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**Advancing the understanding of placebo effects in
psychological outcomes of exercise: lessons learned and
future directions**

Journal:	<i>European Journal of Sports Science</i>
Manuscript ID	TEJS-2018-0995.R1
Manuscript Type:	Special Issue
Keywords:	Cognition, Behavior, Health, Methodology, Neuroscience

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Manuscripts

1
2
3 Thank you very much to the reviewers for your thoughtful comments on our
4 manuscript. We have taken each issue that was raised into consideration and have
5 responded in kind. Your insights have helped us strengthen the manuscript and we
6 hope that our edits and responses are to your satisfaction. Please note that in our
7 attempt to thoroughly address your suggested edits, we had to prioritize some aspects
8 of the manuscript revisions over others to avoid greatly exceeding the word limit that
9 is suggested in *EJSS* author guidelines (4500 words). We made room for addressing
10 your thoughtful comments by consolidating redundant aspects and deleting some
11 sentences/paragraphs/sections from the original version, but we were unable to
12 incorporate every change/consideration that was suggested. Major changes to the
13 manuscript include:
14
15
16

- 17
18 1) Reducing the space given to arguing for the need for three group designs. The
19 theoretical importance of using a placebo and no-treatment group to
20 distinguish placebo effects from non-specific effects is still briefly discussed,
21 but we have toned down specific recommendations for conducting three arm
22 studies.
23
24
- 25 2) Less discussion of whether or not valid exercise placebos can be developed. We
26 still provide some historical context on this matter, but feel that talking about
27 how to develop valid exercise placebos may do more harm than good and may
28 distract readers from more viable options to studying placebo effects and
29 mechanisms that leveraging mechanisms of placebo effects (e.g., expectation,
30 conditioning) to study their impact on psychological responses to exercise.
31
32
33
- 34 3) Removal of language pertaining to “placebo-related” effects.
35
- 36 4) Removal of the section pertaining to measurement of expectations.
37
- 38 5) Removal of the section pertaining the balanced placebo design and figure 2.
39
40
- 41 6) New discussion of several recently published studies with a high degree of
42 relevance to the scope and objectives of this review (Arbinaga et al., 2018;
43 Colloca et al., 2018; Kong et al., 2018).
44
45
- 46 7) Reduction of total word count from 6766 (original version) to 5682 (revised
47 version).
48
49
- 50 8) The abstract, highlights, future directions and conclusion sections have been
51 updated to reflect the changes that have been made to the overall manuscript.
52

53 For your convenience, you will find two versions of our revised manuscript below. The
54 first version shows track changes and the second version is a clean copy.
55
56
57
58
59
60

Reviewer: 1

Comments to the Author

I found the manuscript interesting and believe it will make a meaningful contribution to the literature. However, there are some areas which need clarification as to the purpose of the paper and also providing more information such as summary tables to aid the readers extract important information. The paper is well written and so my comments are mainly based on a few theoretical concerns & observations.

Thank you very much for taking the time to review our manuscript and for the kind words. Please find our point-by-point response to each of your comments below.

Specific comments:

The title is not fully reflective of the paper. If indeed it is a paper about methods then I would like to see comparisons of methods used in current practice across tables which show their strengths and weaknesses. I would suggest including tables and also developing a more theory driven title. Commencing the title 'Methods..' sounds like a technical report and clearly that is not the case.

Thank you for this consideration. We agree that this is not necessarily a technical report. To better reflect the purpose of this review, we have changed the title to the following:

“Advancing the understanding of placebo effects in psychological outcomes of exercise: lessons learned and future research directions”

Introduction L33: is a placebo effect definitely a phenomenon occurring in the brain or are there exceptions? you could argue 1) the supposed mechanism is probably occurring in the brain although small organisms without a brain can still show avoidance behaviour aka to placebo and it is also plausible that tricking an involuntary reaction in a human body is also a placebo? 2) as the mechanism may be occurring in the brain, the placebo 'effect' is on something else other than the brain i.e. the brain effect on the body. So the effect (outcome) is not in the brain but on the body.

Thank you. In response to your comment and those of reviewer 2, we have adjusted our definitions of placebo/nocebo effects to accord with more recent consensus amongst experts.

L35 - Verbal suggestion - surely if the mechanism is deception of the brain then verbal suggestion of perceived benefit can also be a placebo if delivered appropriately compared to another psychological intervention?

1
2
3 **Thank you for this important consideration. We now provide an example of a clinical**
4 **study in section 2.2. that compared pain reductions between a treatment alone group**
5 **and treatment plus expectation.**

6
7 **Kong, J., Wang, Z., Leiser, J., Minicucci, D., Edwards, R., Kirsch, I., Wasan, A. D., et al.**
8 **(2018). Enhancing treatment of osteoarthritis knee pain by boosting expectancy: A**
9 **functional neuroimaging study. NeuroImage: Clinical, 18, 325–334.**

10
11
12 L40: For researchers interested in finding a true exercise effect, surely they are more
13 interested in placebo vs experimental conditions rather than placebo vs control? As such
14 you would need to fully explain here or elsewhere in the paper defects in an
15 experimental model of 2 groups comparing placebo and experimental conditions vs your
16 suggestion of having control, placebo and experimental conditions. If a researcher is
17 simply using placebo as a means to discover a true exercise effect why include a passive
18 control, if the difference between placebo and experimental groups is true? Consider if
19 you have 30 participants available - where you would like the researchers to distribute
20 them? 3 groups of 10 vs 10 vs 10 or 2 groups of 15 vs 15 with more statistical power.
21 Including all 3 groups may be appropriate but it requires discussion throughout the
22 paper or else it may influence the study design of others in a way that is not appropriate
23 to their needs. There may be benefits of both models so please explain this.
24
25
26

27 **We agree and believe your concerns are now addressed in our edits to section 2.**

28
29
30 P6 105-113 - this relates to the same point as above and I urge caution from using
31 1994-1995 papers as definitive advice for models in exercise & consider 2 group models
32 too.
33
34

35 **Please see our substantial edits to section 2. We have toned down this rhetoric**
36 **considerably and clarify to the reader that the choice in study design should depend**
37 **on their primary objective (i.e., precise measurement of the placebo effects versus**
38 **distinguishing treatment effects from placebo+non-specific effects).**

39
40
41 P8 L159 - It would be useful here to include a table of the strengths/weaknesses of
42 current exercise based approaches to using placebos. This would be a valuable inclusion
43 & identify current practice.
44
45

46 **Considering the substantial revisions to the manuscript in response to your earlier**
47 **comments, we believe that a table may no longer be needed. However, we could**
48 **reconsider including a table if you still feel strongly about that after reading the**
49 **revised version of this manuscript.**

50
51
52 P8 L173 - discuss ways in which placebo can be delivered in exercise contexts as
53 presumably in some ways verbal suggestion could be a placebo as could any sham
54 condition if perceived appropriately similar to the experimental aims.
55
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2
3 **Please see our edits to section 2. We now describe a study by Kong and colleagues**
4 **(2018) who compared acupuncture alone to acupuncture plus enhanced treatment**
5 **expectations.**
6

7
8 P9 L53 and elsewhere add a 'u' in behavior
9

10 **Done.**
11

12
13 P21 L461 - presumably hand cycling is one exercise sham exercise that is often used and
14 not discussed here? More examples and a table needed.
15

16 **Considering the shift in tone of this revised manuscript from the importance of**
17 **developing a valid placebo to placing a greater amount of emphasis on acknowledging**
18 **that placebo groups are not necessarily required in order to study their contribution to**
19 **treatment responses, we would prefer not to distract the reader with extra discussion**
20 **of potential sham exercise conditions.**
21
22

23
24 P22 - future directions - you have not mentioned the time course of placebo and this is a
25 major consideration over how many repeated trials this would last etc before wearing
26 off and could justify your use of 3 groups rather than 2? It needs some discussion.
27

28
29 **Thank you. This knowledge gap is now acknowledged in item 1 of the future directions**
30 **section.**
31

32 **Reviewer: 2**
33

34
35 Comments to the Author
36

37 I very much enjoyed reading and reviewing this paper. Authors should be commended
38 on the difficulties involved in writing a narrative on challenges researchers face when
39 aiming to measure the placebo effect on the psychological outcomes of exercise. The
40 paper adds value to the field and it should generate discussion around how to conduct
41 both placebo effect and exercise related research. With this being said, there are a few
42 concerns that I have address these below.
43
44

45
46 **Thank you very much for taking the time to review our manuscript and for the kind**
47 **words. Please find our point-by-point response to each of your comments below.**
48

49
50 Main comments
51

52 The authors state that it if no placebo is administered, then any effect resulting from
53 this administration is not a placebo effect, but instead a placebo-related effect (P8 L
54 173). I disagree with this statement and argue that placebo effects are placebo effects
55 regardless if they have been induced with or without a placebo. Placebo effect research
56
57
58
59

1
2
3 has moved on dramatically over the past decade and authors base their understanding
4 of placebo effects on a reference published over 10 years ago (i.e. Benedetti, 2008). In
5 the 2018 consensus statement of the use of placebos in clinical practice, the authors
6 (one of which is Benedetti) state that placebo effects should be considered as part of
7 regular treatments. They do not differentiate the difference between a placebo effect
8 that is induced by a placebo or by a treatment (see:
9 <https://www.ncbi.nlm.nih.gov/pubmed/29895014>). I would therefore suggest that
10 authors remove the term placebo-related effects and simply state
11 placebo effects throughout. This would make the paper easier to read and follow,
12 especially given the numerous terms already included.
13
14
15

16
17 **We agree and have removed the mention of placebo-related effects throughout the**
18 **manuscript.**
19

20 Based on the above, the placebo effect definition is inaccurate. A placebo effect can be
21 the result of verbal suggestions, prior experiences and participant-clinician interaction,
22 without the need to administer an inert substance or sham treatment. The definition
23 should reflect this.
24
25

26
27 **Thank you. In response to your comments and those of Reviewer 1, we have updated**
28 **our definition of the placebo (and nocebo) effect term to reflect more recent expert**
29 **consensus statements. Please see our edits in the first and second paragraphs of the**
30 **introduction.**
31

32 Authors should also consider the differences and similarities between habitual
33 expectations and conditioning. Authors state that habitual expectations are a result of
34 prior experiences, which is the basis of conditioning. Where is the line between the
35 two? Authors should consider explaining whether the two interact and if they share
36 similar mechanisms. For instance, if a study uses a conditioning design and sample
37 participants who have habitual expectations, would participants need as many
38 trials to be conditioned to the effects?
39
40
41

42
43 **Thank you for this very interesting consideration. This point is now briefly raised in**
44 **our edits to the 4.2 Conditioning section:**
45

46 **“By administering half of the placebo and nocebo trials during light intensity elbow**
47 **extension-flexion (30% of maximum voluntary contraction) and half at rest, the added**
48 **contribution of exercise to placebo and nocebo effects could be determined. The**
49 **authors did not find an added effect of exercise to either placebo or nocebo effects,**
50 **but the study by Colloca and colleagues provides a useful framework for future**
51 **researchers to begin addressing several other questions that could be related to**
52 **placebo and nocebo effects in EI, including (i) intensity (e.g., would the added effect**
53 **of exercise be greater at a higher intensity?), (ii) mode (e.g., does cycling or running**
54 **during placebo/nocebo experimental result in different effects?, (iii) neurobiological**
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3 **mechanisms (e.g., how would blocking the opioid or endocannabinoid system affect**
4 **conditioned placebo and nocebo responses during exercise?), and (iv) habitual**
5 **expectations (e.g., is conditioning easier to implement in participants with stronger**
6 **pre-existing expectations about the effect of exercise on pain?).”**
7
8

9 Finally, authors should consider the influence beliefs can have on the psychological
10 outcomes of exercise. The authors have written extensively about expectations and
11 have not considered the effect beliefs can have on the effect of an intervention. While
12 authors have suggested expectations are fluid, beliefs are generally more resistant to
13 change. Therefore, in a study that aims to manipulate expectations of the effects of
14 exercise, it may also be important to understand participants’ beliefs about the
15 intervention as well, which may provide a greater insight into why people may respond
16 to placebo effects and others don't.
17
18

19
20 **Thank you for this point, however, since beliefs are part of the definition of habitual**
21 **expectations, we believe your concern is addressed with our discussion of habitual**
22 **expectations throughout the manuscript. To help further address your point, in the**
23 **3.1. Classification and definitions section we have made an effort to highlight the**
24 **distinction between habitual and study specific expectations in terms of those that are**
25 **resistant to change versus those that are more dynamic.**
26
27

28 29 **Specific comments**

30
31 P4 L69-70 – Reference is needed
32

33
34 **The specific references being used to support this argument are provided in**
35 **subsequent sentences in this paragraph. If the reviewer and editor feel strongly that**
36 **this is not clear to the reader, we are happy to also add these references to the first**
37 **sentence, but our goal was to reduce reference redundancy and the amount of text in**
38 **the paragraph.**
39

40
41 P8 L159 – The reference given here is over 20 years old. An updated reference that
42 reflects recent advancements in the field is needed.
43

44
45 **Thank you. We have substituted the Ernst and Resch (1995) citation for the more**
46 **recent review by Finniss et al. (2010) who also observe that “In the case of clinical**
47 **populations, the study of long-term placebo responsiveness has been limited to RCTs.**
48 **However, these studies rarely included groups of participants receiving no treatment**
49 **to control for natural history and regression to the mean, making it difficult to**
50 **discern a genuine placebo effect.”**
51

52
53 **Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Biological, clinical and**
54 **ethical advances in placebo effects. *Lancet*, 375, 686–695.**
55
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1
2
3 P9 L185 – An example of a study that has examined this would be useful
4

5 **We now reference Tieman and colleagues (2002) who explored how their results were**
6 **affected before and after accounting for expectations in their statistical model.**
7

8
9 **Tieman, J. G., Peacock, L. J., Cureton, K. J., & Dishman, R. K. (2002). The influence of**
10 **exercise intensity and physical activity. *International Journal Sports Psychology*, 33,**
11 **155–166.**
12

13
14 P11 L235 – Authors should explain the results of this study here
15

16 **We now expand on this study and another recently published study by Arbinaga and**
17 **colleagues (2018).**
18

19
20 **“This issue has also been considered in exercise research where the investigators**
21 **minimized demand characteristics by using deceptive information in the study**
22 **advertisement and informed consent materials to disguise the study purpose**
23 **(Arbinaga, Fernández-Ozcorta, Sáenz-López, & Carmona, 2018; Lindheimer, O’Connor,**
24 **McCully, & Dishman, 2017). Interestingly, this research has shown that even when the**
25 **investigators purposefully tried to alter participant expectations at a later point in the**
26 **study, disguising the true purpose of the study early on may have blunted the**
27 **effectiveness of the experimental manipulations. For example, Lindheimer and**
28 **colleagues measured mood and cognitive responses to light intensity active cycling or**
29 **motorized passive cycling, but informed participants that the purpose was to compare**
30 **cardio-respiratory responses between the two conditions. Although half of these**
31 **participants were exposed to an expectancy manipulation designed to enhance**
32 **expectations for psychological improvements following exercise, the investigators did**
33 **not observe a significant difference in expectations or psychological responses to**
34 **exercise between participants who received the expectancy manipulation and those**
35 **who did not (Lindheimer et al., 2017). In a second investigation that measured self-**
36 **esteem changes following seven weeks of moderate intensity aerobic exercise**
37 **training, participants were told that the purpose was to study brain activity during**
38 **tasks of conditioned discrimination. Again, no differences were found between**
39 **participants who were exposed to information that exercise improves psychological**
40 **variables and those who did not receive such information (Arbinaga et al., 2018).**
41 **These findings have therefore provided some evidence that disguising the study**
42 **purpose may be an effective way to minimize the effect of study specific expectations**
43 **on psychological responses to exercise.”**
44
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50
51 P12 L251 – While the paper is focused on controlling the placebo effect in
52 clinical/research practice, it would be worthwhile for authors to acknowledge that in
53 applied practice the aim is to augment the placebo effect to maximise treatment effects
54 (see <https://insights.ovid.com/crossref?an=00149619-201507000-00009>).
55
56
57
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1
2
3 **We agree and have added the following sentence to item 3 of the “5. Future**
4 **Directions” section.**
5

6
7 **“3. Measuring expectations in expectancy modification studies is also encouraged.**
8 **Verifying the success of the manipulation by measuring expectations would allow**
9 **researchers to begin cataloging which types of expectancy modification procedures**
10 **are most effective. This information may be especially valuable for addressing calls to**
11 **maximize treatment effects in clinical settings by augmenting the contribution of**
12 **placebo effects (Evers et al., 2018).**
13

14
15 P14 L299 – an example of an item on this scale and a psychological outcome would be
16 helpful
17

18
19 **We agree. In order to reduce word count, we have removed the section on measuring**
20 **expectations, but we have addressed this point in item 2 of the future directions**
21 **section.**
22

23
24 **“2. The measurement of expectations for psychological outcomes of exercise would be**
25 **improved by using psychometric instruments that measure study-specific**
26 **expectations. Rather than using questionnaires with inherent biases toward only**
27 **measuring expectations for desirable outcomes, we recommend using questionnaires**
28 **with item phrasing and scales that allow a respondent to indicate expectations for**
29 **either positive or negative changes for neutrally presented psychological outcome. For**
30 **instance, a study of EIH can ask participants to rate their level of expected changes in**
31 **pain on a bipolar Likert-type scale with verbal anchors that allow the participant to**
32 **indicate the expected direction and degree of change (e.g., -3 = “large decrease”, -2 =**
33 **“moderate decrease”, -1 “slight decrease”, 0 “no change”, 1= “slight increase”, 2=**
34 **“moderate increase”, 3= “large increase”).”**
35
36
37

38
39 P10 L310 - this sentence needs rewording
40

41 **Agreed, thank you for catching that. The sentence has been changed to the following:**
42

43 **“The approach to measuring expectations should be guided by several questions.”**
44

45
46 P15 L329 – Authors should acknowledge that if researchers employ questionnaires pre,
47 during and post study, they might allude participants to the nature of the study, which
48 may further alter expectations.
49

50
51 **We agree and have added the following to the end of this paragraph:**
52

53 **“However, researchers who adopt this strategy should also be cautioned that the**
54 **repeated and overt measurement of expectations may increase demand**
55 **characteristics by alerting participants to the study purpose or result in reactivity, a**
56
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3 **behavioral artifact wherein observed changes are confounded by a participant's**
4 **awareness that a given psychological or behavioral construct is being measured**
5 **(French & Sutton, 2010)."**
6

7
8 P16 L352 – Given the recent and numerous debates about whether there are placebo
9 and exercise responders, a short narrative should be written concerning this. It could be
10 argued that those who respond to exercise are also placebo responders.
11

12
13 **This is a very interesting point, but we would prefer not to bring this up in our review.**
14 **The exercise responder vs. non-responder debate appears heavily focused on physical**
15 **and physiological adaptations to exercise rather than psychological responses to**
16 **exercise. Moreover, the revised version of this manuscript is still ~1000 words over**
17 **the limit, thus we would prefer to prioritize other sections of the manuscript that we**
18 **feel are more within the scope and objectives of this review.**
19

20
21 P17 L366 – Would low expectations not induce nocebo effects? It would be better to
22 sample participants who have no awareness of understanding the effects of exercise on
23 psychological outcomes.
24

25
26 **Perhaps, but as we state in our attempt to address your below comment on placebo**
27 **run-in trials, finding individuals with low or negative expectations may be challenging,**
28 **especially when the trial is focused on an endpoint for which information on the**
29 **psychological benefits of exercise is widely publicized such as depression or anxiety.**
30

31
32 P18 L378 - Placebo run in trials are also used to minimise placebo effects. That is,
33 participants enrolled onto a study often report a placebo effect, which is suggested to
34 dissipate as the trial goes on. It would be useful to highlight this here too and determine
35 the effects on exercise over a longer period
36

37
38 **We have added the following to address this comment:**
39

40
41 **"...Considering that placebo run-in trials are also used to decrease placebo or nocebo**
42 **effects by habituating participants to the placebo prior to baseline testing, another**
43 **possibility is to familiarize participants to several acute bouts of exercise before**
44 **starting the trial. In terms of recruitment, this strategy may be more feasible than**
45 **screening for expectations because finding individuals with low or negative**
46 **expectations may be challenging, especially when the trial is focused on an endpoint**
47 **for which the psychological benefits of exercise are widely publicized such as**
48 **depression or anxiety."**
49

50
51 P19 L419 – Manipulation checks should also be used to ensure that the information did
52 not elicit a nocebo effect (as noted on P15 Lines 330)
53

54
55 **We agree and have added the following sentence here:**
56

1
2
3
4 **“...To further improve the understanding of how to effectively elicit or minimize**
5 **nocebo effects, questionnaires that also provide the ability to measure negative**
6 **expectations should be incorporated in manipulation checks.”**
7
8

9 P20 L434 – an explanation of the results from this study would be useful
10

11 **The section of balanced placebo designs has been deleted. This study is now instead**
12 **described in the last paragraph of the expectancy modification section:**
13

14
15 **“Investigators who implement expectancy modification designs should be cautioned**
16 **about the trade-off between effectively modifying expectations and introducing cues**
17 **that might lead participants to guess the purpose of the study. For instance, in the**
18 **expectancy modification study by Lindheimer and colleagues, the investigators were**
19 **successful in terms of preventing a majority of participants from guessing the study**
20 **purpose (~92%), however, expectations for psychological changes were not different**
21 **between participants who received the expectancy modification and those who did**
22 **not, indicating that the expectancy modification was not successful (Lindheimer et al.,**
23 **2017). Thus, one challenge for future investigators who decide to use expectancy**
24 **modification designs is determining how to effectively modify and measure**
25 **participant expectations without increasing demand characteristics by tipping off**
26 **participants to the purpose of the study.”**
27
28
29
30

31 Figure 1 Include Hedges d alongside percentages
32

33
34 **Done.**
35

36 Table 1 The balanced placebo design considers psychological factors other than
37 expectancy related placebo effects. This should be reworded to reflect this. This
38 definition should also reflect cross-over designs.
39
40

41 **As part of our effort to reduce the word count and consolidate information, mention**
42 **of the balanced placebo design has been removed altogether.**
43

44
45 The definition of the placebo and nocebo effect should reflect that they can be induced
46 without the administration of a placebo (see point above)
47

48 **We agree and have changed the definition of placebo/nocebo effect to say the**
49 **following in Table 1:**
50

51
52 **“Placebo/nocebo effect: A desirable (placebo effect) or undesirable (nocebo effect)**
53 **outcome resulting from a person’s expected and/or learned response to a treatment**
54 **or situation. Recent advances indicate that it is not always necessary to administer a**
55 **traditional placebo (i.e., inert substance) in order to observe and measure the**
56
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1
2
3 **contribution placebo/nocebo effects to a treatment (Benedetti, 2008; Finniss et al.**
4 **2010)."**
5

6
7 Table 2 Is this an exhaustive list? If not, then the title needs to reflect that these are
8 examples
9

10 **This table is meant to provide a wide variety of examples rather than an exhaustive**
11 **list. The title has been changed to the following:**
12

13
14 **"Examples of outcomes that have been measured via self-report or task performance**
15 **in exercise studies."**
16

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For Peer Review Only

1 **ABSTRACT:** Despite the apparent strength of scientific evidence suggesting that psychological benefits
2 result from both acute and chronic exercise, concerns remain regarding the extent to which these
3 benefits are explained by placebo effects. Addressing these concerns is methodologically and at times
4 conceptually challenging. However, developments in the conceptualization and study of placebo effects
5 from the fields of psychology, neuroscience, pharmacology, and human performance offer guidance for
6 advancing the understanding of placebo effects in psychological responses to exercise. In clinical trials,
7 expectations can be measured and experimentally manipulated to better understand the influence of
8 placebo effects on treatment responses. Further, compelling evidence has shown that the contribution
9 of placebo effects and their underlying neurobiological mechanisms to treatment effects can be
10 measured without administering a traditional placebo (e.g., inert substance) by leveraging psychological
11 factors such as expectations and conditioning. Hence, the purpose of this focused review is to integrate
12 lessons such as these with the current body of literature on placebo effects in psychological responses
13 to exercise and provide recommendations for future research directions.

14
15
16
17 **KEYWORDS:** Behavior; Cognition; Health; Methodology; Neuroscience
18

19 HIGHLIGHTS:

- 20 • Several methodological factors render investigations of psychological outcomes of acute and
21 chronic exercise vulnerable to placebo effects.
- 22
- 23 ~~• In randomized-controlled studies three conditions, a treatment, no-treatment control, and
24 placebo group, are all required to distinguish treatment effects from placebo effects.~~
- 25
- 26 • ~~True placebo groups may not be possible when studying psychological responses to exercise,
27 but studies from other fields that demonstrate that traditional placebos are not always required
28 to study the impact of psychological mechanisms of placebo effects their on treatment
29 responses.~~
- 30
- 31 • Measurement of expectations can help explain inter-individual variability in psychological
32 responses to exercise.
- 33
- 34 • Expectancy modification and conditioning can each be used to enhance treatment responses
35 and elucidate the neurobiological mechanisms that mediate the influence of placebo and
36 nocebo effects on these responses. There are several potential methods for measuring the
37 influence of placebo effects on the magnitude and mechanisms of psychological responses to
38 exercise.

1. INTRODUCTION

Over the last 50 years ~~or so~~, the concept of a placebo has evolved from a therapeutically inert substance to also ~~include~~ incorporate the sensory and social stimuli that ~~tell~~ inform patients they are receiving a beneficial treatment (Benedetti et al., 2011). The sophistication of approaches to studying placebo effects has also evolved. These range from ~~recognition for the importance of including both placebo and no-treatment control groups~~ distinguishing placebo effects from other non-specific effects in clinical trials (Ernst & Resch, 1995) to the use of elegant multi-condition experimental designs (Enck, Klosterhalfen, & Zipfel, 2011) and neuro-imaging technologies to measure placebo effects and their respective neuro-biological mechanisms in laboratory based studies (Benedetti & Amanzio, 2013). The study of nocebo effects has also progressed and this line of research has made a critical contribution to the understanding of why negative outcomes (e.g., symptom worsening) sometimes result from the administration of placebos (Frisaldi, Piedimonte, & Benedetti, 2015; Webster, Weinman, & Rubin, 2016).

As the understanding of placebo and nocebo effects expands across scientific disciplines, researchers and clinicians are recognizing the need for conceptual clarity as well as guidelines for evidence-based and ethical use of placebo and nocebo effects in clinical practice. Recently, an international working group consisting of 29 experts released a consensus statement to address some of these issues, including the distinction between placebo/nocebo responses versus effects (Evers et al., 2018). The *placebo and nocebo response* was said to include all health changes that result after administration of an inactive treatment, including those that may occur from natural history and regression to the mean. On the other hand, *placebo and nocebo effects* were defined as the changes specifically attributable to placebo and nocebo mechanisms, including the neurobiological and psychological mechanisms of expectancies. These definitions have been adapted in a recent consensus statement on the study of placebo and nocebo effects in sport and exercise, in which placebo and

62 nocebo effects were defined as a desirable or undesirable outcome resulting from a person's expected
63 and/or learned response to a treatment or situation (Beedie et al., 2018).

64 The importance of designing exercise-based studies to account for placebo effects was
65 recognized over three decades ago (McCann & Holmes, 1984); ~~however~~ However, progress toward
66 advancing the current standard of knowledge about placebo effects and their respective mechanisms
67 in elucidation of the incidence, magnitude, and mechanisms of placebo effects in psychological
68 responses to exercise has been relatively slow lower in coming compared ~~to~~ with other scientific fields.
69 Taking into account recent interdisciplinary developments in the conceptualization and study of placebo
70 effects ~~into account~~, ~~the purposes of this review are to~~ the purpose of this review is to highlight discuss
71 topics that are central to advancing the understanding of placebo effects in psychological responses to
72 exercise, including: (i) the theory and practice of controlling for placebo effects, (ii) the importance of
73 ~~measuring outcome~~ expectations, (iii) experimental methods for studying ~~mechanisms~~ the influence of
74 ~~of placebo effects~~ and their neurobiological mechanisms on treatment responses, and (iv) future
75 research directions ~~for advancing the understanding of placebo effects in psychological responses to~~
76 exercise. To aid comprehension of key concepts and facilitate this discussion, a list of key terms is
77 provided in Table 1.

78 [Table 1 about here]

79 Findings from the small body of studies that ~~have attempted to account for~~ examined -placebo
80 or nocebo effects in psychological responses to exercise are ~~also~~ also integrated throughout this review.
81 Herein, outcomes that are measured via self-report in exercise studies are broadly referred to as
82 psychological outcomes or responses. These include variables from the categories of mental health (e.g.,
83 anxiety, depression) and perception (e.g., perceived exertion, muscle pain, pain intensity, symptom
84 severity) as well as other types of constructs (e.g., body image, affect, mood, self-esteem). Although
85 ~~some of these outcomes are clearly more psychological in nature than others, they are all similarly~~

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3 86 ~~subject to limitations that are inherent to self-report measures.~~ Additionally, we recognize that
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5 87 cognition can be assessed by task performance or self-report, but we also consider it to fit within the
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7 88 scope of psychological outcomes/responses (Table 2).
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10 89 [Table 2 about here]

11 90 ~~2. CONTROLLING FOR PLACEBO EFFECTS IN EXERCISE INTERVENTIONS~~

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13
14 91 Effect size estimates from meta-analytic reviews of randomized controlled trials support the
15
16 92 argument that exercise training improves psychological outcomes. For self-reported outcomes such as
17
18 93 anxiety, depression, fatigue, and pain, exercise training appears to result in small (Standardized mean
19
20 94 difference = 0.29) to moderate (Standardized mean difference = 0.62) improvements (Cooney et al.,
21
22 95 2013; Herring, Puetz, O'Connor, & Dishman, 2012; Herring, O'Connor, & Dishman, 2010; Puetz,
23
24 96 O'Connor, & Dishman, 2006; Searle, Spink, Ho, & Chuter, 2015). Additionally, exercise training has a
25
26 97 small, but significant effect on certain domains of cognitive performance (Standardized mean difference
27
28 98 = 0.12-0.16) (Smith et al., 2010). However, there are several methodological ~~factors-issues~~ that have
29
30 99 raised concerns about the ability to distinguish these observed effects of exercise from placebo
31
32 100 effects (Lindheimer, O'Connor, & Dishman, 2015; Ojanen, 1994; Szabo, 2013). ~~These,~~ include:ing, (i) the
33
34 101 inability to perform double-blind studies, (ii) demand characteristics, and (iii) the largely subjective
35
36 102 nature of many psychological outcome measures. ~~Moreover it is difficult to measure placebo effects in~~
37
38 103 ~~randomized controlled trials when both a placebo and control comparison group are not included (Ernst~~
39
40 104 ~~& Resch, 1995).~~ In the following section, we discuss ~~why this design consideration is~~ the theoretical
41
42 105 importance of including placebo and no-treatment control groups to measure placebo effects in clinical
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44 106 trials ~~and also highlight some practical barriers to designing studies with placebo and no-treatment~~
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46 107 control groups why this is difficult in studies of psychological responses to exercise.
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52 108 ~~2.1. The Importance of including placebo and control conditions~~ Characterizing placebo effects in
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54 109 clinical trials
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3 110 The introduction of the terms *true placebo effects* and *perceived placebo effects* has helped
4
5 111 clarify why both placebo and control groups are needed to measure placebo effects in clinical trials
6
7 112 (Ernst & Resch, 1995). An early misconception was that placebo effects could be studied in clinical trials
8
9
10 113 by measuring change from baseline in the placebo group (i.e., perceived placebo effects) (Beecher,
11
12 114 1955). However, this approach fails to consider that the changes in a placebo group can result from that
13
14 115 are could be explained by non-specific effects such as natural history of disease, regression towards the
15
16 116 mean, and unidentified parallel interventions (Ernst & Resch, 1995; Kienle & Kiene, 1997). Presumably, if
17
18 117 the randomization of participants to their respective groups is successful, these same non-specific
19
20 118 effects would presumably have an equal likelihood of occurring in a wait-list or no-treatment control
21
22 119 group. Thus, subtracting the change in the control group from the change in the placebo group
23
24 120 accounts for non-specific effects and therefore, a more precise estimation of the so-called 'true'
25
26 121 placebo effect is measured could be obtained by comparing the change in the placebo group to that of
27
28 122 the control group provides a more precise estimation of the placebo effect in the clinical trial setting.

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31
32 123 Ernst and Resch have also introduced the concepts of *perceived treatment effects* and *true*
33
34 124 *treatment effects*. The perceived treatment effect is considered to be the change from baseline that is
35
36 125 measured in the treatment group and the true treatment effect is therefore obtained after accounting
37
38 126 for placebo effects and other non-specific effects (Ernst & Resch, 1995). In the exercise setting, these
39
40 127 terms are synonymous with *observed effect of exercise* and *true effect of exercise* the observed effect
41
42 128 of exercise is the psychological response resulting from both true effects of exercise and placebo effects
43
44 129 whereas the true effect of exercise is the psychological response that can be solely attributed to the
45
46 130 exercise *per se*. (Ojanen, 1994). That is, in a group that has been assigned to receive the exercise
47
48 131 treatment, the observed effect of exercise is the psychological response resulting from both true effects
49
50 132 of exercise and placebo effects whereas the true effect of exercise is the psychological response that can
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52 133 be solely attributed to the exercise *per se*. Consequently, to obtain the most precise estimation of the
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3 134 ~~effect of exercise on psychological responses in a clinical trial or randomized controlled study design, we~~
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5 135 ~~use the principles outlined by Ernst and Resch (1995) and Ojanen (1994) to offer the following~~
6
7 136 ~~guidelines:~~
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9
10 137 ~~Determining the true effect of exercise/true treatment effect requires separation of the true placebo~~
11
12 138 ~~effect from the observed effect of exercise/perceived treatment effect; however, the true placebo effect~~
13
14 139 ~~must also be distinguished from the perceived placebo effect.~~
15
16 140 ~~In order to distinguish the true placebo effect from the perceived placebo effect, a no-treatment or~~
17
18 141 ~~wait-list control group is needed to rule out other non-specific effects that may explain changes in the~~
19
20 142 ~~outcome measure over time.~~
21
22 143 ~~Obtaining the most precise estimation of the true effect of exercise/true treatment effect in a clinical~~
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24 144 ~~trial or randomized controlled study design requires that participants be allocated to at least three~~
25
26 145 ~~groups—treatment, placebo and control.~~
27
28 146 ~~In line with these recommendations,~~Following this logicline of reasoning, Lindheimer and colleagues
29
30 147 ~~conducted a meta-analysis of randomized controlled studies~~ attempted to quantify ~~quantified~~ the
31
32 148 placebo effect in psychological ~~responses-outcomes of~~ exercise training studies by conducting in a
33
34 149 ~~meta-analysis of randomized controlled studies~~ randomized controlled trials that included with an
35
36 150 ~~exercise treatment arm, a control arm, and a placebo arm n arm that met their operational definition for~~
37
38 151 ~~a placebo condition (n = 9)~~ (Lindheimer et al., 2015). The authors attempted to provide a valid estimate
39
40 152 ~~of the true placebo effect and true effect of exercise by only including randomized controlled studies~~
41
42 153 ~~with an exercise treatment arm, a control arm, and an arm that met their operational definition for a~~
43
44 154 ~~placebo condition (n = 9).~~ In this case, the authors defined a placebo condition ~~was defined~~ as “an
45
46 155 intervention that was not generally recognized as efficacious, that lacked adequate evidence for
47
48 156 efficacy, and that has no direct pharmacological, bio-chemical, or physical mechanism of action
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55 157 according to the current standard of knowledge” (p. 695). After estimating the placebo effect by
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3 158 aggregating the standardized mean difference between the placebo and control groups from each study
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5 159 (Hedges' $d = 0.20$), they further and subtracting the true placebo effect was subtracted (Hedges' $d =$
6
7 160 0.20) from the observed effect of exercise, that is, the aggregated standardized mean difference
8
9 161 between the exercise and control groups from each study (Hedges' $d = 0.37$). Following this procedure,
10
11 162 the authors found concluded that the true effect of exercise training on psychological responses
12
13 163 (Hedges' $d = 0.17$) was less than half of the observed effect of exercise after accounting for placebo
14
15 164 effects (Figure 1). ~~Additional relevant findings included that, (i) placebo effects were larger in~~
16
17 165 ~~subjectively measured outcomes (i.e., anxiety, depression, energy, fatigue) compared to objectively~~
18
19 166 ~~measured outcomes (i.e., cognitive performance), (ii) placebo effects were larger in placebo conditions~~
20
21 167 ~~that resembled exercise, and (iii) few exercise training studies used designs that met the author's~~
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23 168 ~~criteria for measuring the true placebo effect.~~

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28 169 [Figure 1 about here]

29
30 170 **2.2. Practical issues with characterizing placebo effects in clinical trial study designs studies of**
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32 171 **psychological responses to exercise**

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34 172 Despite early recognition ~~for of~~ the importance ~~of for~~ using methods that improve the
35
36 173 estimation of placebo effects (McCann & Holmes, 1984), several barriers have continued to stymied
37
38 174 investigators and prevented widespread implementation of these methods in exercise training studies.
39
40 175 Foremost among these is the ~~apparent~~ inability to perform double-blind studies. Unlike pharmacological
41
42 176 interventions in which the vehicles that are used to deliver the treatment and placebo are identical (e.g.,
43
44 177 capsule, fluid, injection), it is considered to be impossible to truly blind participants to receiving exercise
45
46 178 in research settings. This, which in turn can provoke expectations - potentially positive or negative - that
47
48 179 an exercise treatment is being received. The is also brings up a related and unresolved issue—question
49
50 180 of what might constitutes a valid exercise placebo ~~and is it possible to develop one? is as yet unresolved.~~

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3 181 A review by Ojanen (1994) argued “that the idea of a placebo group in exercise studies is, in
4
5 182 practice, impossible”. Nonetheless, some early studies attempted to create valid exercise placebo
6
7 183 conditions by using very low intensity “minimal exercise” (Roth & Holmes, 1987) or relaxation training
8
9
10 184 (McCann & Holmes, 1984) and even made efforts to manipulate expectations for improvement with
11
12 185 verbal suggestion (McCann & Holmes, 1984). However, even in a study that reported equivalent
13
14 186 expectations, involvement and subjective utility between the treatment and minimal exercise condition
15
16
17 187 (Roth & Holmes, 1987), Ojanen reasoned that a real placebo condition was not used because a placebo
18
19 188 effect was not observed. This interpretation is not entirely accurate, however, because the inclusion of a
20
21 189 placebo condition does not necessarily always result in an observable placebo effect.

22
23 190 To date, Ojanen’s position on the practicality of using placebo groups in exercise still appears to
24
25 191 be supported because little progress has been made in developing a valid exercise placebo, one that is, a
26
27 192 placebo that mirrors every aspect of exercise except the “active ingredients”. Of course, this pursuit is
28
29 193 also limited by a lack of clarity begs the question of for what are the active ingredients (i.e., mechanisms)
30
31 194 responsible for the psychological changes associated with exercise of exercise actually are. Nevertheless,
32
33 195 these somewhat circular issues may be more important to consider when the objective is to study the
34
35 196 placebo effect *per se* rather than to study the involvement of placebo effects in psychological responses
36
37 197 to exercise. As we discuss later in this review, well established psychological mechanisms of placebo
38
39 198 effects such as expectations and conditioning can be used to enhance influence treatment responses,
40
41 199 providing a means of studying the contribution of placebo effects to treatment effects without the
42
43 200 inclusion of a traditional placebo condition. which suggests that placebo groups are not always
44
45 201 necessary in order to study the contribution of placebo effects to the effect of a treatment. For instance,
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47 202 Kong and colleagues showed a greater degree of pain relief in knee osteoarthritis patients assigned to
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49 203 receive acupuncture with enhanced treatment expectations compared to acupuncture alone or no-
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51 204 treatment (Kong et al., 2018). Additionally, compared to the acupuncture only group, the acupuncture
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205 [plus enhanced expectations group showed greater resting state functional connectivity between the](#)
206 [nucleus accumbens and several other brain regions with links to placebo hypoalgesia such as that have](#)
207 [been linked to placebo hypoalgesia such as the rostral anterior cingulate cortex and dorsolateral](#)
208 [prefrontal cortex](#) (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2013). [These findings suggest that](#)
209 [enhancing treatment expectations can change both behavioral and neurobiological outcomes to a](#)
210 [higher degree than treatment alone and this approach may also be considered as a viable option for](#)
211 [studying the impact of placebo effects on treatment responses to exercise. After integrating this](#)
212 [observation from the Roth & Holmes \(1987\) study with their finding that psychological changes in the](#)
213 [treatment group were not correlated with changes in aerobic fitness, Ojanen concluded that placebo](#)
214 [effects arise only after a certain threshold of exercise intensity.](#)

215 In addition to methodological barriers, [resources are](#) another obstacle to characterizing placebo
216 effects in studies of acute and chronic exercise [concerns feasibility](#). Provided that scientific advances
217 eventually lead to the development of a valid exercise placebo, conducting studies that include a
218 treatment, placebo and control arm with enough statistical power to detect [clinically meaningful](#)
219 between-group differences is resource intensive. Given the [amount of funding, time, participants,](#) and
220 personnel needed to conduct [clinical trials with the requisite placebo and no-treatment control arms](#)
221 [needed required to precisely measure the size of the placebo effect,](#) the lack of three-arm studies in the
222 field of exercise and mental health studies is not surprising. Even in research [involving drugs, surgical](#)
223 [procedures, or medical devices](#) where valid placebos are easier to implement, designs that include both
224 a placebo and no-treatment control group are historically scarce ([Finniss, Kaptchuk, Miller, & Benedetti,](#)
225 [2010](#)).

226 3. ~~OUTCOME~~ EXPECTATIONS: A PRIMARY PSYCHOLOGICAL MECHANISM OF PLACEBO EFFECTS

227 ~~Outcome expectations are beliefs that a given will lead to a certain outcome and a~~ wide-body
228 of research has demonstrated their role [of expectations](#) as a psychological mechanism of placebo effects

229 (Benedetti, 2008; Finnis, Kaptchuk, Miller, & Benedetti, 2010; Kirsch, 1997; Price et al., 2008). In the
230 context of an exercise study, these data suggest that placebo effects are more likely to occur in
231 participants who expect that exercising will result in a certain psychological response — (e.g.,
232 “exercise will improve my mood”) compared to those who do not. ~~Thus, considering the present degree
233 of uncertainty about whether it is possible to include placebo groups in exercise studies, the
234 measurement of outcome expectations has generated interest as a solution for controlling placebo
235 effects in psychological responses to exercise.~~

236 Measuring self-reported expectations ~~does not solve the problem of controlling for
237 placebo should not be viewed as a surrogate for a placebo condition, effects in exercise interventions
238 that do not include placebo groups, but it this practice~~ can help explain variability in psychological
239 responses ~~in participants assigned to the exercise condition to exercise. Moreover, designing a study to
240 reduce the likelihood of generating certain expectations for psychological changes following exercise can
241 help minimize placebo effects altogether. This claim is supported by data from laboratory studies and
242 clinical trials which illustrate that treatment effects can be amplified or reduced by expectations
243 (Benedetti, 2008). These studies have important implications in the design and conduct of exercise
244 interventions because the results and interpretation of the study could be affected by whether or not
245 expectations are not taken into consideration. A way to address this issue is to measure expectations
246 and study their influence on psychological responses to exercise.~~ To help researchers accomplish this
247 goal, we operationalize several different types of outcome expectations; ~~describe how they are typically
248 measured,~~ and illustrate scenarios in which it is useful to take them into account.

249 3.1. Classification and definitions

250 ~~When incorporating the measurement of outcome expectations in a study of psychological
251 responses to exercise, investigators should recognize that it is important to recognize that there are
252 several types of expectations, some of which are stable and resistant to change and others that are~~

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2
3 253 ~~more dynamic. -distinction between expectations that were developed prior to involvement in a study~~
4
5 254 ~~and those that can develop as a result of study involvement.~~ **Habitual expectations** are thought to
6
7 255 primarily reflect an individual's previous experiences or cultural beliefs (Mothes et al., 2016). Several
8
9 256 plausible factors may play a role in how habitual expectations are developed and their level of influence
10
11 257 on the measurement of psychological responses to exercise. These include level of habitual physical
12
13 258 activity behaviour, particularly salient memories of psychological responses to exercise, and exposure to
14
15 259 information from various sources (e.g., media, peers, family members, educators, clinicians, prior
16
17 260 research participation) about positive or negative effects of exercise. How these ~~various~~ factors interact
18
19 261 to form habitual expectations is not well studied, but the accumulation of these experiences over time
20
21 262 presumably influences a research participant's interpretation of how they feel during and after
22
23 263 exercisesing.

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28 264 ~~Because expectations are fluid and can change in response to new experiences (Kirsch, 2018),~~
29
30 265 ~~investigators should also recognize that participation in a research study that participation in a research~~
31
32 266 ~~study has the potential to can~~ alter pre-existing expectations or create new ones. Thus, we now
33
34 267 introduce the term **study-specific expectations** to address the expectations that are more fluid than
35
36 268 habitual expectations and can change in response to new experiences such as participating in a research
37
38 269 study (Kirsch, 2018). ~~help increase awareness for the importance of measuring potential changes in~~
39
40 270 ~~expectations that can happen over the course of study participation.~~ Study-specific expectations are
41
42 271 unique because they take experiences that occur *during* the various phases of participation in a
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44 272 laboratory or clinical study into account (e.g., advertising, recruitment, screening, informed consent,
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46 273 familiarization, data collection), whereas habitual expectations ~~solely pertain to more so reflective of a~~
47
48 274 participant's ~~individual history of prior~~ real-world experiences with exercise.

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52 275 ~~Study-specific expectations can be further classified in terms of whether or not an investigator~~
53
54 276 ~~intended for them to develop during research participation.~~ Because expectations are a known

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3 277 psychological mechanism of placebo effects, researchers may-can intentionally manipulate them to
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5 278 study-examine their impact on psychological responses to exercise. Thus, study-specific expectations
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8 279 that are a direct consequence of an experimental manipulation have been referred to as
9
10 280 ***experimentally-induced expectations*** (Mothes et al., 2016) and their importance is discussed in later
11
12 281 sections of this review. Conversely, we introduce the term ***incidentally-induced expectations*** to
13
14 282 acknowledge the study-specific expectations that are created by which results from some aspect of the
15
16 283 study that was unintended by the investigator. Incidentally-induced expectations can introduce error
17
18 284 variance into the measurement of psychological responses to exercise, which is why it is critical to take
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21 285 them into account during the design and conduct of a study.

22
23 286 One way to control for incidentally-induced expectations is to reduce potential sources of
24
25 287 ***demand characteristics***, the totality of cues that can lead a participant to guess the experimental
26
27
28 288 hypothesis of the study (Orne, 1962). A significant source of these cues can-arise-from is information
29
30 289 communicated by study materials (e.g., advertisements, informed consent documents). For instance,
31
32 290 Foroughi and colleagues reported that following one hour of practicing cognitive tasks, performance on
33
34 291 fluid intelligence tests was better among participants who enrolled in the study after viewing an overt
35
36 292 advertisement for a “Brain Training and Cognitive Enhancement” study compared to participants who
37
38 293 responded to a generic advertisement with no information about brain training or cognitive
39
40 294 enhancement (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016). Although the authors did
41
42
43 295 not collect explicit information that would allow them to test for between-group differences in
44
45 296 expectations, their study provided a clear example of how information that overtly communicates the
46
47 297 study purpose can affect a given participant’s behaviour.

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50 298 This issue has also been considered in exercise research where the investigators minimized
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52 299 demand characteristics by using deceptive information in the study advertisement and informed
53
54 300 consent materials to disguise the study purpose (Arbinaga, Fernández-Ozcorta, Sáenz-López, &
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3 301 Carmona, 2018; Lindheimer, O'Connor, McCully, & Dishman, 2017). Interestingly, this research has
4
5 302 shown that even when the investigators purposefully tried to alter participant expectations at a later
6
7 303 point in the study, disguising the true purpose of the study early on may have blunted the effectiveness
8
9 304 of the experimental manipulations. For example, Lindheimer and colleagues measured mood and
10
11 305 cognitive responses to light intensity active cycling or motorized passive cycling, but informed
12
13 306 participants that the purpose was to compare cardio-respiratory responses between the two conditions.
14
15 307 Although half of these participants were exposed to an expectancy manipulation designed to enhance
16
17 308 expectations for psychological improvements following exercise, the investigators did not observe a
18
19 309 significant difference in expectations or psychological responses to exercise between participants who
20
21 310 received the expectancy manipulation and those who did not (Lindheimer et al., 2017). In a second
22
23 311 investigation that measured self-esteem changes following seven weeks of moderate intensity aerobic
24
25 312 exercise training, participants were told that the purpose was to study brain activity during tasks of
26
27 313 conditioned discrimination. Again, no differences were found between participants who were exposed
28
29 314 to information that exercise improves psychological variables and those who did not receive such
30
31 315 information (Arbinaga et al., 2018). These findings have therefore provided some evidence that
32
33 316 disguising the study purpose may be an effective way to minimize the effect of study specific
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35 317 expectations on psychological responses to exercise.
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41 318 Demand characteristics can also stem from interactions between test administrators and study
42
43 319 participants. For instance, consider a clinical trial that examines the effect of exercise training on
44
45 320 cognitive performance compared to a no-treatment control condition. A test administrator may
46
47 321 inadvertently bias a participant who they know is in the exercise group to try harder on the cognitive
48
49 322 task than those assigned to the control group because of their own inherent bias that exercise will
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51 323 improve cognition. To prevent this situation from occurring, an investigator can try implementing a
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324 ~~single blinding procedure by ensuring that study personnel who are involved in exercise training are not~~
325 ~~also involved in test administration.~~

326 Indeed, the role of demand characteristics in psychological responses to exercise has long been
327 recognized (Morgan, 1997). ~~and relatively feasible strategies~~ These can be reduced, for example, by such
328 ~~as~~ using neutral language in study materials and blinding test administrators to condition assignment.
329 ~~can be used to minimize their effects.~~ Although these steps may increase the methodological rigor of
330 exercise research, they are not always practical to implement and unlikely to completely prevent study-
331 specific expectations from developing. Thus, ~~even the most well designed studies~~ researchers should
332 consider ~~including measures~~ measuring of expectations to help ~~control for~~ determine their potential
333 influence on the results.

334 **3.2. Measuring outcome expectations**

335 ~~Substantial between-study variability in the literature indicates that there is no widely accepted~~
336 ~~consensus on best practices for measuring participant expectations for psychological outcomes of~~
337 ~~exercise. This issue is especially complicated by the decision of whether to use psychometrically~~
338 ~~validated or investigator-developed questionnaires because each option has advantages and~~
339 ~~disadvantages. To help illustrate this point and provide guidance for future researchers, we discuss prior~~
340 ~~methods that have been used to measure expectations and potential difficulties with measuring them.~~

341 **3.2.1 Psychometrically validated questionnaires**

342 Several questionnaires have been developed that measure outcome expectations for
343 psychological responses to exercise, including the Exercise Benefits/Barriers Scale (Sechrist, Walker, &
344 Pender, 1987), the Outcome Expectancy Values Scale (Steinhardt & Dishman, 1989), and the Outcome
345 Expectations for Exercise Scale (Resnick, Zimmerman, Orwig, Furstenberg, & Magaziner, 2000). From a
346 psychometric perspective these questionnaires are advantageous to use because their validity and
347 reliability have been tested. However, a practical disadvantage of the validated questionnaires that are

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2
3 348 currently available is their emphasis on general psychological responses (e.g., “a major benefit of
4
5 349 physical activity for me is the positive psychological effect”):

6
7 350 When an investigator is interested in differentiating a specific expectation from the wide span of
8
9 351 expected psychological effects that may come to a participant’s mind when thinking about exercise
10
11 352 (Table 2), a questionnaire that assesses expectations for general psychological responses is somewhat
12
13 353 limited in scope. Thus, there is a need for a validated expectancy questionnaire with a higher level of
14
15 354 specificity for a wide variety of psychological outcomes in the literature that may be of interest in a
16
17 355 given study. Meanwhile, investigators who want to control for expectations for a specific psychological
18
19 356 outcome rather than general psychological effects are faced with the dilemma of using a validated
20
21 357 questionnaire that lacks specificity or creating a study-specific questionnaire that has not been
22
23 358 validated.

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27 359 In addition to greater levels of specificity, A further need for expectancy measurement is a
28
29 360 validated questionnaire that measures expectations for negative psychological responses is also needed.
30
31 361 The validated questionnaires that are currently available in the literature use item phrasing and scales
32
33 362 that do not provide the respondent with the ability to indicate positive *and/or* negative expectations for
34
35 363 psychological responses to exercise (Sechrist et al., 1987; Steinhardt & Dishman, 1989; Wojcicki et al.,
36
37 364 2009). For instance, the Outcome Expectations for Exercise Scale asks participants to rate their level of
38
39 365 agreement or disagreement with positive outcomes items such as “Exercise makes my mood better in
40
41 366 general”, whereas a questionnaire that uses items with neutral instructions such as “rate the degree of
42
43 367 expected *changes* in each outcome” and provides a bi-polar scale to assess expected decreases or
44
45 368 increases for a list of psychological outcome (e.g., anxiety, depression, stress) would permit the
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47 369 assessment of both negative or positive expectations in the same question. This information is valuable
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49 370 to collect because it may help explain why some individuals report negative psychological changes
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3 371 during or following exercise and the extent to which these changes are being caused by a feature of the
4
5 372 exercise stimulus (e.g. intensity).
6

7 373 **3.2.2 Investigator-developed questionnaires**

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9
10 374 Despite the potential psychometric pitfalls of using non-validated questionnaires, the use of
11
12 375 investigator-developed scales has been adopted as a strategy for measuring outcome expectations
13
14 376 (Desharnais, Jobin, Cote, Levesque, & Godin, 1993; King, Taylor, Haskell, & DeBusk, 1989; Moses,
15
16 377 Steptoe, Mathews, & Edwards, 1989). One key advantage of these scales over psychometrically
17
18 378 validated scales is specificity. That is, they can be designed to measure expectations that parallel the
19
20 379 actual outcome measure being used, a strategy which is recommended when measuring expectations
21
22 380 for the purpose of predicting changes in a specific outcome (Kirsch, 2018). For example, a 6-month
23
24 381 exercise training study by King and colleagues created an expectation questionnaire with 14 Likert
25
26 382 scaled items that directly corresponded to each psychological outcome that was measured over the
27
28 383 course of the study (King et al., 1989).
29

30
31
32 384 In addition to providing a greater level of specificity, investigator-developed questionnaires are
33
34 385 well-suited to measuring study-specific expectations because their instructions and items can be
35
36 386 adjusted to make it clear to the respondent that the questionnaire is referring to expected outcomes of
37
38 387 that particular study rather than physical activity in general. For instance, a randomized controlled trial
39
40 388 by McCann and Holmes (1984) measured study-specific expectations with the following investigator-
41
42 389 developed questionnaire items: (i) "Rate the degree of progress you feel you will make in managing
43
44 390 stress more effectively", (ii) "To what extent does the training you will receive seem as though it should
45
46 391 help?", (iii) "How would you rate the probability of the training helping you to manage the stress you
47
48 392 typically feel?" (McCann & Holmes, 1984).
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50 393 **3.3.2. Application of measuring expectations**

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3 394 The approach to measuring participant expectations should be guided by several questions.
4
5 395 These include, (i) are the needs of the study design addressed by measuring habitual expectations,
6
7 396 study-specific expectations, or both?, (ii) what is the required level of specificity needed to answer the
8
9 397 research question?, (iii) how will the information be used to guide the interpretation of the study
10
11 398 results?, and (iv) do the advantages of using a validated questionnaire or investigator-created
12
13 399 questionnaire outweigh the disadvantages? Below we detail several scenarios in which these questions
14
15 400 may be considered.

19 401 **3.32.1. Testing for differential expectations**

21 402 One important application is testing for *differential expectations*, that is, ensuring that study
22
23 403 results are not confounded by differences in habitual or study-specific expectations between the
24
25 404 experimental and control group (Boot, Simons, Stothart, & Stutts, 2013; Stothart, Simons, Boot, &
26
27 405 Kramer, 2014). For instance, in a study of the acute effects of exercise, apparent significant
28
29 406 improvements in state anxiety were nullified after accounting for habitual expectations at baseline
30
31 407 (Tieman, Peacock, Cureton, & Dishman, 2002). Because study-specific expectations are more likely than
32
33 408 habitual expectations to change in the course of a repeated-measures study, performing mid-study
34
35 409 (McCann & Holmes, 1984) or post-study measurements (Desharnais, Jobin, Cote, Levesque, & Godin,
36
37 410 1993) is valuable because it allows the investigator to determine whether differential expectations were
38
39 411 present beyond the baseline period. However, researchers who adopt this strategy should also be
40
41 412 cautioned that the repeated and overt measurement of expectations may increase demand
42
43 413 characteristics by alerting participants to the study purpose or result in reactivity, a behavioral artifact
44
45 414 wherein observed changes are confounded by a participant's awareness that a given psychological or
46
47 415 behavioral construct is being measured (French & Sutton, 2010).

52 416 **3.32.2 Clarifying the role of nocebo effects in negative psychological responses to exercise**

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2
3 417 Negative expectations are centered around anticipation of negative responses to a given
4
5 418 stimulus and are strongly linked to nocebo effects (Benedetti, 2008; Webster, Weinman, & Rubin, 2016).
6
7 419 Similar to how the conceptualization of placebo effects has changed over time, the notion of nocebo
8
9
10 420 effect has been reframed to focus on the negative responses arising from specific psychological and
11
12 421 neurobiological mechanisms (Beedie et al., 2018; Evers et al., 2018), rather than on any negative
13
14 422 response that follows the administration of an inert substance (Kennedy, 1961). Measuring negative
15
16 423 expectations could provide valuable information in terms of understanding why some participants differ
17
18 424 in terms of the direction and magnitude of psychological responses to exercise (e.g., increases vs.
19
20 425 decreases in fatigue) and the variance in that response that is unique to the exercise itself versus
21
22 426 negative expectations of the participant. Little is known about the role of negative expectations in
23
24
25 427 psychological outcomes of exercise, but compelling evidence from other fields highlights their potential
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27
28 428 relevance to exercise studies (Blasini, Corsi, Klinger, & Colloca, 2017; Frisaldi et al., 2015; Webster et al.,
29
30 429 2016).
31
32 430 studies involving Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) indicate
33
34 431 that these are by no means ubiquitous across all healthy and clinical populations. It has repeatedly been
35
36 432 shown that ME/CFS patients often experience an exacerbation of their symptom severity (e.g., fatigue,
37
38 433 pain, mood disturbance) following physical exertion, a phenomenon known as post-exertional malaise
39
40 434 (Clayton, 2015; Loy, O'Connor, & Dishman, 2016). The mechanisms of post-exertional malaise are still
41
42 435 under investigation, but there is evidence that anticipation of a negative experience can influence both
43
44 436 brain activity (Burgmer et al., 2011) and exercise (Heins et al., 2013) in patients with Fibromyalgia, a
45
46 437 musculoskeletal pain condition that is co-morbid with ME/CFS (Clayton, 2015). Additionally, ME/CFS
47
48 438 patients rate exercise as more difficult and painful than matched healthy controls (Cook et al., 2017).
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50
51 439 These preliminary data have led to speculation about the role of negative expectations as a potential
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440 ~~source of variability in symptomatic responses to exercise in ME/CFS patients with and without~~

441 ~~comorbid Fibromyalgia post-exertion malaise (Lindheimer, Meyer, et al., 2017).~~

442 **3.32.3 Identifying participants with low or high likelihood of being placebo or nocebo responders**

443 In randomized controlled trials, the clinical significance of a treatment is judged by comparing
444 the magnitude of the therapeutic improvement in the treatment group to the placebo group. Thus, the
445 clinical trial may fail to demonstrate a therapeutic effect for the treatment if placebo responses are large
446 (Enck, Bingel, Schedlowski, & Rief, 2013). Clinical drug trials have attempted to address this issue via a
447 placebo run-in phase, which involves administering a placebo to eligible participants prior to
448 randomization in order to minimize placebo responses or screen out placebo responders altogether
449 (Lee, Walker, Jakul, & Sexton, 2004).

450 The placebo run-in phase is appealing for conducting clinical exercise trials because reducing
451 placebo responses would presumably help provide a more precise estimation of the true effect of
452 exercise. The absence of a valid exercise placebo prevents the ability to use the placebo run-in approach
453 in exercise studies; however, this concept could be adapted in several ways. One strategy is to measure
454 habitual expectations prior to study enrollment. By screening out participants who endorse changes in
455 psychological outcomes as a habitual expectation of exercise and only including participants with
456 neutral or low expectations about psychological improvements, a more conservative estimate of the
457 true effect of exercise could potentially be acquired (Ojanen, 1994). Conversely, participants who are at-
458 risk for nocebo responses could be screened out by excluding individuals who expect negative
459 psychological consequences of exercise. Considering that placebo run-in trials are also used to decrease
460 of placebo or nocebo effects by habituating participants to the placebo prior to baseline testing, before
461 starting baseline testing by habituating participants to the placebo another possibility is to familiarize
462 participants to several acute bouts of exercise before starting the trial. In terms of recruitment, this
463 strategy may be more feasible than screening for expectations because finding individuals with low or

464 negative expectations may be challenging, especially when the trial is focused on an endpoint for which
465 the psychological benefits of exercise are widely publicized such as depression or anxiety.

466 Although some previous work has indirectly screened for expectations by excluding participants
467 who reported receiving formal education in the health benefits of exercise (Lindheimer et al., 2017), no
468 studies have attempted to recruit or screen participants on the basis of measuring explicit habitual
469 expectations for psychological outcomes of exercise. Prior to implementing this approach, researchers
470 should be cautioned that meta-analyses of clinical drug trials have failed to demonstrate that placebo
471 run-in phases affect subsequent treatment or placebo responses (Greenberg, Fisher, & Riter, 1995; Lee
472 et al., 2004; Trivedi & Rush, 1994). Findings such as these, which may be predicated on the potentially
473 false assumption that placebo responsiveness is stable and predictable, cast doubt about the ability to
474 identify and screen out potential placebo or nocebo responders prior to the beginning-onset of a study.
475 However, ~~but~~ testing this idea in the exercise setting may nevertheless inform the design of future
476 exercise-based clinical trials.

477 **4. EXEMPLAR DESIGNS TO ELUCIDATE MECHANISMS EXPERIMENTAL METHODS FOR OF PLACEBO AND** 478 **NOCEBO EFFECTS IN STUDYING PLACEBO EFFECTS IN PSYCHOLOGICAL RESPONSES TO EXERCISE**

479 ~~Most of the data concerning placebo effects in psychological responses to exercise has been~~
480 ~~generated from the few three-arm intervention studies that have included an exercise, placebo and~~
481 ~~control condition, or from two-arm studies that have compared outcome expectations between the~~
482 ~~exercise and control group. While germane to facilitating the broader understanding of placebo effects~~
483 ~~in exercise, these types of study designs are not well suited to elucidating psychological and neuro-~~
484 ~~biological mechanisms. Measuring expectations is an important step when the objective is to account for~~
485 ~~variability in psychological responses within or between groups. Likewise, experimental manipulation of~~
486 ~~expectations and other potential psychological or contextual causes of placebo effects can provide~~

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3 487 insight into the magnitude of their contribution to treatment responses and the neurobiological
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5 488 mechanisms through which these processes work.
6
7 489 ~~An illuminating review by Benedetti and colleagues has distinguished the application and objectives of~~
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9 490 ~~studying placebo effects in the clinical trial setting from the experimental laboratory setting—“whereas~~
10
11 491 ~~the clinical trialist is interested in any improvement that may take place in a clinical trial, the~~
12
13 492 ~~neurobiologist is only interested in the psychosocial-psychobiological effects after the administration of~~
14
15 493 ~~a placebo” (Benedetti et al., 2011). Thus, while clinical trials are useful for understanding the magnitude~~
16
17 494 ~~of placebo effects, laboratory based studies contribute information about the potential mechanisms~~
18
19 495 ~~underlying these effects.~~ The next section of this review discusses several study designs with potential to
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23 496 advance the understanding of mechanisms of placebo effects in psychological outcomes of exercise.
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27 28 498 **4.1. Expectancy modification**

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30 499 A well-established model for ~~studying expectations as a psychological mechanism of studying the~~
31
32 500 impact of placebo effects on treatment responses is the **expectancy modification** design, which uses
33
34 501 situational or behavioural cues to create or augment the belief that a certain outcome will occur (Kirsch,
35
36 502 1985). Expectancy modification is the most frequently adopted strategy for studying placebo
37
38 503 ~~mechanisms-effects~~ in exercise (Arbinaga et al., 2018; Crum & Langer, 2007; Desharnais et al., 1993;
39
40 504 Flowers, Freeman, & Gladwell, 2018; Helfer, Elhai, & Geers, 2014; Kwan, Stevens, & Bryan, 2017;
41
42 505 Lindheimer et al., 2017; Mothes et al., 2016; Mothes, Leukel, Seelig, & Fuchs, 2017). In exercise studies,
43
44 506 the expectancy modification procedure is typically used to ~~induce-generate~~ placebo effects by
45
46 507 ~~experimentally augmenting the belief~~creating or strengthening expectations that exercise will result in ~~a~~
47
48 508 given psychological outcome (e.g., reduced feelings of fatigue). ~~Following expectancy modification in~~
49
50 509 ~~these studies, the contribution of placebo effects~~ psychological responses to exercise can be studied by
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52 510 ~~in comparing psychological responses to exercise between~~ participants ~~in the experimental condition~~
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3 511 ~~are compared to control condition participants whose expectations were not modified~~ who receive the
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5 512 modification and those who do not.
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7
8 513 Various strategies such as verbal suggestion (Arbinaga et al., 2018; Crum & Langer, 2007;
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10 514 Desharnais et al., 1993; Helfer et al., 2014; Lindheimer et al., 2017; McCann & Holmes, 1984), film clips
11
12 515 (Flowers et al., 2018; Mothes et al., 2016, 2017), and reading standardized scripts (Kwan et al., 2017)
13
14 516 ~~have been to~~are used to manipulate expectations. In some cases, these modifications have been further
15
16 517 enhanced through additional psycho-social and environmental cues (Crum & Langer, 2007; Desharnais
17
18 518 et al., 1993) or engagement of conscious mental processes by asking participants to recapitulate and
19
20 519 record their expectations (Helfer et al., 2014; Kwan et al., 2017). It is not yet clear which types of
21
22 520 modification procedures are most effective for influencing expectations about psychological outcomes
23
24 521 of exercise. To help address this gap, studies can incorporate *manipulation checks* by measuring and
25
26 522 comparing expectations between the experimental and control group to provide insight into why some
27
28 523 studies ~~are~~ have been more successful ~~with-in~~ manipulating expectations (Arbinaga et al., 2018) than
29
30 524 others (Lindheimer et al., 2017). ~~In order to further improve the understanding of how to effectively~~
31
32 525 elicit or minimize nocebo effects, questionnaires that also provide the ability to measure negative
33
34 526 expectations should be incorporated in manipulation checks.
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39 527 Investigators who implement expectancy modification designs should be cautioned about the
40
41 528 trade-off between effectively modifying expectations and introducing cues that might lead participants
42
43 529 to guess the purpose of the study. For instance, in the expectancy modification study by Lindheimer and
44
45 530 colleagues, the investigators were successful in terms of preventing a majority of participants from
46
47 531 guessing the study purpose (~92%), however, expectations for psychological changes were not different
48
49 532 between participants who received the expectancy modification and those who did not, indicating that
50
51 533 the expectancy modification was not successful (Lindheimer et al., 2017). Thus, one challenge for future
52
53 534 investigators who decide to use expectancy modification designs is determining how to effectively
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3 535 modify and measure participant expectations without increasing demand characteristics by tipping off
4
5 536 participants to the purpose of the study.

6 7 537 **4.1.1 The balanced placebo design**

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9
10 538 ——— A special case of an expectancy modification study is the **balanced placebo design** (Rohsenow &
11
12 539 Marlatt, 1981; Ross, Krugman, Lysterly, & Clyde, 1962). By assigning participants to a drug or placebo
13
14 540 condition and manipulating their expectations about condition assignment, this design allows the
15
16 541 investigator to differentiate between the treatment effect (i.e., participants who receive the treatment,
17
18 542 but are told they received the placebo) and placebo effect (i.e., participants who receive the placebo,
19
20 543 but are told they received the treatment) (Figure 2).

21
22
23 544 **[Figure 2 about here]**

24
25
26 545 The balanced placebo design was developed for researching expectancy effects in drug
27
28 546 responses (Enck et al., 2011), but it has also been modified to the study of placebo effects in
29
30 547 psychological responses to exercise. Using a recumbent motorized cycle to provide either a sham/inert
31
32 548 or treatment stimulus, Lindheimer and colleagues assigned participants to a passive condition in which
33
34 549 participant's legs were involuntarily moved for them (i.e., sham/inert) or an active condition in which
35
36 550 participants cycled under their own volition (i.e., treatment) (Lindheimer, O'Connor, et al., 2017).
37
38 551 Additionally, half of participants in each condition were exposed to an expectancy modification
39
40 552 procedure to generate expectations that active or passive cycling would result in post-treatment
41
42 553 improvements in mood and cognitive performance.

43 44 45 46 554 **4.2. Conditioning**

47
48 555 Conditioning represents a promising approach to studying placebo effects in exercise,
49
50 556 particularly in the study of exercise induced hypoalgesia (EIH), a phenomenon in which pain sensitivity is
51
52 557 reduced during or following exercise (Koltyn, 2002). This area of inquiry is especially intriguing because
53
54
55 558 EIH and placebo hypoalgesia appear to involve similar biochemical mechanisms such as the opioid and

1
2
3 559 endocannabinoid systems (Benedetti, Amanzio, Rosato, & Blanchard, 2011; Crombie, Brellenthin,
4
5 560 Hillard, & Koltyn, 2018). Yet, despite extensive interest among both exercise and placebo researchers in
6
7 561 studying pain, EIH studies are seldom designed to experimentally manipulate psychological mechanisms
8
9
10 562 of placebo or nocebo effects.

11
12 563 ~~Interested researchers can take several~~ A recent investigation by Colloca and colleagues has
13
14 564 provided one potential approach to studying placebo and nocebo effects in EIH by adapting a well
15
16 565 validated conditioning model to isotonic exercise (Colloca, Corsi, & Fiorio, 2018). During an initial
17
18 566 acquisition phase, participants learned to associate three different visual color cues (i.e., green, yellow,
19
20 567 red) with three distinct thermal pain stimulus intensities (i.e., low, medium, high) and were led to
21
22 568 believe that these same visual color cue-thermal stimulus intensity pairings would be presented during a
23
24 569 subsequent test phase. During the test phase, however, a series of trials were administered wherein the
25
26 570 presentation of each color cue was followed only by a medium intensity stimulus and participants were
27
28 571 asked to rate their perceived pain on a 0-100 visual analog scale. Thus, placebo effects were measured
29
30 572 by comparing pain ratings between trials where the medium intensity stimulus followed the expectation
31
32 573 of medium pain intensity (i.e., yellow cue-medium stimulus intensity) to trials where the medium
33
34 574 intensity stimulus followed the expectation of a low pain intensity (i.e., green cue-medium stimulus
35
36 575 intensity). Similarly, nocebo effects were measured by comparing yellow cue-medium stimulus intensity
37
38 576 trials to trials where the medium stimulus followed the expectation of high pain intensity (i.e., red cue-
39
40 577 medium stimulus intensity).

41
42 578 By administering half of the placebo and nocebo trials during light intensity elbow extension-
43
44 579 flexion (30% of maximum voluntary contraction) and half at rest, the added contribution of exercise to
45
46 580 placebo and nocebo effects could be determined. The authors did not find an added effect of exercise to
47
48 581 either placebo or nocebo effects, but the study by Colloca and colleagues provides a useful framework
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50 582 for future researchers to begin addressing several other questions that could be related to placebo and
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3 583 nocebo effects in EIH, including (i) intensity (e.g., would the added effect of exercise be greater at a
4
5 584 higher intensity?), (ii) mode (e.g., does cycling or running during placebo/nocebo experimental result in
6
7 585 different effects?, (iii) neurobiological mechanisms (e.g., how would blocking the opioid or
8
9 586 endocannabinoid system affect conditioned placebo and nocebo responses during exercise?), -and (iv)
10
11 587 habitual expectations (e.g., is conditioning easier to implement in participants with stronger pre-existing
12
13 588 expectations about the effect of exercise on pain?).

14
15
16 589 ~~A powerful psychological mechanism of placebo effects that is untested in exercise studies is~~
17
18 590 ~~conditioning. Placebo conditioning has been studied in a variety of settings that are beyond the scope of~~
19
20 591 ~~this review such as immunosuppression (Hadamitzky, Sondermann, Benson, & Schedlowski, 2018); but~~
21
22 592 ~~one directly relevant application to this review is conditioned placebo hypoalgesia. Following an initial~~
23
24 593 ~~familiarization period during which participants are introduced to a painful stimulus (unconditioned~~
25
26 594 ~~stimulus), placebo hypoalgesia can be conditioned by pairing the administration of a placebo~~
27
28 595 ~~(conditioned stimulus) with surreptitious reduction of the pain stimulus intensity. This is often repeated~~
29
30 596 ~~several times to ensure that the conditioned response to the placebo has taken effect (Colloca, Petrovic,~~
31
32 597 ~~Wager, Ingvar, & Benedetti, 2010) and is followed by an experimental phase to examine the strength~~
33
34 598 ~~and duration of the placebo effect. In order to do so, the full-intensity painful stimulus is re-~~
35
36 599 ~~administered and perceptual ratings are compared between participants who received the conditioning~~
37
38 600 ~~procedure and a control group who did not. By repeatedly conducting the experimental phase over the~~
39
40 601 ~~course of several days, the investigator can also determine the time-course for the conditioned placebo~~
41
42 602 ~~response to be extinguished.~~

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48 603 ~~One idea is to condition placebo hypoalgesia responses to a minimal exercise condition such as~~
49
50 604 ~~passive motorized cycling. Passive motorized cycling has potential to be used as a placebo in exercise~~
51
52 605 ~~because it closely mirrors the movement involved in cycle ergometry, results in relatively minimal~~
53
54 606 ~~perceptual and cardio-respiratory responses compared to active cycling, and does not appear to affect~~
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3 607 certain psychological outcomes (Lindheimer, O'Connor, et al., 2017; Weng, Pierce, Darling, & Voss,
4
5 608 2015). Thus, there is a higher degree of confidence that passive cycling is truly an inert stimulus
6
7 609 compared to other minimal exercise conditions that have been used as placebos. However, to increase
8
9 610 confidence that decreases in pain sensitivity following a placebo hyperalgesia conditioning procedure
10
11 611 are the result of placebo effects, preliminary work is needed to verify that passive cycling does not affect
12
13 612 pain sensitivity.

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15
16 613 Another useful application of conditioning is to study placebo effects by comparing the
17
18 614 magnitude of pain reduction in volitional exercise with and without a conditioning procedure. By
19
20 615 measuring how closely biological changes (e.g., increases in plasma endocannabinoids) track with
21
22 616 perceptual changes (e.g., decreases in pain sensitivity), researchers could further understand how the
23
24 617 psycho-social context surrounding exercise influences EIH mechanisms. Finally, in light of evidence that
25
26 618 exercise can sometimes increase pain sensitivity or symptoms in certain clinical populations (Cook,
27
28 619 Stegner, & Ellingson, 2010; Light et al., 2012), it is worth pointing out that conditioning has also been
29
30 620 used to study nocebo hyperalgesia (Blasini et al., 2017) and adapting these methods to the exercise
31
32 621 setting may help researchers understand why exercise-induced hyperalgesia occurs and how much of
33
34 622 this effect can be attributed to nocebo effects and mechanisms.

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38
39 623 There is promise in implementing the conditioning procedures used by Colloca and colleagues to
40
41 624 study placebo and nocebo effects, particularly when experimental pain (e.g., tolerance, threshold,
42
43 625 ratings of painful stimuli) is the outcome of interest. A far more elusive pursuit concerns conditioned
44
45 626 placebo responses to exercise that take place in real world settings and how they affect placebo effects
46
47 627 in a controlled laboratory environment. Presumably Ostensibly, a greater level of exposure to a given
48
49 628 behavioural stimulus is more likely to lead to a conditioned response. Therefore, one potential approach
50
51 629 to untangling the influence of conditioning effects that take place outside of the laboratory is to study
52
53 630 how conditioned placebo hypoalgesia differs between participants who frequently engage in exercise
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631 and sedentary individuals. Demonstrating that conditioned placebo hypoalgesia is greater in active
632 participants would suggest that those who are more familiar with the pain alleviating effects of exercise
633 are more likely to respond positively to exercise and that increasing exercise behaviour in sedentary
634 participants may improve subsequent responses to exercise.

635 5. FUTURE DIRECTIONS

636 A number of research directions can be pursued to improve the conceptualization and study of
637 placebo effects in exercise studies. Below we highlight potential next steps to prioritize in future work.

638 1. As suggested above, understanding of placebo and nocebo effects in psychological responses to
639 exercise has lagged behind other scientific disciplines. We assert that continuing to focus efforts on
640 developing a valid exercise placebo may further delay progress. Researchers should acknowledge
641 the growing body of literature demonstrating that psychological mechanisms of placebo and nocebo
642 effects (e.g., expectations and conditioning) can be used *en lieu* of placebos when seeking to
643 understand the contribution of placebo effects to treatment responses. Therefore, we recommend
644 shifting attention toward continuing to develop valid and effective methodological strategies for
645 measuring and experimentally manipulating these placebo/nocebo mechanisms in exercise based
646 research.

647 1.—The understanding of the role measurement of outcome expectations in for psychological responses
648 to outcomes of exercise would be improved by developing psychometrically validated using
649 psychometric instruments that address-measure study-specific specific expectations. Rather than
650 using questionnaires with inherent biases toward only measuring expectations for desirable
651 outcomes, we recommend using questionnaires with item phrasing and scales that allow a
652 respondent to indicate expectations for either positive or negative changes for neutrally presented
653 psychological outcome. For instance, a study of EIH can ask participants to rate their level of
654 expected changes in pain on a bipolar Likert-type scale with verbal anchors that allow the

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2
3 655 participant to indicate the expected direction and degree of change (e.g., -3 = "large decrease", -2 =
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5 656 "moderate decrease", -1 "slight decrease", 0 "no change", 1= "slight increase", 2= "moderate
6
7 657 increase", 3= "large increase").

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10 658 ~~2.—~~

11
12 659 ~~Until a valid exercise placebo is developed, it is not possible to investigate mechanisms of~~
13 ~~placebo effects in psychological outcomes of exercise. However, mechanisms of placebo effects~~
14 ~~can be investigated with expectancy modification and conditioning studies. These designs can~~
15 ~~be used to explore potential biological mechanisms that are involved in amplifying the effect of~~
16 ~~exercise on psychological outcomes.~~

17 663
18 664 ~~3.2.~~

19
20 665 ~~4.—Expectancy modification studies~~ Measuring expectations are in expectancy modification studies is
21 also encouraged to test for within group changes over time or between group differences in study
22 specific expectations as a manipulation check. ~~Verifying the success of the manipulation by~~
23
24 667 ~~measuring expectations would allow researchers to begin cataloging which types of expectancy~~
25
26 668 ~~modification procedures are most effective. This information may be especially valuable for~~
27
28 669 addressing calls to maximize treatment effects in clinical settings by augmenting the contribution of
29
30 670 placebo effects (Evers et al., 2018).

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36 672 ~~5.3.~~

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38 673 ~~6.—Conditioning studies are a promising strategy for investigating mechanisms of placebo~~ and nocebo
39 effects, although this approach has only been tested in one study of exercise and experimental pain
40 (Colloca et al., 2018). More work is needed to determine whether conditioning could also be applied
41 to the study of placebo effects in other psychological outcomes of exercise such as mood and
42 cognition in certain psychological outcomes of exercise, especially pain. Further insight into whether
43 it is possible to condition placebo responses to inert minimal exercise modalities such as passive
44 cycling would provide preliminary evidence that exercise placebos can be used to study placebo
45 effects in laboratory settings and possibly even clinical trial settings.
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3 681 7.4.

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5 682 ~~8.~~—The extant data on nocebo effects and their respective mechanisms in psychological responses to
6
7 683 exercise can be traced to two studies (Colloca et al., 2018; Kwan et al., 2017). This line of research
8
9 684 requires further attention and may have particularly important implications for explaining inter-
10
11 685 individual variability in how healthy and clinical populations respond negatively to exercise.
12
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14 686 9.5.

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16 687 ~~10.~~The question of whether study participants reliably demonstrate placebo responses across different
17
18 688 clinical conditions (Kaptchuk et al., 2008) and whether biological or psychological markers can
19
20 689 distinguish such individuals from non-responders (Hall, Loscalzo, & Kaptchuk, 2015; Jakšič, Aukst-
21
22 690 Margeti, & Jakovljevi, 2013) has attracted the attention of placebo researchers and clinical trialists
23
24 691 alike. In the absence of having a valid exercise placebo, these concepts may be worthwhile to
25
26 692 investigate.
27
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29
30 693 11.6.

31
32 694 ~~12.7.~~ That patient-physician interactions can influence placebo effects in a therapeutic setting (Zion
33
34 695 and Crum, 2018) opens the possibility that interactions between test administrators and participants
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36 696 can elicit placebo or nocebo effects. Such effects should not be discounted in any research setting.
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38 697 The testing, either observationally or experimentally, of the degree to which personality
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40 698 characteristics and behaviours of study personnel who interact with study participants has a similar
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42 699 effect on treatment responses is a valid line of inquiry.
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46 700 6. CONCLUSION

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48 701 Embracing and adopting the notion of studying placebo and nocebo effects without traditional
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50 702 placebo treatments is germane to advancing the understanding of their impact on psychological
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52 703 responses to exercise. RDistinguishing the effect of exercise from placebo effects requires a placebo
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54 704 group. Whether it is possible to create a valid exercise placebo that closely mirrors the movements
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3 705 involved in exercise and is also inert remains to be determined. While efforts to develop a valid exercise
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5 706 placebo are underway, researchers can capitalize on using established psychological mechanisms of
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7 707 placebo effects to better understand how psycho-social context influences psychological responses to
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9 708 exercise in clinical trial and laboratory settings. Measuring outcome expectations in clinical
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11 709 trials measurement of habitual and study-specific expectations can help explain inter-individual variability
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13 710 in positive and negative outcomes of exercise whereas expectancy modification and conditioning can
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15 711 Expectancy modification and conditioning designs can be used in laboratory studies to help elucidate
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17 712 the neurobiological mechanisms that are involved in placebo effects that mediate the influence of
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19 713 placebo and nocebo effects on these responses. These endeavors would make a valuable contribution
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21 714 toward advancing the current standard of knowledge about placebo and nocebo placebo effects in
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23 715 psychological responses to exercise which in turn may help inform the design of effective exercise
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25 716 interventions in the future.
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3 851 **Figure legends**

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5 853 **Figure 1.** Distinguishing ~~the true treatment~~ effects ~~of exercise on psychological responses~~ from ~~placebo~~
6 854 ~~effects and~~ non-specific effects requires the inclusion of a placebo and no-treatment control group.

7 855 Panel A shows what is typically measured in exercise studies, the observed effect of exercise, which is
8 856 estimated by comparing the change in the exercise group to the control group. Panel B shows the ~~true~~
9 857 placebo effect, which is estimated by comparing the change in the placebo group to the control group.
10 858 Panel C shows that the true effect of exercise can be estimated by subtracting the ~~true~~ placebo effect
11 859 from the observed effect of exercise. In a meta-analysis of randomized controlled studies that included
12 860 an exercise, placebo, and control group, approximately half of the observed effect of exercise on
13 861 psychological outcomes was attributed to placebo effects (Lindheimer et al., 2015).

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15 863 **Figure 2.** ~~The balanced placebo design is a model for observing expectancy-related placebo effects that~~
16 864 ~~can be adapted to studying psychological responses to exercise if a valid exercise placebo is ever~~
17 865 ~~developed. Study participants are randomized to a treatment or inert/sham condition and half of the~~
18 866 ~~participants in each condition are subjected to an expectancy modification procedure that is designed to~~
19 867 ~~increase expectations for psychological improvements following the exposure to the treatment or~~
20 868 ~~inert/sham stimulus.~~

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Figure 1. Placebo effects may explain over half of the psychological effect of exercise

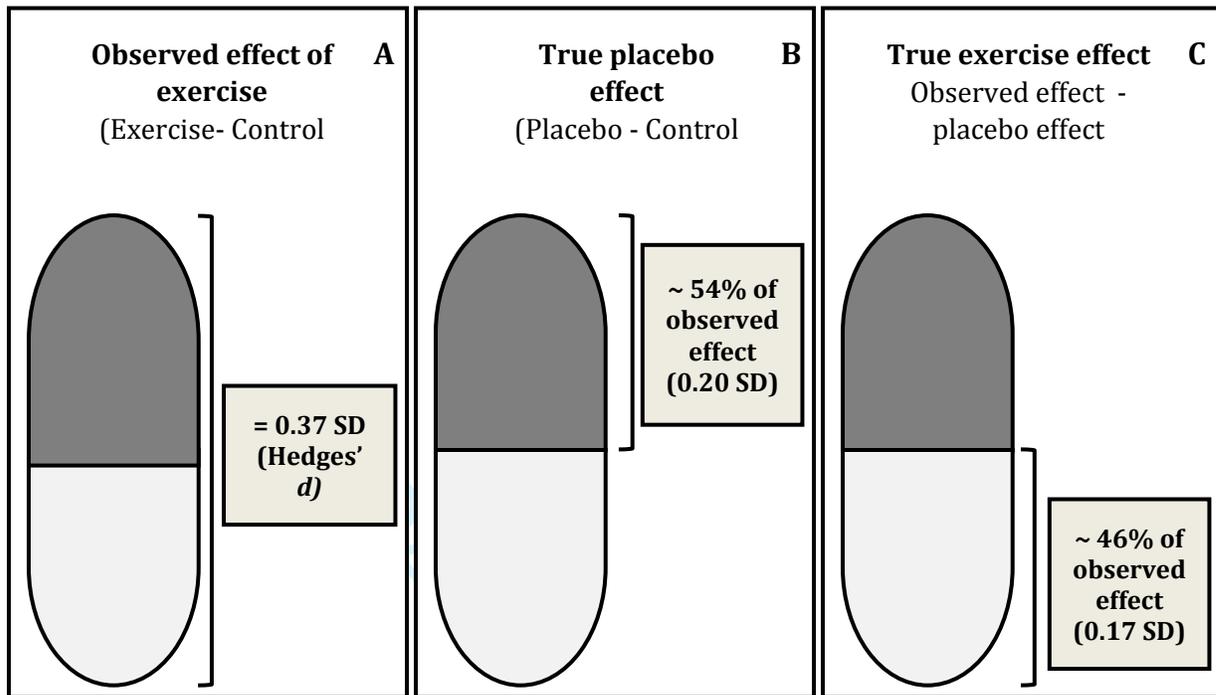


Table 1. Key terms

Demand characteristics	The totality of cues that can lead a participant to guess the experimental hypothesis of the study (Orne, 1962).
Differential expectations	A potential confounding variable that arises from differences in outcome expectations between an experimental and control group (Boot et al. 2013).
Expectancy modification	An experimental procedure in which situational or behavioral cues are used to create or augment the belief that a certain outcome will occur (Kirsch, 1985).
Experimentally-induced expectation	A type of study-specific expectation that is generated from an experimental procedure such as expectancy manipulation or conditioning (Mothes et al., 2016).
Habitual expectation	A type of outcome expectation that is a reflection of an individual's previous experiences or cultural beliefs (Mothes et al., 2016). These expectations are developed prior to participation in a research study.
Incidentally-induced expectation	A type of study-specific expectation that the investigator did not intend for the participant to develop. These may threaten the internal validity of the study.
Manipulation check	A procedure for confirming the success of an experimental manipulation. This is applied to expectancy modification studies by measuring and comparing expectations between the experimental and control group following the expectancy modification procedure.
<u>Placebo/nocebo effect</u>	<u>A desirable (placebo effect) or undesirable (nocebo effect) outcome resulting from a person's expected and/or learned response to a treatment or situation. Recent advances indicate that it is not always necessary to administer a traditional placebo (i.e., inert substance) in order to observe and measure the contribution placebo/nocebo effects to a treatment (Benedetti, 2008; Finniss et al. 2010).</u>
<u>Study-specific expectation</u>	<u>A type of outcome expectation that is formed from experiences that occur during the various phases of a study (e.g., advertisement, recruitment, screening, informed consent, familiarization, data collection).</u>

balanced-placebo-design	A model for observing expectancy-related placebo effects. Study participants are randomized to a treatment or inert/sham condition and half of the participants in each condition are subjected to an expectancy modification procedure that is designed to increase expectations that a certain outcome will occur following the exposure to the treatment or inert/sham stimulus (Ross et al. 1962)
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Table 1 continued. Key terms

Outcome expectation	The belief that a given behavior will lead to a certain outcome (Bandura, 1977).
Perceived placebo effect (clinical trial setting)	The measured change from baseline in the placebo group that is a combined result of the true placebo effect and several other potential non-specific effects such as spontaneous remission, regression to the mean, and unidentified parallel treatments (Ernst and Resch, 1995).
Perceived treatment effect (clinical trial setting)	The measured change from baseline in the treatment group that is a combined result of the true treatment effect and the placebo effect (Ernst and Resch, 1995). In exercise research, this has also referred to as the <i>observed effect of exercise</i> (Ojanen, 1994).
Placebo effect	
Study-specific expectation	A type of outcome expectation that is formed from experiences that occur during the various phases of a study (e.g., advertisement, recruitment, screening, informed consent, familiarization, data collection).
True placebo effect (clinical trial setting)	The measured change in the placebo group after accounting for variance explained by other non-specific effects such as spontaneous remission, regression to the mean, and unidentified parallel treatments (Ernst and Resch, 1995).

Commented [JL1]: I deleted these some over these terms to be consistent with my edits to the manuscript and reduce the overall amount of jargon. I think this is for the best and will reduce potential reader confusion.

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True treatment effect (clinical trial setting)	The change in the dependent variable that is observed in the treatment group after accounting for variance explained by non-specific effects (Ernst and Resch, 1995). This has also been referred to as the <i>true effect of exercise</i> (Ojanen, 1994).
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Table 2. Examples of outcomes that have been measured via self-report or task performance in exercise studies.

Perceptual/sensory	Mental Health	Cognition	Miscellaneous
Muscle pain	Anxiety	Executive function	Affect
Perceived exertion	Depression	Sustained attention	Body Image
Pain intensity	Sleep quality	Processing speed	Mood
Symptom severity	Stress	Working memory	Self-esteem

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3 1 **ABSTRACT:** Despite the apparent strength of scientific evidence suggesting that psychological benefits
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5 2 result from both acute and chronic exercise, concerns remain regarding the extent to which these
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7 3 benefits are explained by placebo effects. Addressing these concerns is methodologically and at times
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9 4 conceptually challenging. However, developments in the conceptualization and study of placebo effects
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11 5 from the fields of psychology, neuroscience, pharmacology, and human performance offer guidance for
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13 6 advancing the understanding of placebo effects in psychological responses to exercise. In clinical trials,
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15 7 expectations can be measured and experimentally manipulated to better understand the influence of
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17 8 placebo effects on treatment responses. Further, compelling evidence has shown that the contribution
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19 9 of placebo effects and their underlying neurobiological mechanisms to treatment effects can be
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21 10 measured without administering a traditional placebo (e.g., inert substance) by leveraging psychological
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23 11 factors such as expectations and conditioning. Hence, the purpose of this focused review is to integrate
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25 12 lessons such as these with the current body of literature on placebo effects in psychological responses
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27 13 to exercise and provide recommendations for future research directions.
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17 **KEYWORDS:** Behavior; Cognition; Health; Methodology; Neuroscience
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19 **HIGHLIGHTS:**

- 20 • Several methodological factors render investigations of psychological outcomes of acute and
21 chronic exercise vulnerable to placebo effects.
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- 23 • Placebo groups may not be possible when studying psychological responses to exercise, but
24 traditional placebos are not always required to study the impact of psychological mechanisms of
25 placebo effects on treatment responses.
26
- 27 • Measurement of expectations can help explain inter-individual variability in psychological
28 responses to exercise.
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- 30 • Expectancy modification and conditioning can each be used to enhance treatment responses
31 and elucidate the neurobiological mechanisms that mediate the influence of placebo and
32 nocebo effects on these responses.

33 1. INTRODUCTION

34 Over the last 50 years, the concept of a placebo has evolved from a therapeutically inert
35 substance to also incorporate the sensory and social stimuli that inform patients they are receiving a
36 beneficial treatment (Benedetti et al., 2011). The sophistication of approaches to studying placebo
37 effects has also evolved. These range from distinguishing placebo effects from other non-specific effects
38 in clinical trials (Ernst & Resch, 1995) to the use of elegant multi-condition experimental designs (Enck,
39 Klosterhalfen, & Zipfel, 2011) and neuroimaging technologies to measure placebo effects and their
40 respective neurobiological mechanisms in laboratory based studies (Benedetti & Amanzio, 2013). The
41 study of nocebo effects has also progressed and this line of research has made a critical contribution to
42 the understanding of why negative outcomes (e.g., symptom worsening) sometimes result from the
43 administration of placebos (Frisaldi, Piedimonte, & Benedetti, 2015; Webster, Weinman, & Rubin, 2016).

44 As the understanding of placebo and nocebo effects expands across scientific disciplines,
45 researchers and clinicians are recognizing the need for conceptual clarity as well as guidelines for
46 evidence-based and ethical use of placebo and nocebo effects in clinical practice. Recently, an
47 international working group consisting of 29 experts released a consensus statement to address some of
48 these issues, including the distinction between placebo/nocebo responses versus effects (Evers et al.,
49 2018). The **placebo and nocebo response** was said to include all health changes that result after
50 administration of an inactive treatment, including those that may occur from natural history and
51 regression to the mean. On the other hand, **placebo and nocebo effects** were defined as the changes
52 specifically attributable to placebo and nocebo mechanisms, including the neurobiological and
53 psychological mechanisms of expectancies. These definitions have been adapted in a recent consensus
54 statement on the study of placebo and nocebo effects in sport and exercise, in which placebo and
55 nocebo effects were defined as a desirable or undesirable outcome resulting from a person's expected
56 and/or learned response to a treatment or situation (Beedie et al., 2018).

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3 57 The importance of designing exercise-based studies to account for placebo effects was
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5 58 recognized over three decades ago (McCann & Holmes, 1984). However, elucidation of the incidence,
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7 59 magnitude, and mechanisms of placebo effects in psychological responses to exercise has been slower
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9 60 in coming compared with other scientific fields. Taking into account recent interdisciplinary
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11 61 developments in the conceptualization and study of placebo effects, the purpose of this review is to
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13 62 highlight topics that are central to advancing the understanding of placebo effects in psychological
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15 63 responses to exercise, including: (i) the theory and practice of controlling for placebo effects, (ii) the
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17 64 importance of expectations, (iii) experimental methods for studying the influence of placebo effects and
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19 65 their neurobiological mechanisms on treatment responses, and (iv) future research directions. To aid
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21 66 comprehension of key concepts and facilitate this discussion, a list of key terms is provided in Table 1.
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28 68 Findings from the small body of studies that examined placebo or nocebo effects in
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30 69 psychological responses to exercise are also integrated throughout this review. Herein, outcomes that
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32 70 are measured via self-report in exercise studies are broadly referred to as psychological outcomes or
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34 71 responses. These include variables from the categories of mental health (e.g., anxiety, depression) and
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36 72 perception (e.g., perceived exertion, muscle pain, pain intensity, symptom severity) as well as other
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38 73 types of constructs (e.g., body image, affect, mood, self-esteem). Additionally, we recognize that
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40 74 cognition can be assessed by task performance or self-report, but we also consider it to fit within the
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42 75 scope of psychological outcomes/responses (Table 2).
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45 76 [Table 2 about here]

46 77 2. PLACEBO EFFECTS IN EXERCISE INTERVENTIONS

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50 78 Effect size estimates from meta-analytic reviews of randomized controlled trials support the
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52 79 argument that exercise training improves psychological outcomes. For self-reported outcomes such as
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54 80 anxiety, depression, fatigue, and pain, exercise training appears to result in small (Standardized mean
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3 81 difference = 0.29) to moderate (Standardized mean difference = 0.62) improvements (Cooney et al.,
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5 82 2013; Herring, Puetz, O'Connor, & Dishman, 2012; Herring, O'Connor, & Dishman, 2010; Puetz,
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7 83 O'Connor, & Dishman, 2006; Searle, Spink, Ho, & Chuter, 2015). Additionally, exercise training has a
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10 84 small, but significant effect on certain domains of cognitive performance (Standardized mean difference
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12 85 = 0.12-0.16) (Smith et al., 2010). However, there are several methodological issues that have raised
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14 86 concerns about the ability to distinguish these observed effects of exercise from placebo effects
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16 87 (Lindheimer, O'Connor, & Dishman, 2015; Ojanen, 1994; Szabo, 2013). These include: (i) the inability to
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18 88 perform double-blind studies, (ii) demand characteristics, and (iii) the largely subjective nature of many
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21 89 psychological outcome measures. In the following section, we discuss the theoretical importance of
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23 90 including placebo and no-treatment control groups to measure placebo effects in clinical trials and why
24
25 91 this is difficult in studies of psychological responses to exercise.

28 92 **2.1. Characterizing placebo effects in clinical trials**

30 93 An early misconception was that placebo effects could be studied in clinical trials by measuring
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32 94 change from baseline in the placebo group (i.e., perceived placebo effects) (Beecher, 1955). However,
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34 95 this approach fails to consider the changes in a placebo group that could be explained by non-specific
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36 96 effects such as natural history of disease, regression to the mean, and unidentified parallel interventions
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38 97 (Ernst & Resch, 1995; Kienle & Kiene, 1997). If the randomization of participants to their respective
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41 98 groups is successful, these non-specific effects would presumably have an equal likelihood of occurring
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43 99 in a wait-list or no-treatment control group. Thus, subtracting the change in the control group from the
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46 100 change in the placebo group accounts for non-specific effects and provides a more precise estimation of
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48 101 the placebo effect in the clinical trial setting.

50 102 Following this line of reasoning, Lindheimer and colleagues quantified the placebo effect in
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52 103 psychological outcomes of exercise training studies in a meta-analysis of randomized controlled trials
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55 104 that included an exercise treatment, control, and placebo arm ($n = 9$) (Lindheimer et al., 2015). In this

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3 105 case, a placebo condition was defined as “an intervention that was not generally recognized as
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5 106 efficacious, that lacked adequate evidence for efficacy, and that has no direct pharmacological, bio-
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7 107 chemical, or physical mechanism of action according to the current standard of knowledge” (p. 695).
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10 108 After estimating the placebo effect by aggregating the standardized mean difference between the
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12 109 placebo and control groups from each study (Hedges’ $d = 0.20$), the placebo effect was subtracted from
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14 110 the observed effect of exercise, that is, the aggregated standardized mean difference between the
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16 111 exercise and control groups from each study (Hedges’ $d = 0.37$). Following this procedure, the authors
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18 112 concluded that the effect of exercise training on psychological responses (Hedges’ $d = 0.17$) was less
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20 113 than half of the observed effect of exercise after accounting for placebo effects (Figure 1).
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23 114 [Figure 1 about here]

25 115 **2.2. Practical issues with characterizing placebo effects in studies of psychological responses to** 26 27 28 116 **exercise**

29
30 117 Despite early recognition of the importance for using methods that improve the estimation of
31
32 118 placebo effects (McCann & Holmes, 1984), several barriers have continued to stymie investigators and
33
34 119 prevent widespread implementation of these methods in exercise training studies. Foremost among
35
36 120 these is the inability to perform double-blind studies. Unlike pharmacological interventions in which the
37
38 121 vehicles that are used to deliver the treatment and placebo are identical (e.g., capsule, fluid, injection),
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40 122 it is considered to be impossible to truly blind participants to receiving exercise in research settings. This
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42 123 in turn can provoke expectations - potentially positive or negative - that an exercise treatment is being
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44 124 received. The question of what might constitute a valid exercise placebo is as yet unresolved.
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48 125 A review by Ojanen (1994) argued “that the idea of a placebo group in exercise studies is, in
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50 126 practice, impossible”. Nonetheless, some early studies attempted to create valid exercise placebo
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52 127 conditions by using very low intensity “minimal exercise” (Roth & Holmes, 1987) or relaxation training
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54 128 (McCann & Holmes, 1984) and even made efforts to manipulate expectations for improvement with
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3 129 verbal suggestion (McCann & Holmes, 1984). However, even in a study that reported equivalent
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5 130 expectations, involvement and subjective utility between the treatment and minimal exercise condition
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7 131 (Roth & Holmes, 1987), Ojanen reasoned that a real placebo condition was not used because a placebo
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9 132 effect was not observed. This interpretation is not entirely accurate, however, because the inclusion of a
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11 133 placebo condition does not necessarily always result in an observable placebo effect.
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14 134 To date, little progress has been made in developing a valid exercise placebo, one that mirrors
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16 135 every aspect of exercise except the “active ingredients”. Of course, this begs the question of what are
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18 136 the active ingredients (i.e., mechanisms) responsible for the psychological changes associated with
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20 137 exercise. Nevertheless, these somewhat circular issues may be more important to consider when the
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22 138 objective is to study the placebo effect *per se* rather than to study the involvement of placebo effects in
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24 139 psychological responses to exercise. As we discuss later in this review, well established psychological
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26 140 mechanisms of placebo effects such as expectations and conditioning can be used to influence
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28 141 treatment responses, providing a means of studying the contribution of placebo effects to treatment
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30 142 effects without the inclusion of a traditional placebo condition. For instance, Kong and colleagues
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32 143 showed a greater degree of pain relief in knee osteoarthritis patients assigned to receive acupuncture
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34 144 with enhanced treatment expectations compared to acupuncture alone or no-treatment (Kong et al.,
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36 145 2018). Additionally, compared to the acupuncture only group, the acupuncture plus enhanced
37
38 146 expectations group showed greater resting state functional connectivity between the nucleus
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40 147 accumbens and several other brain regions with links to placebo hypoalgesia such as the rostral anterior
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42 148 cingulate cortex and dorsolateral prefrontal cortex (Amanzio, Benedetti, Porro, Palermo, & Cauda,
43
44 149 2013). These findings suggest that enhancing treatment expectations can change both behavioral and
45
46 150 neurobiological outcomes to a higher degree than treatment alone and this approach may also be
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48 151 considered as a viable option for studying the impact of placebo effects on treatment responses to
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50 152 exercise.
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3 153 In addition to methodological barriers, resources are another obstacle to characterizing placebo
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5 154 effects in studies of acute and chronic exercise. Provided that scientific advances eventually lead to the
6
7 155 development of a valid exercise placebo, conducting studies that include a treatment, placebo and
8
9 156 control arm with enough statistical power to detect clinically meaningful between-group differences is
10
11 157 resource intensive. Given the amount of funding, time, participants, and personnel needed to conduct
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13 158 clinical trials with the requisite placebo and no-treatment control arms required to precisely measure
14
15 159 the size of the placebo effect, the lack of three-arm studies in the field of exercise and mental health
16
17 160 studies is not surprising. Even in research involving drugs, surgical procedures, or medical devices where
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19 161 valid placebos are easier to implement, designs that include both a placebo and no-treatment control
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21 162 group are historically scarce (Finniss, Kaptchuk, Miller, & Benedetti, 2010).

25 163 **3. EXPECTATIONS: A PRIMARY PSYCHOLOGICAL MECHANISM OF PLACEBO EFFECTS**

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27 164 A wide-body of research has demonstrated the role of expectations as a psychological
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29 165 mechanism of placebo effects (Benedetti, 2008; Finniss, Kaptchuk, Miller, & Benedetti, 2010; Kirsch,
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31 166 1997; Price et al., 2008). In the context of an exercise study, these data suggest that placebo effects are
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33 167 more likely to occur in participants who expect that exercising will result in a certain psychological
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35 168 response (e.g., “exercise will improve my mood”) compared to those who do not. Measuring self-
36
37 169 reported expectations should not be viewed as a surrogate for a placebo condition, but this practice can
38
39 170 help explain variability in psychological responses to exercise. Moreover, designing a study to reduce the
40
41 171 likelihood of generating certain expectations for psychological changes following exercise can help
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43 172 minimize placebo effects altogether. To help researchers accomplish this goal, we operationalize several
44
45 173 different types of expectations and illustrate scenarios in which it is useful to take them into account.

49 174 **3.1. Classification and definitions**

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51 175 It is important to recognize that there are several types of expectations, some of which are
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53 176 stable and resistant to change and others that are more dynamic. *Habitual expectations* are thought to

177 primarily reflect an individual's previous experiences or cultural beliefs (Mothes et al., 2016). Several
178 plausible factors may play a role in how habitual expectations are developed and their level of influence
179 on the measurement of psychological responses to exercise. These include level of habitual physical
180 activity behaviour, particularly salient memories of psychological responses to exercise, and exposure to
181 information from various sources (e.g., media, peers, family members, educators, clinicians, prior
182 research participation) about positive or negative effects of exercise. How these factors interact to form
183 habitual expectations is not well studied, but the accumulation of these experiences over time
184 presumably influences a research participant's interpretation of how they feel during and after exercise.

185 Investigators should also recognize that participation in a research study has the potential to
186 alter preexisting expectations or create new ones. Thus, we now introduce the term **study-specific**
187 **expectations** to address the expectations that are more fluid than habitual expectations and can change
188 in response to new experiences such as participating in a research study (Kirsch, 2018). Study-specific
189 expectations are unique because they take experiences that occur *during* the various phases of
190 participation in a laboratory or clinical study into account (e.g., advertising, recruitment, screening,
191 informed consent, familiarization, data collection), whereas habitual expectations more so reflective of a
192 participant's prior real-world experiences with exercise.

193 Because expectations are a known psychological mechanism of placebo effects, researchers can
194 intentionally manipulate them to examine their impact on psychological responses to exercise. Thus,
195 study-specific expectations that are a direct consequence of an experimental manipulation have been
196 referred to as **experimentally-induced expectations** (Mothes et al., 2016) and their importance is
197 discussed in later sections of this review. Conversely, we introduce the term **incidentally-induced**
198 **expectations** to acknowledge the study-specific expectations which results from some aspect of the
199 study that was unintended by the investigator. Incidentally-induced expectations can introduce error

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3 200 variance into the measurement of psychological responses to exercise, which is why it is critical to take
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5 201 them into account during the design and conduct of a study.
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7 202 One way to control for incidentally-induced expectations is to reduce potential sources of
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9 203 **demand characteristics**, the totality of cues that can lead a participant to guess the experimental
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11 204 hypothesis of the study (Orne, 1962). A significant source of these cues is information communicated by
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13 205 study materials (e.g., advertisements, informed consent documents). For instance, Foroughi and
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15 206 colleagues reported that following one hour of practicing cognitive tasks, performance on fluid
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17 207 intelligence tests was better among participants who enrolled in the study after viewing an overt
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19 208 advertisement for a “Brain Training and Cognitive Enhancement” study compared to participants who
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21 209 responded to a generic advertisement with no information about brain training or cognitive
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23 210 enhancement (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016). Although the authors did
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25 211 not collect explicit information that would allow them to test for between-group differences in
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27 212 expectations, their study provided a clear example of how information that overtly communicates the
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29 213 study purpose can affect a given participant’s behaviour.
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34 214 This issue has also been considered in exercise research where the investigators minimized
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36 215 demand characteristics by using deceptive information in the study advertisement and informed
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38 216 consent materials to disguise the study purpose (Arbinaga, Fernández-Ozcorta, Sáenz-López, &
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40 217 Carmona, 2018; Lindheimer, O’Connor, McCully, & Dishman, 2017). Interestingly, this research has
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42 218 shown that even when the investigators purposefully tried to alter participant expectations at a later
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44 219 point in the study, disguising the true purpose of the study early on may have blunted the effectiveness
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46 220 of the experimental manipulations. For example, Lindheimer and colleagues measured mood and
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48 221 cognitive responses to light intensity active cycling or motorized passive cycling, but informed
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50 222 participants that the purpose was to compare cardio-respiratory responses between the two conditions.
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53 223 Although half of these participants were exposed to an expectancy manipulation designed to enhance
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3 224 expectations for psychological improvements following exercise, the investigators did not observe a
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5 225 significant difference in expectations or psychological responses to exercise between participants who
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7 226 received the expectancy manipulation and those who did not (Lindheimer et al., 2017). In a second
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9 227 investigation that measured self-esteem changes following seven weeks of moderate intensity aerobic
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11 228 exercise training, participants were told that the purpose was to study brain activity during tasks of
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13 229 conditioned discrimination. Again, no differences were found between participants who were exposed
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15 230 to information that exercise improves psychological variables and those who did not receive such
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17 231 information (Arbinaga et al., 2018). These findings have therefore provided some evidence that
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19 232 disguising the study purpose may be an effective way to minimize the effect of study specific
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21 233 expectations on psychological responses to exercise.
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25 234 Indeed, the role of demand characteristics in psychological responses to exercise has long been
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27 235 recognized (Morgan, 1997). These can be reduced, for example, by using neutral language in study
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29 236 materials and blinding test administrators to condition assignment. Although these steps may increase
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31 237 the methodological rigor of exercise research, they are not always practical to implement and unlikely to
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33 238 completely prevent study-specific expectations from developing. Thus, researchers should consider
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35 239 measuring expectations to help determine their potential influence on the results.
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38 39 240 **3.2. Application of measuring expectations**

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41 241 The approach to measuring participant expectations should be guided by several questions.
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43 242 These include, (i) are the needs of the study design addressed by measuring habitual expectations,
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45 243 study-specific expectations, or both?, (ii) what is the required level of specificity needed to answer the
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47 244 research question?, (iii) how will the information be used to guide the interpretation of the study
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49 245 results?, and (iv) do the advantages of using a validated questionnaire or investigator-created
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51 246 questionnaire outweigh the disadvantages? Below we detail several scenarios in which these questions
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53 247 may be considered.
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3.2.1. Testing for differential expectations

One important application is testing for *differential expectations*, that is, ensuring that study results are not confounded by differences in habitual or study-specific expectations between the experimental and control group (Boot, Simons, Stothart, & Stutts, 2013; Stothart, Simons, Boot, & Kramer, 2014). For instance, in a study of the acute effects of exercise, apparent significant improvements in state anxiety were nullified after accounting for habitual expectations at baseline (Tieman, Peacock, Cureton, & Dishman, 2002). Because study-specific expectations are more likely than habitual expectations to change in the course of a repeated-measures study, performing mid-study (McCann & Holmes, 1984) or post-study measurements (Desharnais, Jobin, Cote, Levesque, & Godin, 1993) is valuable because it allows the investigator to determine whether differential expectations were present beyond the baseline period. However, researchers who adopt this strategy should also be cautioned that the repeated and overt measurement of expectations may increase demand characteristics by alerting participants to the study purpose or result in reactivity, a behavioral artifact wherein observed changes are confounded by a participant's awareness that a given psychological or behavioral construct is being measured (French & Sutton, 2010).

3.2.2 Clarifying the role of nocebo effects in negative psychological responses to exercise

Negative expectations are centered around anticipation of negative responses to a given stimulus and are strongly linked to nocebo effects (Benedetti, 2008; Webster, Weinman, & Rubin, 2016). Similar to how the conceptualization of placebo effects has changed over time, the notion of nocebo effect has been reframed to focus on the negative responses arising from specific psychological and neurobiological mechanisms (Beedie et al., 2018; Evers et al., 2018), rather than on any negative response that follows the administration of an inert substance (Kennedy, 1961). Measuring negative expectations could provide valuable information in terms of understanding why some participants differ in terms of the direction and magnitude of psychological responses to exercise (e.g., increases vs.

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3 272 decreases in fatigue) and the variance in that response that is unique to the exercise itself versus
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5 273 negative expectations of the participant. Little is known about the role of negative expectations in
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7 274 psychological outcomes of exercise, but compelling evidence from other fields highlights their potential
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10 275 relevance to exercise studies (Blasini, Corsi, Klinger, & Colloca, 2017; Frisaldi et al., 2015; Webster et al.,
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12 276 2016).

14 277 **3.2.3 Identifying participants with low or high likelihood of being placebo or nocebo responders**

16 278 In randomized controlled trials, the clinical significance of a treatment is judged by comparing
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18 279 the magnitude of the therapeutic improvement in the treatment group to the placebo group. Thus, the
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20 280 clinical trial may fail to demonstrate a therapeutic effect for the treatment if placebo responses are large
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22 281 (Enck, Bingel, Schedlowski, & Rief, 2013). Clinical drug trials have attempted to address this issue via a
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24 282 placebo run-in phase, which involves administering a placebo to eligible participants prior to
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26 283 randomization in order to minimize placebo responses or screen out placebo responders altogether
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28 284 (Lee, Walker, Jakul, & Sexton, 2004).

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32 285 The placebo run-in phase is appealing for conducting clinical exercise trials because reducing
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34 286 placebo responses would presumably help provide a more precise estimation of the true effect of
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36 287 exercise. The absence of a valid exercise placebo prevents the ability to use the placebo run-in approach
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38 288 in exercise studies; however, this concept could be adapted in several ways. One strategy is to measure
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40 289 habitual expectations prior to study enrollment. By screening out participants who endorse changes in
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42 290 psychological outcomes as a habitual expectation of exercise and only including participants with
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44 291 neutral or low expectations about psychological improvements, a more conservative estimate of the
45
46 292 true effect of exercise could potentially be acquired (Ojanen, 1994). Conversely, participants who are at-
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48 293 risk for nocebo responses could be screened out by excluding individuals who expect negative
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50 294 psychological consequences of exercise. Considering that placebo run-in trials are also used to decrease
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52 295 placebo or nocebo effects by habituating participants to the placebo prior to baseline testing, another
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3 296 possibility is to familiarize participants to several acute bouts of exercise before starting the trial. In
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5 297 terms of recruitment, this strategy may be more feasible than screening for expectations because
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7 298 finding individuals with low or negative expectations may be challenging, especially when the trial is
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10 299 focused on an endpoint for which the psychological benefits of exercise are widely publicized such as
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12 300 depression or anxiety.

14 301 Although some previous work has indirectly screened for expectations by excluding participants
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16 302 who reported receiving formal education in the health benefits of exercise (Lindheimer et al., 2017), no
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18 303 studies have attempted to recruit or screen participants on the basis of measuring explicit habitual
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20 304 expectations for psychological outcomes of exercise. Prior to implementing this approach, researchers
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22 305 should be cautioned that meta-analyses of clinical drug trials have failed to demonstrate that placebo
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24 306 run-in phases affect subsequent treatment or placebo responses (Greenberg, Fisher, & Riter, 1995; Lee
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26 307 et al., 2004; Trivedi & Rush, 1994). Findings such as these, which may be predicated on the potentially
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28 308 false assumption that placebo responsiveness is stable and predictable, cast doubt about the ability to
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30 309 identify and screen out potential placebo or nocebo responders prior to the onset of a study. However,
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32 310 testing this idea in the exercise setting may nevertheless inform the design of future exercise-based
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34 311 clinical trials.

39 312 **4. EXPERIMENTAL METHODS FOR STUDYING PLACEBO EFFECTS IN PSYCHOLOGICAL RESPONSES TO** 40 41 313 **EXERCISE**

43 314 Measuring expectations is an important step when the objective is to account for variability in
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45 315 psychological responses within or between groups. Likewise, experimental manipulation of expectations
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47 316 and other potential psychological or contextual causes of placebo effects can provide insight into the
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49 317 magnitude of their contribution to treatment responses and the neurobiological mechanisms through
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51 318 which these processes work. The next section of this review discusses several study designs with
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3 319 potential to advance the understanding of mechanisms of placebo effects in psychological outcomes of
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5 320 exercise.

6 321 **4.1. Expectancy modification**

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10 322 A well-established model for studying the impact of placebo effects on treatment responses is
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12 323 the **expectancy modification** design, which uses situational or behavioural cues to create or augment
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14 324 the belief that a certain outcome will occur (Kirsch, 1985). Expectancy modification is the most
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16 325 frequently adopted strategy for studying placebo effects in exercise (Arbinaga et al., 2018; Crum &
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18 326 Langer, 2007; Desharnais et al., 1993; Flowers, Freeman, & Gladwell, 2018; Helfer, Elhai, & Geers, 2014;
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20 327 Kwan, Stevens, & Bryan, 2017; Lindheimer et al., 2017; Mothes et al., 2016; Mothes, Leukel, Seelig, &
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22 328 Fuchs, 2017). In exercise studies, the expectancy modification procedure is typically used to generate
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24 329 placebo effects by creating or strengthening expectations that exercise will result in given psychological
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26 330 outcome (e.g., reduced feelings of fatigue). In these studies, the contribution of placebo effects can be
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28 331 studied by comparing psychological responses to exercise between participants who receive the
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30 332 modification and those who do not.

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34 333 Various strategies such as verbal suggestion (Arbinaga et al., 2018; Crum & Langer, 2007;
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36 334 Desharnais et al., 1993; Helfer et al., 2014; Lindheimer et al., 2017; McCann & Holmes, 1984), film clips
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38 335 (Flowers et al., 2018; Mothes et al., 2016, 2017), and reading standardized scripts (Kwan et al., 2017) are
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40 336 used to manipulate expectations. In some cases, these modifications have been further enhanced
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42 337 through additional psycho-social and environmental cues (Crum & Langer, 2007; Desharnais et al., 1993)
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44 338 or engagement of conscious mental processes by asking participants to recapitulate and record their
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46 339 expectations (Helfer et al., 2014; Kwan et al., 2017). It is not yet clear which types of modification
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48 340 procedures are most effective for influencing expectations about psychological outcomes of exercise. To
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50 341 help address this gap, studies can incorporate **manipulation checks** by measuring and comparing
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52 342 expectations between the experimental and control group to provide insight into why some studies
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3 343 have been more successful in manipulating expectations (Arbinaga et al., 2018) than others (Lindheimer
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5 344 et al., 2017). To further improve the understanding of how to effectively elicit or minimize nocebo
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7 345 effects, questionnaires that also provide the ability to measure negative expectations should be
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10 346 incorporated in manipulation checks.

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12 347 Investigators who implement expectancy modification designs should be cautioned about the
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14 348 trade-off between effectively modifying expectations and introducing cues that might lead participants
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16 349 to guess the purpose of the study. For instance, in the expectancy modification study by Lindheimer and
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18 350 colleagues, the investigators were successful in terms of preventing a majority of participants from
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20 351 guessing the study purpose (~92%), however, expectations for psychological changes were not different
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22 352 between participants who received the expectancy modification and those who did not, indicating that
23
24 353 the expectancy modification was not successful (Lindheimer et al., 2017). Thus, one challenge for future
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26 354 investigators who decide to use expectancy modification designs is determining how to effectively
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28 355 modify and measure participant expectations without increasing demand characteristics by tipping off
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30 356 participants to the purpose of the study.

31 32 33 34 357 **4.2. Conditioning**

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36 358 Conditioning represents a promising approach to studying placebo effects in exercise,
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38 359 particularly in the study of exercise induced hypoalgesia (EIH), a phenomenon in which pain sensitivity is
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40 360 reduced during or following exercise (Koltyn, 2002). This area of inquiry is especially intriguing because
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42 361 EIH and placebo hypoalgesia appear to involve similar biochemical mechanisms such as the opioid and
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44 362 endocannabinoid systems (Benedetti, Amanzio, Rosato, & Blanchard, 2011; Crombie, Brellenthin,
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46 363 Hillard, & Koltyn, 2018). Yet, despite extensive interest among both exercise and placebo researchers in
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48 364 studying pain, EIH studies are seldom designed to experimentally manipulate psychological mechanisms
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50 365 of placebo or nocebo effects.
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3 366 A recent investigation by Colloca and colleagues has provided one potential approach to
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5 367 studying placebo and nocebo effects in EIH by adapting a well validated conditioning model to isotonic
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7 368 exercise (Colloca, Corsi, & Fiorio, 2018). During an initial acquisition phase, participants learned to
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9 369 associate three different visual color cues (i.e., green, yellow, red) with three distinct thermal pain
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11 370 stimulus intensities (i.e., low, medium, high) and were led to believe that these same visual color cue-
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13 371 thermal stimulus intensity pairings would be presented during a subsequent test phase. During the test
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15 372 phase, however, a series of trials were administered wherein the presentation of each color cue was
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17 373 followed only by a medium intensity stimulus and participants were asked to rate their perceived pain
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19 374 on a 0-100 visual analog scale. Thus, placebo effects were measured by comparing pain ratings between
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21 375 trials where the medium intensity stimulus followed the expectation of medium pain intensity (i.e.,
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23 376 yellow cue-medium stimulus intensity) to trials where the medium intensity stimulus followed the
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25 377 expectation of a low pain intensity (i.e., green cue-medium stimulus intensity). Similarly, nocebo effects
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27 378 were measured by comparing yellow cue-medium stimulus intensity trials to trials where the medium
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29 379 stimulus followed the expectation of high pain intensity (i.e., red cue-medium stimulus intensity).

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31 380 By administering half of the placebo and nocebo trials during light intensity elbow extension-
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33 381 flexion (30% of maximum voluntary contraction) and half at rest, the added contribution of exercise to
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35 382 placebo and nocebo effects could be determined. The authors did not find an added effect of exercise to
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37 383 either placebo or nocebo effects, but the study by Colloca and colleagues provides a useful framework
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39 384 for future researchers to begin addressing several other questions that could be related to placebo and
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41 385 nocebo effects in EIH, including (i) intensity (e.g., would the added effect of exercise be greater at a
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43 386 higher intensity?), (ii) mode (e.g., does cycling or running during placebo/nocebo experimental result in
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45 387 different effects?), (iii) neurobiological mechanisms (e.g., how would blocking the opioid or
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47 388 endocannabinoid system affect conditioned placebo and nocebo responses during exercise?), and (iv)

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3 389 habitual expectations (e.g., is conditioning easier to implement in participants with stronger pre-existing
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5 390 expectations about the effect of exercise on pain?).
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8 391 There is promise in implementing the conditioning procedures used by Colloca and colleagues to
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10 392 study placebo and nocebo effects, particularly when experimental pain (e.g., tolerance, threshold,
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12 393 ratings of painful stimuli) is the outcome of interest. A far more elusive pursuit concerns conditioned
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14 394 placebo responses to exercise that take place in real world settings and how they affect placebo effects
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16 395 in a controlled laboratory environment. Ostensibly, a greater level of exposure to a given behavioural
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18 396 stimulus is more likely to lead to a conditioned response. Therefore, one potential approach to
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20 397 untangling the influence of conditioning effects that take place outside of the laboratory is to study how
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22 398 conditioned placebo hypoalgesia differs between participants who frequently engage in exercise and
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24 399 sedentary individuals. Demonstrating that conditioned placebo hypoalgesia is greater in active
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26 400 participants would suggest that those who are more familiar with the pain alleviating effects of exercise
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28 401 are more likely to respond positively to exercise and that increasing exercise behaviour in sedentary
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30 402 participants may improve subsequent responses to exercise.
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34 403 **5. FUTURE DIRECTIONS**

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37 404 A number of research directions can be pursued to improve the conceptualization and study of
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39 405 placebo effects in exercise studies. Below we highlight potential next steps to prioritize in future work.
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41 406 1. As suggested above, understanding of placebo and nocebo effects in psychological responses to
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43 407 exercise has lagged behind other scientific disciplines. We assert that continuing to focus efforts on
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45 408 developing a valid exercise placebo may further delay progress. Researchers should acknowledge
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47 409 the growing body of literature demonstrating that psychological mechanisms of placebo and nocebo
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49 410 effects (e.g., expectations and conditioning) can be used *en lieu* of placebos when seeking to
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51 411 understand the contribution of placebo effects to treatment responses. Therefore, we recommend
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53 412 shifting attention toward continuing to develop valid and effective methodological strategies for
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3 413 measuring and experimentally manipulating these placebo/nocebo mechanisms in exercise based
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5 414 research.
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8 415 2. The measurement of expectations for psychological outcomes of exercise would be improved by
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10 416 using psychometric instruments that measure study-specific expectations. Rather than using
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12 417 questionnaires with inherent biases toward only measuring expectations for desirable outcomes, we
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14 418 recommend using questionnaires with item phrasing and scales that allow a respondent to indicate
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16 419 expectations for either positive *or* negative changes for neutrally presented psychological outcome.
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18 420 For instance, a study of EIH can ask participants to rate their level of expected changes in pain on a
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20 421 bipolar Likert-type scale with verbal anchors that allow the participant to indicate the expected
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22 422 direction and degree of change (e.g., -3 = "large decrease", -2 = "moderate decrease", -1 "slight
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24 423 decrease", 0 "no change", 1= "slight increase", 2= "moderate increase", 3= "large increase").
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28 424 3. Measuring expectations in expectancy modification studies is also encouraged. Verifying the success
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30 425 of the manipulation by measuring expectations would allow researchers to begin cataloging which
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32 426 types of expectancy modification procedures are most effective. This information may be especially
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34 427 valuable for addressing calls to maximize treatment effects in clinical settings by augmenting the
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36 428 contribution of placebo effects (Evers et al., 2018).
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39 429 4. Conditioning studies are a promising strategy for investigating mechanisms of placebo and nocebo
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41 430 effects, although this approach has only been tested in one study of exercise and experimental pain
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43 431 (Colloca et al., 2018). More work is needed to determine whether conditioning could also be applied
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45 432 to the study of placebo effects in other psychological outcomes of exercise such as mood and
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47 433 cognition.
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50 434 5. The extant data on nocebo effects and their respective mechanisms in psychological responses to
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52 435 exercise can be traced to two studies (Colloca et al., 2018; Kwan et al., 2017). This line of research
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3 436 requires further attention and may have particularly important implications for explaining inter-
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5 437 individual variability in how healthy and clinical populations respond negatively to exercise.
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7 438 6. The question of whether study participants reliably demonstrate placebo responses across different
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10 439 clinical conditions (Kaptchuk et al., 2008) and whether biological or psychological markers can
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12 440 distinguish such individuals from non-responders (Hall, Loscalzo, & Kaptchuk, 2015; Jakši, Aukst-
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14 441 Margeti, & Jakovljevi, 2013) has attracted the attention of placebo researchers and clinical trialists
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16 442 alike. In the absence of having a valid exercise placebo, these concepts may be worthwhile to
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18 443 investigate.
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21 444 7. That patient-physician interactions can influence placebo effects in a therapeutic setting (Zion and
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23 445 Crum, 2018) opens the possibility that interactions between test administrators and participants can
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25 446 elicit placebo or nocebo effects. Such effects should not be discounted in any research setting. The
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27 447 testing, either observationally or experimentally, of the degree to which personality characteristics
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29 448 and behaviours of study personnel who interact with study participants has a similar effect on
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31 449 treatment responses is a valid line of inquiry.
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35 450 6. CONCLUSION

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37 451 Embracing and adopting the notion of studying placebo and nocebo effects without traditional
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39 452 placebo treatments is germane to advancing the understanding of their impact on psychological
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41 453 responses to exercise. Researchers can capitalize on using established psychological mechanisms of
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43 454 placebo effects to better understand how psycho-social context influences psychological responses to
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45 455 exercise in clinical trial and laboratory settings. Measurement of habitual and study-specific
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47 456 expectations can help explain inter-individual variability in positive and negative outcomes of exercise
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49 457 whereas expectancy modification and conditioning can elucidate the neurobiological mechanisms that
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51 458 mediate the influence of placebo and nocebo effects on these responses. These endeavors would make
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53 459 a valuable contribution toward advancing the current standard of knowledge about placebo and nocebo
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3 460 effects in psychological responses to exercise which in turn may help inform the design of effective
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5 461 exercise interventions in the future.
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3 596 **Figure legends**

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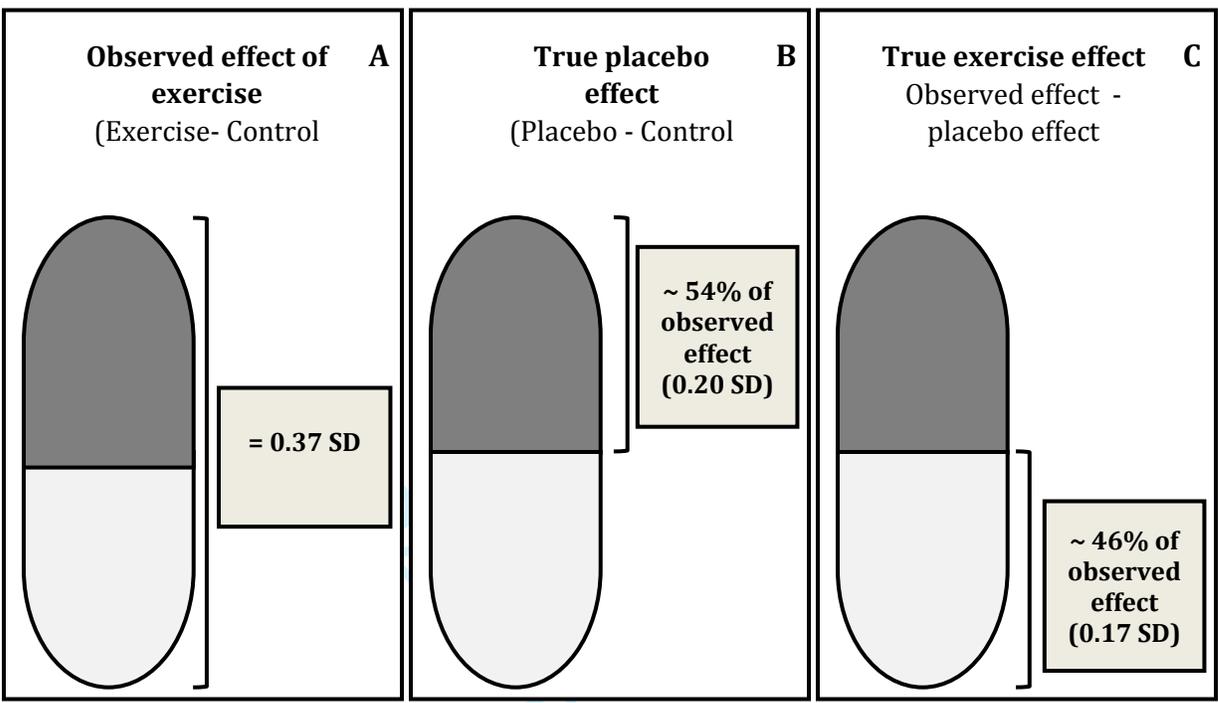
5 598 **Figure 1.** Distinguishing treatment effects from placebo effects and non-specific effects requires the
6 599 inclusion of a placebo and no-treatment control group. Panel A shows what is typically measured in
7 600 exercise studies, the observed effect of exercise, which is estimated by comparing the change in the
8 601 exercise group to the control group. Panel B shows the placebo effect, which is estimated by comparing
9 602 the change in the placebo group to the control group. Panel C shows that the true effect of exercise can
10 603 be estimated by subtracting the placebo effect from the observed effect of exercise. In a meta-analysis
11 604 of randomized controlled studies that included an exercise, placebo, and control group, approximately
12 605 half of the observed effect of exercise on psychological outcomes was attributed to placebo effects
13 606 (Lindheimer et al., 2015).
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Figure 1. Placebo effects may explain over half of the psychological effect of exercise



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Table 1. Key terms

Demand characteristics	The totality of cues that can lead a participant to guess the experimental hypothesis of the study (Orne, 1962).
Differential expectations	A potential confounding variable that arises from differences in outcome expectations between an experimental and control group (Boot et al. 2013).
Expectancy modification	An experimental procedure in which situational or behavioral cues are used to create or augment the belief that a certain outcome will occur (Kirsch, 1985).
Experimentally-induced expectation	A type of study-specific expectation that is generated from an experimental procedure such as expectancy manipulation or conditioning (Mothes et al., 2016).
Habitual expectation	A type of outcome expectation that is a reflection of an individual's previous experiences or cultural beliefs (Mothes et al., 2016). These expectations are developed prior to participation in a research study.
Incidentally-induced expectation	A type of study-specific expectation that the investigator did not intend for the participant to develop. These may threaten the internal validity of the study.
Manipulation check	A procedure for confirming the success of an experimental manipulation. This is applied to expectancy modification studies by measuring and comparing expectations between the experimental and control group following the expectancy modification procedure.
Placebo/nocebo effect	A desirable (placebo effect) or undesirable (nocebo effect) outcome resulting from a person's expected and/or learned response to a treatment or situation. Recent advances indicate that it is not always necessary to administer a traditional placebo (i.e., inert substance) in order to observe and measure the contribution placebo/nocebo effects to a treatment (Benedetti, 2008; Finniss et al. 2010).
Study-specific expectation	A type of outcome expectation that is formed from experiences that occur during the various phases of a study (e.g., advertisement, recruitment, screening, informed consent, familiarization, data collection).

Table 2. Examples of outcomes that have been measured via self-report or task performance in exercise studies.

Perceptual/sensory	Mental Health	Cognition	Miscellaneous
Muscle pain	Anxiety	Executive function	Affect
Perceived exertion	Depression	Sustained attention	Body Image
Pain intensity	Sleep quality	Processing speed	Mood
Symptom severity	Stress	Working memory	Self-esteem