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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

34 **Abstract**

35 This investigation aimed to explore the effects of inert sugar free drinks described as
36 either ‘performance enhancing’ (placebo) or ‘fatigue inducing’ (nocebo) on peak
37 minute power (PMP;W) during incremental arm crank ergometry (ACE). Twelve -
38 healthy, non - specifically trained individuals volunteered to take part. A single blind
39 randomized controlled trial with repeated measures was used to assess for differences
40 in PMP;W and oxygen uptake, heart rate, minute ventilation, respiratory exchange
41 ratio, and subjective reports of local (LRPE) and central (CRPE) ratings of perceived
42 exertion, between three separate, but identical ACE tests. Participants were required
43 to drink either 500ml of a ‘sports performance’ drink (placebo), a ‘fatigue inducing’
44 drink (nocebo), or water prior to exercise. The placebo caused a significant increase in
45 PMP;W, and a significant decrease in LRPE compared to the placebo ($p=0.01$;
46 $p=0.001$) and water trials ($p=0.01$). No significant differences in PMP;W between the
47 placebo and water were found. However, the placebo drink did cause a significant
48 increase in LRPE ($p=0.01$). These results suggest that the time has come to broaden
49 our understanding of the placebo and placebo effect and their potential to impact
50 sports performance.

51

52 Keywords: Placebo, Nocebo, upper body exercise

53

54

55 **Introduction**

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

62 Despite suggestions of its existence in sports science, less is known about the nocebo
63 effect (Beedie and Foad, 2009), defined as ‘the undesirable effects an individual
64 experiences after ingesting an inert substance’. However, it is axiomatic to propose
65 that the nocebo effect may be just as relevant to sports performance (Maganaris *et al.*,
66 2000; Kalasountas *et al.*, 2007). For example, Maganaris *et al.* (2000) and
67 Kalasountas *et al.* (2007) reported significant decreases in performance when subjects
68 were told that their improvements in weightlifting were the result of a sham anabolic
69 steroid. Such a suggestion assumes the nocebo effect is simply reversing a positive
70 outcome, which may underestimate its true potential to negatively impact
71 performance if studied in isolation.

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

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

87
88 Contrary to this, ambiguity surrounding the proposed treatment may produce results
89 that are incongruent with expectation (Foad, Beedie and Coleman, 2008). More
90 specifically, Foad *et al.* (2008) reported that the effects of caffeine were greatest when
91 participants believed that they had not ingested caffeine as opposed to when they
92 believed they had. The mere presence of potential placebo and/or a placebo design
93 made individuals question treatment allocation and thus had a contradictory effect on
94 the anticipated outcome. Despite the link between expectation and the placebo effect,
95 few studies have assessed this experimentally in the sports science domain (Pollo,
96 Carlino and Benedetti, 2008). A better understanding here may help to clarify the
97 relationship between the effect an individual expects to experience, and the actual
98 experience itself. A meta-analysis by Berdi, Koteles, Szabo, and Bardos (2011) has
99 established that further research is needed to determine the importance of the placebo
100 effect on sports performance and that a more balanced placebo design is required
101 along with comparing a no treatment group. Therefore, the current investigation
102 aimed to explore the effects of inert sugar free drinks described either as ‘performance
103 enhancing’ (Sports performance drink - placebo) or ‘fatigue inducing’ (nocebo) or
104 plain water on peak minute power (PMP;W) during an incremental arm crank

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

111

112

113 **Methods**

114

115 *Participants*

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

124

125 *Design:*

126

127 Participants were required to perform three separate (one week apart), incremental
128 tests using a Monark arm crank ergometer (Monark Inc, London UK) to determine
129 PMP;W. Thirty minutes prior to each test, participants were required to drink either
130 500ml of water, or the same volume of a 'sports performance' (placebo) or 'fatigue
131 inducing' drink (nocebo). These drinks were in fact identical commercial sugar - free
132 drinks that had no known physiological effect on performance. The study was
133 performed in a randomized cross over design and was single blinded.

134

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

139

140

141 *Procedures:*

142

143

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

149

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

154

155 Oxygen consumption (VO₂) respiratory exchange ratio (RER), carbon dioxide
156 production (VCO₂) and minute ventilation were analysed using an online breath-by-
157 breath analysis system (Cosmed Quark b² metabolic analyse-gas analysis) and
158 averaged over the final 15 seconds of each workload, and over the final 15 seconds of
159 the test for peak responses. Heart rate (HR) was monitored using a heart rate monitor,
160 and measured at the same intervals (Price, Bottoms, Smith and Nicholettos, 2011).

161

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

167

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

175

176 *Statistical analysis*

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

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

191

192

193 **Results**

194 *PMP;W*

195

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

199

200 ***Table 1 near here***

201

202 A significant difference in PMP;W was found between the three conditions ($F_{2, 22}$
203 $= 5.8$; $p = .001$, $\eta^2 = .347$, with the highest PMP;W values occurring in the placebo trial
204 (Figure 1). Post - hoc analyses demonstrated a significant increase in PMP;W using
205 the placebo compared to water ($p = .013$), and the nocebo ($p = .044$). No significant
206 difference in PMP; W was found between the nocebo and water ($p = 1.00$).

207

208 *Physiological measurements*

209 A significant increase in LRPE with exercise intensity was observed (main effect of
210 time ($F_{5, 30} = 130.0$; $p < .001$, $\eta^2 = .956$). Furthermore, significant differences in LRPE
211 values between the conditions (main effect of condition ($F_{2, 12} = 4.81$; $p = .03$, $\eta^2 =$
212 $.445$). Post - hoc analyses demonstrated significantly lower LRPE for placebo
213 compared to water ($p = .004$), and significantly greater LRPE values for nocebo

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

217
218 HR, VO_2 , VCO_2 RER and subjective scores of central ratings of perceived exertion
219 increased significantly with exercise intensity as they all demonstrated significant
220 main effects for time ($F_{5, 15} = 39.0$: $p < .001$, $\eta^2 = .929$, $F_{5, 20} = 33.4$: $p < .001$, $\eta^2 = .893$,
221 $F_{5, 20} = 9.5$: $p < .001$, $\eta^2 = .759$, $F_{5, 15} = 11.99$: $p < .001$, $\eta^2 = .800$ and $F_{5, 25} = 60.4$: $p <$
222 $.001$, $\eta^2 = .930$ respectively). However, no significant condition and time * condition
223 interactions were found. Post blood lactate levels did not differ between the three
224 conditions ($F_{2, 22} = 1.897$: $p = .174$, $\eta^2 = .147$; Table 2).

225
226 ***Table 2 near here***

227
228 A significant difference between the three Likert scores (expectation) was found ($F_{2,22}$
229 $= 14.2$: $p < .001$, $\eta^2 = .563$). Post hoc tests revealed significantly greater scores for
230 placebo compared to water ($p < .001$), and for nocebo compared to water ($p < .001$),
231 with no significant difference observed between the placebo and nocebo ($p = .80$).

232
233
234 Spearman's rank correlation co-efficients revealed a significant correlation ($\rho = 0.85$
235 ; $p < .001$) between individuals who had the greatest increase in PMP;W (compared to
236 water) and those who had the highest expectation of the placebo drink (Likert).
237 Similarly, a significant weak correlation was found between individuals who had the
238 largest decrease in performance (compared to water) and individuals with the highest
239 expectation of the nocebo drink (Figures 1 and 2 respectively).

240

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

242

243 **Discussion**

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

249
250 These data add to an increasing number of studies that have reported improvements in
251 performance as a result of ingesting a placebo aid. The percentage increases in
252 performance here (6.3%; percentage increase in PMP;W compared to the water and
253 nocebo trial) are both lower (Pollo *et al.*, 2008; Kalasountas *et al.*, 2007; Ariel and
254 Saville, 1972) and higher than values previously recorded (Foad *et al.*, 2008; Beedie
255 *et al.*, 2007; McClung and Collins, 2007; Beedie *et al.*, 2006; Clark *et al.*, 2000;
256 Maganaris *et al.*, 2000). However, methodological variances between the studies,
257 including the mode of exercise and its outcome measure, and the duration of the study
258 make direct comparisons difficult. The present study used a water trial as a no
259 treatment group to more accurately assess the extent of the placebo effect as
260 suggested by Berdi *et al.* (2011). The collective data do suggest that the placebo can
261 exert its effect across several exercise modalities and protocols of different durations.

262
263 Contrary to the hypothesis the nocebo drink failed to cause a significant decrease in
264 performance. This asymmetry between the placebo and nocebo may be due to
265 discrepancies in the participant's appreciation of the two drinks. That is, participants
266 better understood that a drink could increase, rather than decrease performance.
267 Statistical tests suggested that there was no significant difference in the expectation
268 assigned to the two drinks (Likert scale). This finding may highlight a possible

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

275
276 It is important to highlight an observation from the current investigation that provides
277 evidence for the nocebo. Evidence for a nocebo response was the response of LRPE
278 with the nocebo causing a significant increase in LRPE compared to water and the
279 placebo. These data add to previous data that suggest that expectations alter somatic
280 perception (Caspi and Bootzin, 2002; Lundh, 1987; Ross and Olson, 1981) by causing
281 individuals to selectively attend to an increase or decrease in their symptoms (seen in
282 the present study as an increase or decrease in LRPE).

283

284 The present study used an incremental VO₂ peak test. This design was chosen because
285 it is a valid and objective test of performance in the exercise domain (Bassett and
286 Howley, 2000). The potential to impact performance during this mode of exercise has
287 implications for a number of different individuals such as kayakers. Due to the
288 smaller muscle mass of the arms in comparison to lower body exercise, a different
289 response may have been expected to that previously shown with lower body exercise.

290 The current study used well - defined objective physiological measures to identify a
291 maximal effort to limit potential suggestions that the 'placebo effect' was simply
292 attributable to participants trying harder (Kalasountas *et al.*, 2007).

293

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

305

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

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

321
322 In conclusion, the current investigation reported a significant increase in PMP; W
323 together with a decrease in LRPE, following the ingestion of an inert 'sports
324 performance' drink. The current study failed to report a significant nocebo effect on
325 PMP;W. However, a significant increase in LRPE was observed compared to water
326 and the placebo drink. These results suggest that the time has come to broaden our
327 understanding of the placebo and nocebo effect and their potential to impact sports
328 performance. Future work should supplement quantitative measures of physical
329 function, with qualitative interviews to better understand the factors that influence an
330 individual's response. More specifically, participants can be asked to report their
331 sensations during the placebo and nocebo conditions. This data can then be
332 referenced against objective physiological measures to provide a wider picture of the
333 human response to the consumption of performance enhancing or inhibiting drinks.
334 Ultimately, a better understanding here may enable clinicians and coaches to develop
335 techniques to harness the placebo and or avoid the nocebo and with it open a
336 potentially very large and important door.

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346 **References**

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432 expectancy versus conditioning debate. *Psychological Bulletin*, 130, 324–340.

433 Tables:

434

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*

437

438

439 **Table 2.** Mean \pm SD for the physiological variables. *+#denotes significant
 440 differences.

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

457

458 List of Figures:

459 **Figure 1:** Relationship between the increase in PMP;W (placebo drink compared to
460 the water trial) and the expectation of an increase in performance (Likert score) (r
461 $=0.95$; $p < 0.001$)

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

465

466