best method of activating a nocebo response.

It is important to highlight an observation from the current investigation that provides evidence for the nocebo. Evidence for a nocebo response was the response of LRPE with the nocebo causing a significant increase in LRPE compared to water and the placebo. These data add to previous data that suggest that expectations alter somatic perception (Caspi and Bootzin, 2002; Lundh, 1987; Ross and Olson, 1981) by causing individuals to selectively attend to an increase or decrease in their symptoms (seen in the present study as an increase or decrease in LRPE).

The present study used an incremental VO_2 peak test. This design was chosen because it is a valid and objective test of performance in the exercise domain (Bassett and Howley, 2000). The potential to impact performance during this mode of exercise has implications for a number of different individuals such as kayakers. Due to the smaller muscle mass of the arms in comparison to lower body exercise, a different response may have been expected to that previously shown with lower body exercise. The current study used well - defined objective physiological measures to identify a maximal effort to limit potential suggestions that the 'placebo effect' was simply attributable to participants trying harder (Kalasountas *et al*., 2007).

The current investigation used a Likert scale, in order to identify the relationship between the expectation of a change in performance and those individuals with who had the greatest change in PMP;W. This assessment tool was easy to use, and significant correlations were found between individuals with the highest expectations of the placebo and nocebo drink and individuals who subsequently had the greatest changes in PMP; W compared to the water trial. However, this scale failed to identify any individual factors that may have increased an individual's expectations of the two drinks, possibly because it was presented after the test rather than prior to the test. This may be particularly important since not all participants experienced a placebo/ nocebo effect. Qualitative data may have provided more information about individual experiences, and should feature in future research (Mengshoel, 2012).

These data, together with previous work, suggests that the placebo and nocebo have the capacity to influence sport performance. Further work should be focused on how coaches and clinicians can develop techniques to harness the placebo, whilst avoiding a potential nocebo response. From a theoretical standpoint, further research into the placebo/nocebo may also broaden our understanding of how the brain governs peripheral processes that influence sports performance. For example, it has been suggested that fatigue during exercise involves a complex interaction between a number of peripheral physiological systems and the brains evaluation of the 'exercising body' (Gibson *et al.,* 2006; Lambert, Gibson and Noakes, 2005). Thus, whilst peripheral factors such as metabolite accumulation are important, the brain orchestrates the final decision, based on all relevant factors, including for example, the knowledge that a drink has been consumed that is 'sport enhancing'. This may manifest in a situation like that seen in the current investigation where an increase in

PMP';W is observed despite there being no significant difference between the groups for objective physiological markers.

In conclusion, the current investigation reported a significant increase in PMP; W together with a decrease in LRPE, following the ingestion of an inert 'sports performance' drink. The current study failed to report a significant nocebo effect on PMP;W. However, a significant increase in LRPE was observed compared to water and the placebo drink. These results suggest that the time has come to broaden our understanding of the placebo and nocebo effect and their potential to impact sports performance. Future work should supplement quantitative measures of physical function, with qualitative interviews to better understand the factors that influence an individual's response. More specifically, participants can be asked to report their sensations during the placebo and nocebo conditions. This data can then be referenced against objective physiological measures to provide a wider picture of the human response to the consumption of performance enhancing or inhibiting drinks. Ultimately, a better understanding here may enable clinicians and coaches to develop techniques to harness the placebo and or avoid the nocebo and with it open a potentially very large and important door.

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431 Stewart-Williams, S. and Podd, J. (2004). The placebo effect: Dissolving the
432 expectancy versus conditioning debate. *Psychological Bulletin*, 130, 324–340.
433 Tables:
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435 **Table 1:** PMP;W values for the three trials * significant difference between tests (p

436 <0.05).

	Water	Nocebo	Placebo
Participant	**PMP;W (watts)**	**PMP;W (watts)**	**PMP;W (watts)**
1	138	136	148
2	130	130	130
3	145	130	155
4	90	90	110
5	110	117	114
6	145	130	150
7	158	145	162
8	153	150	158
9	130	150	150
10	110	113	110
11	125	125	130
12	130	130	130
Mean ± SD	**130 ± 20**	**129±17**	**137±19***

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Table 2. Mean ±SD for the physiological variables. *+#denotes significant differences.

	Peak Value (water)	Peak Value (Nocebo)	Peak Value (placebo)
VO_2 ($l.min^{-1}$)	2.95 ± 0.99	2773 ± 397	2.62 ± 0.98
VCO_2 ($l.min^{-1}$)	3.72 ± 0.13	2.67 ± 0.88	3.23 ± 0.12
RER	1.19 ± 0.1	1.14 ± 0.1	1.29 ± 0.1
VE ($l.min^{-1}$)	120 ± 28	127 ± 15	123 ± 4
HR ($beats.min^{-1}$)	168 ± 16	159 ± 21	167 ± 20
CRPE (borg scale)	18 ± 2	16 ± 2	17 ± 2
LRPE (borg scale)	19 ± 1*#	20 ± 1*+	18 ± 1#+
Blood lactate (mmol)	9.0 ± 2.5	8.2 ± 2.1	10.0 ± 2.8

List of Figures:

Figure 1: Relationship between the increase in PMP:W (placebo drink compared to the water trial) and the expectation of an increase in performance (Likert score) (r =0.95; p<0.001)

Figure 2: Relationship between the decrease in PMP;W (nocebo drink compared to the water trial) and the expectation of a decrease in performance (Likert score) (r=0.97; *p* <0.001)