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

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

1) **Reducing the space given to arguing for the need for three group designs. The theoretical importance of using a placebo and no-treatment group to distinguish placebo effects from non-specific effects is still briefly discussed, but we have toned down specific recommendations for conducting three arm studies.**

2) **Less discussion of whether or not valid exercise placebos can be developed. We still provide some historical context on this matter, but feel that talking about how to develop valid exercise placebos may do more harm than good and may distract readers from more viable options to studying placebo effects and mechanisms that leveraging mechanisms of placebo effects (e.g., expectation, conditioning) to study their impact on psychological responses to exercise.**

3) **Removal of language pertaining to "placebo-related" effects.**

4) **Removal of the section pertaining to measurement of expectations.**

5) **Removal of the section pertaining the balanced placebo design and figure 2.**

6) **New discussion of several recently published studies with a high degree of relevance to the scope and objectives of this review (Arbinaga et al., 2018; Colloca et al., 2018; Kong et al., 2018).**

7) **Reduction of total word count from 6766 (original version) to 5682 (revised version).**

8) **The abstract, highlights, future directions and conclusion sections have been updated to reflect the changes that have been made to the overall manuscript.**

For your convenience, you will find two versions of our revised manuscript below. The first version shows track changes and the second version is a clean copy.

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?

Thank you for this important consideration. We now provide an example of a clinical study in section 2.2. that compared pain reductions between a treatment alone group and treatment plus expectation.
Kong, J., Wang, Z., Leiser, J., Minicucci, D., Edwards, R., Kirsch, I., Wasan, A. D., et al. (2018). Enhancing treatment of osteoarthritis knee pain by boosting expectancy: A functional neuroimaging study. NeuroImage: Clinical, 18, 325–334.

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

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

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

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

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

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

P8 l173 - discuss ways in which placebo can be delivered in exercise contexts as presumably in some ways verbal suggestion could be a placebo as could any sham condition if perceived appropriately similar to the experimental aims.

Please see our edits to section 2. We now describe a study by Kong and colleagues (2018) who compared acupuncture alone to acupuncture plus enhanced treatment expectations.

P9 L53 and elsewhere add a 'u' in behavior

Done.

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

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

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

Thank you. This knowledge gap is now acknowledged in item 1 of the future directions section.

Reviewer: 2

Comments to the Author

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

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.

Main comments

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

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

We agree and have removed the mention of placebo-related effects throughout the manuscript.

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

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

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

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

"By administering half of the placebo and nocebo trials during light intensity elbow extension-flexion (30% of maximum voluntary contraction) and half at rest, the added contribution of exercise to placebo and nocebo effects could be determined. The authors did not find an added effect of exercise to either placebo or nocebo effects, but the study by Colloca and colleagues provides a useful framework for future researchers to begin addressing several other questions that could be related to placebo and nocebo effects in EIH, including (i) intensity (e.g., would the added effect of exercise be greater at a higher intensity?), (ii) mode (e.g., does cycling or running during placebo/nocebo experimental result in different effects?, (iii) neurobiological

mechanisms (e.g., how would blocking the opioid or endocannabinoid system affect conditioned placebo and nocebo responses during exercise?), and (iv) habitual expectations (e.g., is conditioning easier to implement in participants with stronger pre-existing expectations about the effect of exercise on pain?).”

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

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

Specific comments

P4 L69-70 – Reference is needed

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

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

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

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Biological, clinical and ethical advances in placebo effects. *Lancet*, *375*, 686–695.

P9 L185 – An example of a study that has examined this would be useful

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

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

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

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

"This issue has also been considered in exercise research where the investigators minimized demand characteristics by using deceptive information in the study advertisement and informed consent materials to disguise the study purpose (Arbinaga, Fernández-Ozcorta, Sáenz-López, & Carmona, 2018; Lindheimer, O'Connor, McCully, & Dishman, 2017). Interestingly, this research has shown that even when the investigators purposefully tried to alter participant expectations at a later point in the study, disguising the true purpose of the study early on may have blunted the effectiveness of the experimental manipulations. For example, Lindheimer and colleagues measured mood and cognitive responses to light intensity active cycling or motorized passive cycling, but informed participants that the purpose was to compare cardio-respiratory responses between the two conditions. Although half of these participants were exposed to an expectancy manipulation designed to enhance expectations for psychological improvements following exercise, the investigators did not observe a significant difference in expectations or psychological responses to exercise between participants who received the expectancy manipulation and those who did not (Lindheimer et al., 2017). In a second investigation that measured self-esteem changes following seven weeks of moderate intensity aerobic exercise training, participants were told that the purpose was to study brain activity during tasks of conditioned discrimination. Again, no differences were found between participants who were exposed to information that exercise improves psychological variables and those who did not receive such information (Arbinaga et al., 2018). These findings have therefore provided some evidence that disguising the study purpose may be an effective way to minimize the effect of study specific expectations on psychological responses to exercise."

P12 L251 – While the paper is focused on controlling the placebo effect in clinical/research practice, it would be worthwhile for authors to acknowledge that in applied practice the aim is to augment the placebo effect to maximise treatment effects (see https://insights.ovid.com/crossref?an=00149619- 201507000-00009).

We agree and have added the following sentence to item 3 of the "5. Future Directions" section.

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

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

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

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

P10 L310 - this sentence needs rewording

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

"The approach to measuring expectations should be guided by several questions."

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

We agree and have added the following to the end of this paragraph:

"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)."

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

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

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

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

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

We have added the following to address this comment:

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

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

We agree and have added the following sentence here:

"…To further improve the understanding of how to effectively elicit or minimize nocebo effects, questionnaires that also provide the ability to measure negative expectations should be incorporated in manipulation checks."

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

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

"Investigators who implement expectancy modification designs should be cautioned about the trade-off between effectively modifying expectations and introducing cues that might lead participants to guess the purpose of the study. For instance, in the expectancy modification study by Lindheimer and colleagues, the investigators were successful in terms of preventing a majority of participants from guessing the study purpose (~92%), however, expectations for psychological changes were not different between participants who received the expectancy modification and those who did not, indicating that the expectancy modification was not successful (Lindheimer et al., 2017). Thus, one challenge for future investigators who decide to use expectancy modification designs is determining how to effectively modify and measure participant expectations without increasing demand characteristics by tipping off participants to the purpose of the study."

Figure 1 Include Hedges d alongside percentages

Done.

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

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

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

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

"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).”

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

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

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

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

KEYWORDS: Behavior; Cognition; Health; Methodology; Neuroscience

HIGHLIGHTS:

- Several methodological factors render investigations of psychological outcomes of acute and chronic exercise vulnerable to placebo effects.

- ~~In randomized-controlled studies three conditions, a treatment, no-treatment control, and placebo group, are all required to distinguish treatment effects from placebo effects.~~

- ~~True p~~Placebo groups may not be possible when studying psychological responses to exercise, but ~~studies from other fields that demonstrate that~~traditional placebos are not always required to study the impact of psychological mechanisms of placebo effects ~~their~~on treatment responses.

- Measurement of expectations can help explain inter-individual variability in psychological responses to exercise.

- Expectancy modification and conditioning can each be used to enhance treatment responses and elucidate the neurobiological mechanisms that mediate the influence of placebo and nocebo effects on these responses.~~There are several potential methods for measuring the influence of placebo effects on the magnitude and mechanisms of psychological responses to 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 a~~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

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

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

[Table 1 about here]

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

~~subject to limitations that are inherent to self-report measures.~~ Additionally, we recognize that cognition can be assessed by task performance or self-report, but we also consider it to fit within the scope of psychological outcomes/responses (Table 2).

[Table 2 about here]

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

Effect size estimates from meta-analytic reviews of randomized controlled trials support the argument that exercise training improves psychological outcomes. For self-reported outcomes such as anxiety, depression, fatigue, and pain, exercise training appears to result in small (Standardized mean difference = 0.29) to moderate (Standardized mean difference = 0.62) improvements (Cooney et al., 2013; Herring, Puetz, O'Connor, & Dishman, 2012; Herring, O'Connor, & Dishman, 2010; Puetz, O'Connor, & Dishman, 2006; Searle, Spink, Ho, & Chuter, 2015). Additionally, exercise training has a small, but significant effect on certain domains of cognitive performance (Standardized mean difference = 0.12-0.16) (Smith et al., 2010). However, there are several methodological ~~factors~~ issues that have raised concerns about the ability to distinguish~~ing~~ these observed effects of exercise from placebo effects (Lindheimer, O'Connor, & Dishman, 2015; Ojanen, 1994; Szabo, 2013). These~~,~~ include:~~ing,~~ (i) the inability to perform double-blind studies, (ii) demand characteristics, and (iii) the largely subjective nature of many psychological outcome measures. ~~Moreover it is difficult to measure placebo effects in randomized controlled trials when both a placebo *and* control comparison group are not included (Ernst & Resch, 1995).~~ In the following section, we discuss ~~why this design consideration is~~the theoretical importance of including placebo and no-treatment control groups to measure placebo effects in clinical trials tand ~~also highlight some practical barriers to designing studies with placebo and no-treatment control groups~~why this is difficult in studies of psychological responses to exercise.

2.1. ~~The Importance of including placebo and control conditions~~Characterizing placebo effects in clinical trials

~~The introduction of the terms ***true placebo effects*** and ***perceived placebo effects*** has helped clarify why both placebo and control groups are needed to measure placebo effects in clinical trials (Ernst & Resch, 1995).~~ An early misconception was that placebo effects could be studied in clinical trials by measuring change from baseline in the placebo group (i.e., perceived placebo effects) (Beecher, 1955). However, this approach fails to consider ~~that~~ the changes in a placebo group ~~can result from~~that ~~are~~could be explained by non-specific effects such as natural history of disease, regression to~~wards~~ the mean, and unidentified parallel interventions (Ernst & Resch, 1995; Kienle & Kiene, 1997). ~~Presumably,~~ If the randomization of participants to their respective groups is successful, these ~~same~~ non-specific effects would presumably have an equal likelihood of occurring in a wait-list or no-treatment control group.~~;~~ Thus, subtracting the change in the control group from the change in the placebo group accounts for non-specific effects and ~~T~~therefore, ~~a more precise estimation of the so-called 'true' placebo effect is measured~~could be obtained ~~by comparing the change in the placebo group to that of the control group~~provides a more precise estimation of the placebo effect in the clinical trial setting.

~~Ernst and Resch have also introduced the concepts of ***perceived treatment effects*** and ***true treatment effects***. The perceived treatment effect is considered to be the change from baseline that is measured in the treatment group and the true treatment effect is therefore obtained after accounting for placebo effects and other non-specific effects (Ernst & Resch, 1995). In the exercise setting, these terms are synonymous with ***observed effect of exercise*** and ***true effect of exercise*** the observed effect of exercise is the psychological response resulting from both true effects of exercise and placebo effects whereas the true effect of exercise is the psychological response that can be solely attributed to the exercise *per se*. (Ojanen, 1994). That is, in a group that has been assigned to receive the exercise treatment, the observed effect of exercise is the psychological response resulting from both true effects of exercise and placebo effects whereas the true effect of exercise is the psychological response that can be solely attributed to the exercise *per se*. Consequently, to obtain the most precise estimation of the~~

~~effect of exercise on psychological responses in a clinical trial or randomized controlled study design, we use the principles outlined by Ernst and Resch (1995) and Ojanen (1994) to offer the following guidelines:~~

~~Determining the true effect of exercise/true treatment effect requires separation of the true placebo effect from the observed effect of exercise/perceived treatment effect; however, the true placebo effect must also be distinguished from the perceived placebo effect.~~

~~In order to distinguish the true placebo effect from the perceived placebo effect, a no-treatment or wait-list control group is needed to rule out other non-specific effects that may explain changes in the outcome measure over time.~~

~~Obtaining the most precise estimation of the true effect of exercise/true treatment effect in a clinical trial or randomized controlled study design requires that participants be allocated to at least three groups - treatment, placebo and control.~~

~~In line with these recommendations,~~Following this ~~logic~~line of reasoning, Lindheimer and colleagues ~~conducted a meta-analysis of randomized controlled studies~~ attempted ~~to quantify~~quantified the placebo effect in psychological ~~responses~~ outcomes of~~to~~ exercise training studies ~~by conducting~~in a meta-analysis of ~~randomized controlled studies~~randomized controlled trials that included ~~with~~ an exercise treatment ~~arm~~, ~~a~~ control ~~arm~~, and aplacebo arm ~~n arm that met their operational definition for a placebo condition~~ (*n* = 9) (Lindheimer et al., 2015). ~~The authors attempted to provide a valid estimate of the true placebo effect and true effect of exercise by only including randomized controlled studies with an exercise treatment arm, a control arm, and an arm that met their operational definition for a placebo condition (*n* = 9).~~ In this case, ~~the authors defined~~ a placebo condition was defined as "an intervention that was not generally recognized as efficacious, that lacked adequate evidence for efficacy, and that has no direct pharmacological, bio-chemical, or physical mechanism of action according to the current standard of knowledge" (p. 695). After estimating the placebo effect by

aggregating the standardized mean difference between the placebo and control groups from each study (Hedges' *d* = 0.20), ~~they further and subtractinged~~ the ~~true~~ placebo effect was subtracted ~~(Hedges' *d* = 0.20)~~ from the observed effect of exercise, that is, ~~e~~ the aggregated standardized mean difference between the exercise and control groups from each study (Hedges' *d* = 0.37). Following this procedure, ~~,~~ the authors ~~found~~ concluded that the ~~true~~ effect of exercise training on psychological responses (Hedges' *d* = 0.17) was less than half of the observed effect of exercise after accounting for placebo effects (Figure 1). ~~Additional relevant findings included that, (i) placebo effects were larger in subjectively measured outcomes (i.e., anxiety, depression, energy, fatigue) compared to objectively measured outcomes (i.e., cognitive performance), (ii) placebo effects were larger in placebo conditions that resembled exercise, and (iii) few exercise training studies used designs that met the author's criteria for measuring the true placebo effect.~~

[Figure 1 about here]

2.2. Practical issues with characterizing placebo effects in ~~clinical trial study designs~~studies of psychological responses to exercise

Despite early recognition ~~for~~ of the importance ~~of~~ for using methods that improve the estimation of placebo effects (McCann & Holmes, 1984), several barriers have continued to stymie~~d~~ investigators and prevent~~ed~~ widespread implementation of these methods in exercise training studies. Foremost among these is the ~~apparent~~ inability to perform double-blind studies. Unlike pharmacological interventions in which the vehicles that are used to deliver the treatment and placebo are identical (e.g., capsule, fluid, injection), it is considered to be impossible to truly blind participants to receiving exercise in research settings. This ~~,~~ ~~which~~ in turn can provoke expectations - potentially positive or negative - that an exercise treatment is being received. The ~~is also brings up a related and unresolved issue –~~question of what might constitute~~s~~ a valid exercise placebo ~~and is it possible to develop one?~~ is as yet unresolved.

A review by Ojanen (1994) argued "that the idea of a placebo group in exercise studies is, in practice, impossible". Nonetheless, some early studies attempted to create valid exercise placebo conditions by using very low intensity "minimal exercise" (Roth & Holmes, 1987) or relaxation training (McCann & Holmes, 1984) and even made efforts to manipulate expectations for improvement with verbal suggestion (McCann & Holmes, 1984). However, even in a study that reported equivalent expectations, involvement and subjective utility between the treatment and minimal exercise condition (Roth & Holmes, 1987), Ojanen reasoned that a real placebo condition was not used because a placebo effect was not observed. This interpretation is not entirely accurate, however, because the inclusion of a placebo condition does not necessarily always result in an observable placebo effect.

To date, ~~Ojanen's position on the practicality of using placebo groups in exercise still appears to be supported because~~ little progress has been made in developing a valid exercise placebo, one that ~~is, a placebo that~~ mirrors every aspect of exercise except the "active ingredients". Of course, this ~~pursuit is also limited by a lack of clarity~~begs the question of ~~for~~ what are the active ingredients (i.e., mechanisms) responsible for the psychological changes associated with exercise ~~of exercise actually are~~. Nevertheless, these somewhat circular issues may be more important to consider when the objective is to study the placebo effect *per se* rather than to study the involvement of placebo effects in psychological responses to exercise. As we discuss later in this review, well established psychological mechanisms of placebo effects such as expectations and conditioning can be used to ~~enhance~~influence treatment responses, providing a means of studying the contribution of placebo effects to treatment effects without the inclusion of a traditional placebo condition. ~~which suggests that placebo groups are not always necessary in order to study the contribution of placebo effects to the effect of a treatment.~~ For instance, Kong and colleagues showed a greater degree of pain relief in knee osteoarthritis patients assigned to receive acupuncture with enhanced treatment expectations compared to acupuncture alone or no-treatment (Kong et al., 2018). Additionally, compared to the acupuncture only group, the acupuncture

plus enhanced expectations group showed greater resting state functional connectivity between the nucleus accumbens and several other brain regions with links to placebo hypoalgesia such as ~~that have been linked to placebo hypoalgesia such as~~ the rostral anterior cingulate cortex and dorsolateral prefrontal cortex (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2013). These findings suggest that enhancing treatment expectations can change both behavioral and neurobiological outcomes to a higher degree than treatment alone and this approach may also be considered as a viable option for studying the impact of placebo effects on treatment responses to exercise. ~~After integrating this observation from the Roth & Holmes (1987) study with their finding that psychological changes in the treatment group were not correlated with changes in aerobic fitness, Ojanen concluded that placebo effects arise only after a certain threshold of exercise intensity.~~

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

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

~~*Outcome expectations* are beliefs that a given will lead to a certain outcome and a~~A wide-body of research has demonstrated the~~ir~~ role of expectations as a psychological mechanism of placebo effects

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

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

3.1. Classification and definitions

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

more dynamic. ~~distinction between expectations that were developed *prior to* involvement in a study and those that can develop *as a result* of study involvement.~~ ***Habitual expectations*** are thought to primarily reflect an individual's previous experiences or cultural beliefs (Mothes et al., 2016). Several plausible factors may play a role in how habitual expectations are developed and their level of influence on the measurement of psychological responses to exercise. These include level of habitual physical activity behaviour, particularly salient memories of psychological responses to exercise, and exposure to information from various sources (e.g., media, peers, family members, educators, clinicians, prior research participation) about positive or negative effects of exercise. How these ~~various~~ factors interact to form habitual expectations is not well studied, but the accumulation of these experiences over time presumably influences a research participant's interpretation of how they feel during and after exercisesing~~ing~~.

~~Because expectations are fluid and can change in response to new experiences (Kirsch, 2018),~~ Iinvestigators should also recognize ~~that participation in a research study~~ that participation in a research study has the potential to ~~can~~ alter pre-existing expectations or create new ones. Thus, we now introduce the term ***study-specific expectations*** to address the expectations that are more fluid than habitual expectations and can change in response to new experiences such as participating in a research study (Kirsch, 2018). ~~help increase awareness for the importance of measuring potential changes in expectations that can happen over the course of study participation.~~ Study-specific expectations are unique because they take experiences that occur *during* the various phases of participation in a laboratory or clinical study into account (e.g., advertising, recruitment, screening, informed consent, familiarization, data collection), whereas habitual expectations ~~solely pertain to~~ more so reflective of a participant's ~~individual history of~~prior real-world experiences with exercise.

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

psychological mechanism of placebo effects, researchers ~~may~~ can intentionally manipulate them to ~~study~~ examine their impact on psychological responses to exercise. Thus, study-specific expectations that are a direct consequence of an experimental manipulation have been referred to as ***experimentally-induced expectations*** (Mothes et al., 2016) and their importance is discussed in later sections of this review**.** Conversely, we introduce the term ***incidentally-induced expectations*** to acknowledge the study-specific expectations ~~that are created by~~which results from some aspect of the study that was unintended by the investigator. Incidentally-induced expectations can introduce error variance into the measurement of psychological responses to exercise, which is why it is critical to take them into account during the design and conduct of a study.

One way to control for incidentally-induced expectations is to reduce potential sources of ***demand characteristics***, the totality of cues that can lead a participant to guess the experimental hypothesis of the study (Orne, 1962). A significant source of these cues ~~can arise from~~is information communicated by study materials (e.g., advertisements, informed consent documents). For instance, Foroughi and colleagues reported that following one hour of practicing cognitive tasks, performance on fluid intelligence tests was better among participants who enrolled in the study after viewing an overt advertisement for a "Brain Training and Cognitive Enhancement" study compared to participants who responded to a generic advertisement with no information about brain training or cognitive enhancement (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016). Although the authors did not collect explicit information that would allow them to test for between-group differences in expectations, their study provided a clear example of how information that overtly communicates the study purpose can affect a given participant's behaviour.

This issue has also been considered in exercise research where the investigators minimized demand characteristics by using deceptive information in the study advertisement and informed consent materials to disguise the study purpose (Arbinaga, Fernández-Ozcorta, Sáenz-López, &

Carmona, 2018; Lindheimer, O'Connor, McCully, & Dishman, 2017). Interestingly, this research has shown that even when the investigators purposefully tried to alter participant expectations at a later point in the study, disguising the true purpose of the study early on may have blunted the effectiveness of the experimental manipulations. For example, Lindheimer and colleagues measured mood and cognitive responses to light intensity active cycling or motorized passive cycling, but informed participants that the purpose was to compare cardio-respiratory responses between the two conditions. Although half of these participants were exposed to an expectancy manipulation designed to enhance expectations for psychological improvements following exercise, the investigators did not observe a significant difference in expectations or psychological responses to exercise between participants who received the expectancy manipulation and those who did not (Lindheimer et al., 2017). In a second investigation that measured self-esteem changes following seven weeks of moderate intensity aerobic exercise training, participants were told that the purpose was to study brain activity during tasks of conditioned discrimination. Again, no differences were found between participants who were exposed to information that exercise improves psychological variables and those who did not receive such information (Arbinaga et al., 2018). These findings have therefore provided some evidence that disguising the study purpose may be an effective way to minimize the effect of study specific expectations on psychological responses to exercise.

~~Demand characteristics can also stem from interactions between test administrators and study participants. For instance, consider a clinical trial that examines the effect of exercise training on cognitive performance compared to a no-treatment control condition. A test administrator may inadvertently bias a participant who they know is in the exercise group to try harder on the cognitive task than those assigned to the control group because of their own inherent bias that exercise will improve cognition. To prevent this situation from occurring, an investigator can try implementing a~~

~~single blinding procedure by ensuring that study personnel who are involved in exercise training are not also involved in test administration.~~

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

~~3.2. Measuring outcome expectations~~

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

~~3.2.1 Psychometrically validated questionnaires~~

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

currently available is their emphasis on general psychological responses (e.g., "a major benefit of physical activity for me is the positive psychological effect").

When an investigator is interested in differentiating a specific expectation from the wide span of expected psychological effects that may come to a participant's mind when thinking about exercise (Table 2), a questionnaire that assesses expectations for general psychological responses is somewhat limited in scope. Thus, there is a need for a validated expectancy questionnaire with a higher level of specificity for a wide variety of psychological outcomes in the literature that may be of interest in a given study. Meanwhile, investigators who want to control for expectations for a specific psychological outcome rather than general psychological effects are faced with the dilemma of using a validated questionnaire that lacks specificity or creating a study-specific questionnaire that has not been validated.

In addition to greater levels of specificity, A further need for expectancy measurement is a validated questionnaire that measures expectations for negative psychological responses is also needed. The validated questionnaires that are currently available in the literature use item phrasing and scales that do not provide the respondent with the ability to indicate positive *and/or* negative expectations for psychological responses to exercise (Sechrist et al., 1987; Steinhardt & Dishman, 1989; Wojcicki et al., 2009). For instance, the Outcome Expectations for Exercise Scale asks participants to rate their level of agreement or disagreement with positive outcomes items such as "Exercise makes my mood better in general", whereas a questionnaire that uses items with neutral instructions such as "rate the degree of expected *changes* in each outcome" and provides a bi-polar scale to assess expected decreases or increases for a list of psychological outcome (e.g., anxiety, depression, stress) would permit the assessment of both negative or positive expectations in the same question. This information is valuable to collect because it may help explain why some individuals report negative psychological changes

~~during or following exercise and the extent to which these changes are being caused by a feature of the exercise stimulus (e.g. intensity).~~

~~**3.2.2 Investigator-developed questionnaires**~~

~~Despite the potential psychometric pitfalls of using non-validated questionnaires, the use of investigator-developed scales has been adopted as a strategy for measuring outcome expectations (Desharnais, Jobin, Cote, Levesque, & Godin, 1993; King, Taylor, Haskell, & DeBusk, 1989; Moses, Steptoe, Mathews, & Edwards, 1989). One key advantage of these scales over psychometrically validated scales is specificity. That is, they can be designed to measure expectations that parallel the actual outcome measure being used, a strategy which is recommended when measuring expectations for the purpose of predicting changes in a specific outcome (Kirsch, 2018). For example, a 6-month exercise training study by King and colleagues created an expectation questionnaire with 14 Likert scaled items that directly corresponded to each psychological outcome that was measured over the course of the study (King et al., 1989).~~

~~In addition to providing a greater level of specificity, investigator-developed questionnaires are well suited to measuring study-specific expectations because their instructions and items can be adjusted to make it clear to the respondent that the questionnaire is referring to expected outcomes of that particular study rather than physical activity in general. For instance, a randomized controlled trial by McCann and Holmes (1984) measured study-specific expectations with the following investigator-developed questionnaire items: (i) "Rate the degree of progress you feel you will make in managing stress more effectively", (ii) "To what extent does the training you will receive seem as though it should help?", (iii) "How would you rate the probability of the training helping you to manage the stress you typically feel?" (McCann & Holmes, 1984).~~

3.~~3~~2. Application of measuring expectations

The approach to measuring participant expectations should be guided by several questions. These include, (i) are the needs of the study design addressed by measuring habitual expectations, study-specific expectations, or both?, (ii) what is the required level of specificity needed to answer the research question?, (iii) how will the information be used to guide the interpretation of the study results?, and (iv) do the advantages of using a validated questionnaire or investigator-created questionnaire outweigh the disadvantages? Below we detail several scenarios in which these questions may be considered.

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

~~studies involving Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) indicate thatthese are by no means ubiquitous across all healthy and clinical populations It has repeatedly been shown that ME/CFS patients often experience an exacerbation of their symptom severity (e.g., fatigue, pain, mood disturbance) following physical exertion, a phenomenon known as post-exertional malaise (Clayton, 2015; Loy, O'Connor, & Dishman, 2016). The mechanisms of post-exertional malaise are still under investigation, but there is evidence that anticipation of a negative experience can influence both brain activity (Burgmer et al., 2011) and exercise (Heins et al., 2013) in patients with Fibromyalgia, a musculoskeletal pain condition that is co-morbid with ME/CFS (Clayton, 2015). Additionally, ME/CFS patients rate exercise as more difficult and painful than matched healthy controls (Cook et al., 2017). These preliminary data have led to speculation about the role of negative expectations as a potential~~

~~source of variability in symptomatic responses to exercise in ME/CFS patients with and without comorbid Fibromyalgia post-exertion malaise (Lindheimer, Meyer, et al., 2017).~~

3.~~3~~2.3 Identifying participants with low or high likelihood of being placebo or nocebo responders

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

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

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

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

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

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

insight into the magnitude of their contribution to treatment responses and the neurobiological mechanisms through which these processes work.

~~An illuminating review by Benedetti and colleagues has distinguished the application and objectives of studying placebo effects in the clinical trial setting from the experimental laboratory setting – "whereas the clinical trialist is interested in any improvement that may take place in a clinical trial, the neurobiologist is only interested in the psychosocial-psychobiological effects after the administration of a placebo" (Benedetti et al., 2011). Thus, while clinical trials are useful for understanding the magnitude of placebo effects, laboratory based studies contribute information about the potential mechanisms underlying these effects.~~ The next section of this review discusses several study designs with potential to advance the understanding of mechanisms of placebo effects in psychological outcomes of exercise.

4.1. Expectancy modification

A well-established model for ~~studying expectations as a psychological mechanism of~~studying the impact of placebo effects on treatment responses is the ***expectancy modification*** design, which uses situational or behavioural cues to create or augment the belief that a certain outcome will occur (Kirsch, 1985). Expectancy modification is the most frequently adopted strategy for studying placebo ~~mechanisms~~ effects in exercise (Arbinaga et al., 2018; Crum & Langer, 2007; Desharnais et al., 1993; Flowers, Freeman, & Gladwell, 2018; Helfer, Elhai, & Geers, 2014; Kwan, Stevens, & Bryan, 2017; Lindheimer et al., 2017; Mothes et al., 2016; Mothes, Leukel, Seelig, & Fuchs, 2017). In exercise studies, the expectancy modification procedure is typically used to ~~induce~~ generate placebo effects by ~~experimentally augmenting the belief~~creating or strengthening expectations that exercise will result in ~~a~~ given psychological outcome (e.g., reduced feelings of fatigue). ~~Following expectancy modification~~In these studies, the contribution of placebo effects ~~psychological responses to exercise~~can be studied by ~~in~~ comparing psychological responses to exercise between participants ~~in the experimental condition~~

~~are compared to control condition participants whose expectations were not modified~~who receive the modification and those who do not.

Various strategies such as verbal suggestion (Arbinaga et al., 2018; Crum & Langer, 2007; Desharnais et al., 1993; Helfer et al., 2014; Lindheimer et al., 2017; McCann & Holmes, 1984), film clips (Flowers et al., 2018; Mothes et al., 2016, 2017), and reading standardized scripts (Kwan et al., 2017) ~~have been to~~are used to manipulate expectations. In some cases, these modifications have been further enhanced through additional psycho-social and environmental cues (Crum & Langer, 2007; Desharnais et al., 1993) or engagement of conscious mental processes by asking participants to recapitulate and record their expectations (Helfer et al., 2014; Kwan et al., 2017). It is not yet clear which types of modification procedures are most effective for influencing expectations about psychological outcomes of exercise. To help address this gap, studies can incorporate ***manipulation checks*** by measuring and comparing expectations between the experimental and control group to provide insight into why some studies ~~are~~ have been more successful ~~with~~ in manipulating expectations (Arbinaga et al., 2018) than others (Lindheimer et al., 2017). T~~In order t~~o further improve the understanding of how to effectively elicit or minimize nocebo effects, questionnaires that also provide the ability to measure negative expectations should be incorporated in manipulation checks.

Investigators who implement expectancy modification designs should be cautioned about the trade-off between effectively modifying expectations and introducing cues that might lead participants to guess the purpose of the study. For instance, in the expectancy modification study by Lindheimer and colleagues, the investigators were successful in terms of preventing a majority of participants from guessing the study purpose (~92%), however, expectations for psychological changes were not different between participants who received the expectancy modification and those who did not, indicating that the expectancy modification was not successful (Lindheimer et al., 2017). Thus, one challenge for future investigators who decide to use expectancy modification designs is determining how to effectively

modify and measure participant expectations without increasing demand characteristics by tipping off participants to the purpose of the study.

~~**4.1.1 The balanced placebo design**~~

~~A special case of an expectancy modification study is the ***balanced placebo design*** (Rohsenow & Marlatt, 1981; Ross, Krugman, Lyerly, & Clyde, 1962). By assigning participants to a drug or placebo condition and manipulating their expectations about condition assignment, this design allows the investigator to differentiate between the treatment effect (i.e., participants who receive the treatment, but are told they received the placebo) and placebo effect (i.e., participants who receive the placebo, but are told they received the treatment) (Figure 2).~~

~~**[Figure 2 about here]**~~

~~The balanced placebo design was developed for researching expectancy effects in drug responses (Enck et al., 2011), but it has also been modified to the study of placebo effects in psychological responses to exercise. Using a recumbent motorized cycle to provide either a sham/inert or treatment stimulus, Lindheimer and colleagues assigned participants to a passive condition in which participant's legs were involuntarily moved for them (i.e., sham/inert) or an active condition in which participants cycled under their own volition (i.e., treatment) (Lindheimer, O'Connor, et al., 2017). Additionally, half of participants in each condition were exposed to an expectancy modification procedure to generate expectations that active or passive cycling would result in post-treatment improvements in mood and cognitive performance.~~

4.2. Conditioning

Conditioning represents a promising approach to studying placebo effects in exercise, particularly in the study of exercise induced hypoalgesia (EIH), a phenomenon in which pain sensitivity is reduced during or following exercise (Koltyn, 2002). This area of inquiry is especially intriguing because EIH and placebo hypoalgesia appear to involve similar biochemical mechanisms such as the opioid and

endocannabinoid systems (Benedetti, Amanzio, Rosato, & Blanchard, 2011; Crombie, Brellenthin, Hillard, & Koltyn, 2018). Yet, despite extensive interest among both exercise and placebo researchers in studying pain, EIH studies are seldom designed to experimentally manipulate psychological mechanisms of placebo or nocebo effects.

~~Interested researchers can take several~~ A recent investigation by Colloca and colleagues has provided one potential approach to studying placebo and nocebo effects in EIH by adapting a well validated conditioning model to isotonic exercise (Colloca, Corsi, & Fiorio, 2018). During an initial acquisition phase, participants learned to associate three different visual color cues (i.e., green, yellow, red) with three distinct thermal pain stimulus intensities (i.e., low, medium, high) and were led to believe that these same visual color cue-thermal stimulus intensity pairings would be presented during a subsequent test phase. During the test phase, however, a series of trials were administered wherein the presentation of each color cue was followed only by a medium intensity stimulus and participants were asked to rate their perceived pain on a 0-100 visual analog scale. Thus, placebo effects were measured by comparing pain ratings between trials where the medium intensity stimulus followed the expectation of medium pain intensity (i.e., yellow cue-medium stimulus intensity) to trials where the medium intensity stimulus followed the expectation of a low pain intensity (i.e., green cue-medium stimulus intensity). Similarly, nocebo effects were measured by comparing yellow cue-medium stimulus intensity trials to trials where the medium stimulus followed the expectation of high pain intensity (i.e., red cue-medium stimulus intensity).

By administering half of the placebo and nocebo trials during light intensity elbow extension-flexion (30% of maximum voluntary contraction) and half at rest, the added contribution of exercise to placebo and nocebo effects could be determined. The authors did not find an added effect of exercise to either placebo or nocebo effects, but the study by Colloca and colleagues provides a useful framework for future researchers to begin addressing several other questions that could be related to placebo and

nocebo effects in EIH, including (i) intensity (e.g., would the added effect of exercise be greater at a higher intensity?), (ii) mode (e.g., does cycling or running during placebo/nocebo experimental result in different effects?, (iii) neurobiological mechanisms (e.g., how would blocking the opioid or endocannabinoid system affect conditioned placebo and nocebo responses during exercise?), and (iv) habitual expectations (e.g., is conditioning easier to implement in participants with stronger pre-existing expectations about the effect of exercise on pain?).

~~A powerful psychological mechanism of placebo effects that is untested in exercise studies is conditioning. Placebo conditioning has been studied in a variety of settings that are beyond the scope of this review such as immunosuppression (Hadamitzky, Sondermann, Benson, & Schedlowski, 2018); but one directly relevant application to this review is conditioned placebo hypoalgesia. Following an initial familiarization period during which participants are introduced to a painful stimulus (unconditioned stimulus), placebo hypoalgesia can be conditioned by pairing the administration of a placebo (conditioned stimulus) with surreptitious reduction of the pain stimulus intensity. This is often repeated several times to ensure that the conditioned response to the placebo has taken effect (Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010) and is followed by an experimental phase to examine the strength and duration of the placebo effect. In order to do so, the full-intensity painful stimulus is re-administered and perceptual ratings are compared between participants who received the conditioning procedure and a control group who did not. By repeatedly conducting the experimental phase over the course of several days, the investigator can also determine the time-course for the conditioned placebo response to be extinguished.~~

~~One idea is to condition placebo hypoalgesia responses to a minimal exercise condition such as passive motorized cycling. Passive motorized cycling has potential to be used as a placebo in exercise because it closely mirrors the movement involved in cycle ergometry, results in relatively minimal perceptual and cardio-respiratory responses compared to active cycling, and does not appear to affect~~

~~certain psychological outcomes (Lindheimer, O'Connor, et al., 2017; Weng, Pierce, Darling, & Voss, 2015). Thus, there is a higher degree of confidence that passive cycling is truly an inert stimulus compared to other minimal exercise conditions that have been used as placebos. However, to increase confidence that decreases in pain sensitivity following a placebo hyperalgesia conditioning procedure are the result of placebo effects, preliminary work is needed to verify that passive cycling does not affect pain sensitivity.~~

~~Another useful application of conditioning is to study placebo effects by comparing the magnitude of pain reduction in volitional exercise with and without a conditioning procedure. By measuring how closely biological changes (e.g., increases in plasma endocannabinoids) track with perceptual changes (e.g., decreases in pain sensitivity), researchers could further understand how the psycho-social context surrounding exercise influences EIH mechanisms. Finally, in light of evidence that exercise can sometimes increase pain sensitivity or symptoms in certain clinical populations (Cook, Stegner, & Ellingson, 2010; Light et al., 2012), it is worth pointing out that conditioning has also been used to study nocebo hyperalgesia (Blasini et al., 2017) and adapting these methods to the exercise setting may help researchers understand why exercise induced hyperalgesia occurs and how much of this effect can be attributed to nocebo effects and mechanisms.~~

There is promise in implementing the conditioning procedures used by Colloca and colleagues to study placebo and nocebo effects, particularly when experimental pain (e.g., tolerance, threshold, ratings of painful stimuli) is the outcome of interest. A far more elusive pursuit concerns conditioned placebo responses to exercise that take place in real world settings and how they affect placebo effects in a controlled laboratory environment. ~~Presumably~~Ostensibly, a greater level of exposure to a given behavioural stimulus is more likely to lead to a conditioned response. Therefore, one potential approach to untangling the influence of conditioning effects that take place outside of the laboratory is to study how conditioned placebo hypoalgesia differs between participants who frequently engage in exercise

and sedentary individuals. Demonstrating that conditioned placebo hypoalgesia is greater in active participants would suggest that those who are more familiar with the pain alleviating effects of exercise are more likely to respond positively to exercise and that increasing exercise behaviour in sedentary participants may improve subsequent responses to exercise.

5. FUTURE DIRECTIONS

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

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

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

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

~~2.~~

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

~~3.~~2.

~~4. Expectancy modification studies~~Measuring expectations ~~are~~ in expectancy modification studies is also encouraged. ~~to test for within-group changes over time or between-group differences in study-specific expectations as a manipulation check.~~ Verifying the success of the manipulation by measuring expectations would allow researchers to begin cataloging which types of expectancy modification procedures are most effective. This information may be especially valuable for addressing calls to maximize treatment effects in clinical settings by augmenting the contribution of placebo effects (Evers et al., 2018).

~~5.~~3.

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

~~7.~~4.

~~8.~~ The extant data on nocebo effects and their respective mechanisms in psychological responses to exercise can be traced to two studies (Colloca et al., 2018; Kwan et al., 2017). This line of research requires further attention and may have particularly important implications for explaining inter-individual variability in how healthy and clinical populations respond negatively to exercise.

~~9.~~5.

~~10.~~ The question of whether study participants reliably demonstrate placebo responses across different clinical conditions (Kaptchuk et al., 2008) and whether biological or psychological markers can distinguish such individuals from non-responders (Hall, Loscalzo, & Kaptchuk, 2015; Jakši, Aukst-Margeti, & Jakovljevi, 2013) has attracted the attention of placebo researchers and clinical trialists alike. In the absence of having a valid exercise placebo, these concepts may be worthwhile to investigate.

~~11.~~6.

~~12.~~7. That patient-physician interactions can influence placebo effects in a therapeutic setting (Zion and Crum, 2018) opens the possibility that interactions between test administrators and participants can elicit placebo or nocebo effects. Such effects should not be discounted in any research setting. The testing, either observationally or experimentally, of the degree to which personality characteristics and behaviours of study personnel who interact with study participants has a similar effect on treatment responses is a valid line of inquiry.

6. CONCLUSION

Embracing and adopting the notion of studying placebo and nocebo effects without traditional placebo treatments is germane to advancing the understanding of their impact on psychological responses to exercise. R~~Distinguishing the effect of exercise from placebo effects requires a placebo group. Whether it is possible to create a valid exercise placebo that closely mirrors the movements~~

~~involved in exercise and is also inert remains to be determined. While efforts to develop a valid exercise placebo are underway, r~~researchers can capitalize on using established psychological mechanisms of placebo effects to better understand how psycho-social context influences psychological responses to exercise in clinical trial and laboratory settings. ~~Measuring outcome expectations M in clinical trial~~easurement of habitual and study-specific expectations~~s~~ can help explain inter-individual variability in positive and negative outcomes of exercise whereas expectancy modification and conditioning can ~~Expectancy modification and conditioning designs can be used in laboratory studies to help e~~lucidate the neurobiological mechanisms ~~that are involved in placebo effects~~that mediate the influence of placebo and nocebo effects on these responses. These endeavors would make a valuable contribution toward advancing the current standard of knowledge about placebo and nocebo ~~placebo~~ effects in psychological responses to exercise which in turn may help inform the design of effective exercise interventions in the future.

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Figure legends

Figure 1. Distinguishing ~~the true~~treatment effects ~~of exercise on psychological responses~~ from placebo effects and non-specific effects requires the inclusion of a placebo and no-treatment control group. Panel A shows what is typically measured in exercise studies, the observed effect of exercise, which is estimated by comparing the change in the exercise group to the control group. Panel B shows the ~~true~~ placebo effect, which is estimated by comparing the change in the placebo group to the control group. Panel C shows that the true effect of exercise can be estimated by subtracting the ~~true~~ placebo effect from the observed effect of exercise. In a meta-analysis of randomized controlled studies that included an exercise, placebo, and control group, approximately half of the observed effect of exercise on psychological outcomes was attributed to placebo effects (Lindheimer et al., 2015).

~~**Figure 2**. The balanced placebo design is a model for observing expectancy-related placebo effects that can be adapted to studying psychological responses to exercise if a valid exercise placebo is ever developed. 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 for psychological improvements following the exposure to the treatment or inert/sham stimulus.~~

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

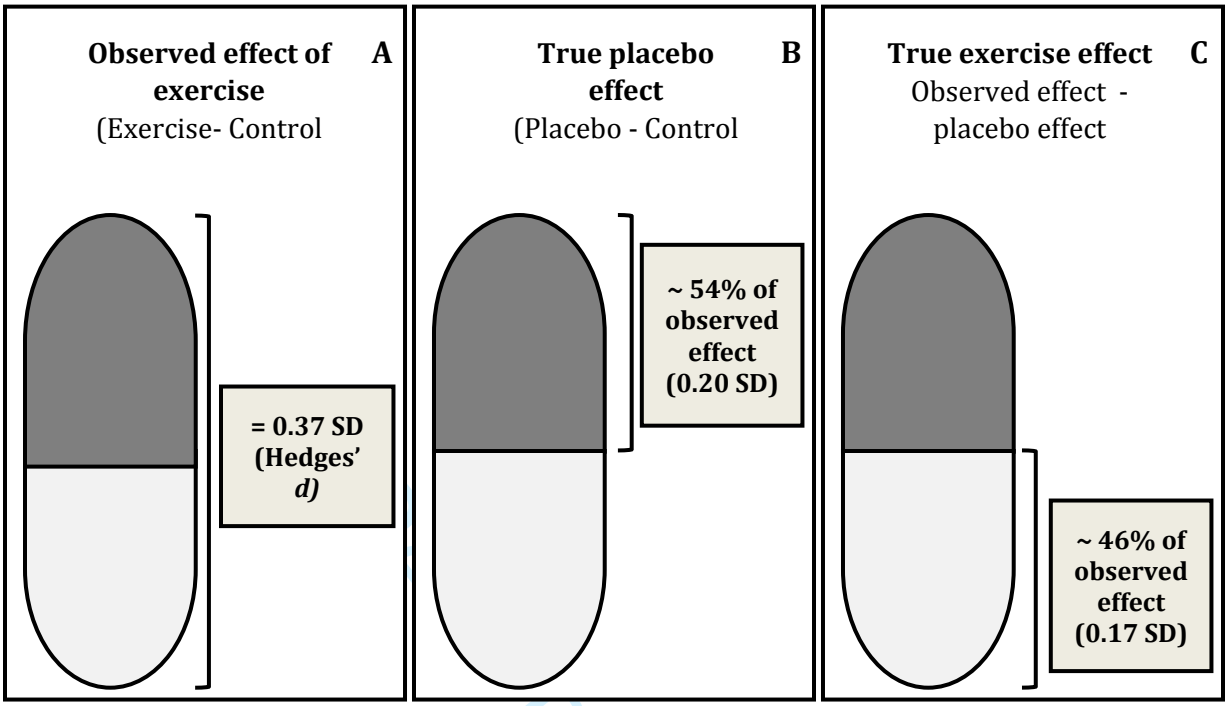

Table 1. Key terms

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.
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).

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)

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 *observed effect of exercise* (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.

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 *true effect of exercise* (Ojanen, 1994).

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

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

KEYWORDS: Behavior; Cognition; Health; Methodology; Neuroscience

HIGHLIGHTS:

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

1. INTRODUCTION

Over the last 50 years, the concept of a placebo has evolved from a therapeutically inert substance to also incorporate the sensory and social stimuli that 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 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 neuroimaging technologies to measure placebo effects and their respective neurobiological 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 nocebo effects were defined as a desirable or undesirable outcome resulting from a person's expected and/or learned response to a treatment or situation (Beedie et al., 2018).

The importance of designing exercise-based studies to account for placebo effects was recognized over three decades ago (McCann & Holmes, 1984). However, elucidation of the incidence, magnitude, and mechanisms of placebo effects in psychological responses to exercise has been slower in coming compared with other scientific fields. Taking into account recent interdisciplinary developments in the conceptualization and study of placebo effects, the purpose of this review is to highlight topics that are central to advancing the understanding of placebo effects in psychological responses to exercise, including: (i) the theory and practice of controlling for placebo effects, (ii) the importance of expectations, (iii) experimental methods for studying the influence of placebo effects and their neurobiological mechanisms on treatment responses, and (iv) future research directions. To aid comprehension of key concepts and facilitate this discussion, a list of key terms is provided in Table 1.

[Table 1 about here]

Findings from the small body of studies that examined placebo or nocebo effects in psychological responses to exercise are also integrated throughout this review. Herein, outcomes that are measured via self-report in exercise studies are broadly referred to as psychological outcomes or responses. These include variables from the categories of mental health (e.g., anxiety, depression) and perception (e.g., perceived exertion, muscle pain, pain intensity, symptom severity) as well as other types of constructs (e.g., body image, affect, mood, self-esteem). Additionally, we recognize that cognition can be assessed by task performance or self-report, but we also consider it to fit within the scope of psychological outcomes/responses (Table 2).

[Table 2 about here]

2. PLACEBO EFFECTS IN EXERCISE INTERVENTIONS

Effect size estimates from meta-analytic reviews of randomized controlled trials support the argument that exercise training improves psychological outcomes. For self-reported outcomes such as anxiety, depression, fatigue, and pain, exercise training appears to result in small (Standardized mean

difference = 0.29) to moderate (Standardized mean difference = 0.62) improvements (Cooney et al., 2013; Herring, Puetz, O'Connor, & Dishman, 2012; Herring, O'Connor, & Dishman, 2010; Puetz, O'Connor, & Dishman, 2006; Searle, Spink, Ho, & Chuter, 2015). Additionally, exercise training has a small, but significant effect on certain domains of cognitive performance (Standardized mean difference = 0.12-0.16) (Smith et al., 2010). However, there are several methodological issues that have raised concerns about the ability to distinguish these observed effects of exercise from placebo effects (Lindheimer, O'Connor, & Dishman, 2015; Ojanen, 1994; Szabo, 2013). These include: (i) the inability to perform double-blind studies, (ii) demand characteristics, and (iii) the largely subjective nature of many psychological outcome measures. In the following section, we discuss the theoretical importance of including placebo and no-treatment control groups to measure placebo effects in clinical trials and why this is difficult in studies of psychological responses to exercise.

2.1. Characterizing placebo effects in clinical trials

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

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

case, a placebo condition was defined as "an intervention that was not generally recognized as efficacious, that lacked adequate evidence for efficacy, and that has no direct pharmacological, bio-chemical, or physical mechanism of action according to the current standard of knowledge" (p. 695). After estimating the placebo effect by aggregating the standardized mean difference between the placebo and control groups from each study (Hedges' d = 0.20), the placebo effect was subtracted from the observed effect of exercise, that is, the aggregated standardized mean difference between the exercise and control groups from each study (Hedges' d = 0.37). Following this procedure, the authors concluded that the effect of exercise training on psychological responses (Hedges' d = 0.17) was less than half of the observed effect of exercise after accounting for placebo effects (Figure 1).

[Figure 1 about here]

2.2. Practical issues with characterizing placebo effects in studies of psychological responses to exercise

Despite early recognition of the importance for using methods that improve the estimation of placebo effects (McCann & Holmes, 1984), several barriers have continued to stymie investigators and prevent widespread implementation of these methods in exercise training studies. Foremost among these is the inability to perform double-blind studies. Unlike pharmacological interventions in which the vehicles that are used to deliver the treatment and placebo are identical (e.g., capsule, fluid, injection), it is considered to be impossible to truly blind participants to receiving exercise in research settings. This in turn can provoke expectations - potentially positive or negative - that an exercise treatment is being received. The question of what might constitute a valid exercise placebo is as yet unresolved.

A review by Ojanen (1994) argued "that the idea of a placebo group in exercise studies is, in practice, impossible". Nonetheless, some early studies attempted to create valid exercise placebo conditions by using very low intensity "minimal exercise" (Roth & Holmes, 1987) or relaxation training (McCann & Holmes, 1984) and even made efforts to manipulate expectations for improvement with

verbal suggestion (McCann & Holmes, 1984). However, even in a study that reported equivalent expectations, involvement and subjective utility between the treatment and minimal exercise condition (Roth & Holmes, 1987), Ojanen reasoned that a real placebo condition was not used because a placebo effect was not observed. This interpretation is not entirely accurate, however, because the inclusion of a placebo condition does not necessarily always result in an observable placebo effect.

To date, little progress has been made in developing a valid exercise placebo, one that mirrors every aspect of exercise except the "active ingredients". Of course, this begs the question of what are the active ingredients (i.e., mechanisms) responsible for the psychological changes associated with exercise. Nevertheless, these somewhat circular issues may be more important to consider when the objective is to study the placebo effect *per se* rather than to study the involvement of placebo effects in psychological responses to exercise. As we discuss later in this review, well established psychological mechanisms of placebo effects such as expectations and conditioning can be used to influence treatment responses, providing a means of studying the contribution of placebo effects to treatment effects without the inclusion of a traditional placebo condition. For instance, Kong and colleagues showed a greater degree of pain relief in knee osteoarthritis patients assigned to receive acupuncture with enhanced treatment expectations compared to acupuncture alone or no-treatment (Kong et al., 2018). Additionally, compared to the acupuncture only group, the acupuncture plus enhanced expectations group showed greater resting state functional connectivity between the nucleus accumbens and several other brain regions with links to placebo hypoalgesia such as the rostral anterior cingulate cortex and dorsolateral prefrontal cortex (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2013). These findings suggest that enhancing treatment expectations can change both behavioral and neurobiological outcomes to a higher degree than treatment alone and this approach may also be considered as a viable option for studying the impact of placebo effects on treatment responses to exercise.

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

3. EXPECTATIONS: A PRIMARY PSYCHOLOGICAL MECHANISM OF PLACEBO EFFECTS

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

3.1. Classification and definitions

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

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

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

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

variance into the measurement of psychological responses to exercise, which is why it is critical to take them into account during the design and conduct of a study.

One way to control for incidentally-induced expectations is to reduce potential sources of ***demand characteristics***, the totality of cues that can lead a participant to guess the experimental hypothesis of the study (Orne, 1962). A significant source of these cues is information communicated by study materials (e.g., advertisements, informed consent documents). For instance, Foroughi and colleagues reported that following one hour of practicing cognitive tasks, performance on fluid intelligence tests was better among participants who enrolled in the study after viewing an overt advertisement for a "Brain Training and Cognitive Enhancement" study compared to participants who responded to a generic advertisement with no information about brain training or cognitive enhancement (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016). Although the authors did not collect explicit information that would allow them to test for between-group differences in expectations, their study provided a clear example of how information that overtly communicates the study purpose can affect a given participant's behaviour.

This issue has also been considered in exercise research where the investigators minimized demand characteristics by using deceptive information in the study advertisement and informed consent materials to disguise the study purpose (Arbinaga, Fernández-Ozcorta, Sáenz-López, & Carmona, 2018; Lindheimer, O'Connor, McCully, & Dishman, 2017). Interestingly, this research has shown that even when the investigators purposefully tried to alter participant expectations at a later point in the study, disguising the true purpose of the study early on may have blunted the effectiveness of the experimental manipulations. For example, Lindheimer and colleagues measured mood and cognitive responses to light intensity active cycling or motorized passive cycling, but informed participants that the purpose was to compare cardio-respiratory responses between the two conditions. Although half of these participants were exposed to an expectancy manipulation designed to enhance

expectations for psychological improvements following exercise, the investigators did not observe a significant difference in expectations or psychological responses to exercise between participants who received the expectancy manipulation and those who did not (Lindheimer et al., 2017). In a second investigation that measured self-esteem changes following seven weeks of moderate intensity aerobic exercise training, participants were told that the purpose was to study brain activity during tasks of conditioned discrimination. Again, no differences were found between participants who were exposed to information that exercise improves psychological variables and those who did not receive such information (Arbinaga et al., 2018). These findings have therefore provided some evidence that disguising the study purpose may be an effective way to minimize the effect of study specific expectations on psychological responses to exercise.

Indeed, the role of demand characteristics in psychological responses to exercise has long been recognized (Morgan, 1997). These can be reduced, for example, by using neutral language in study materials and blinding test administrators to condition assignment. Although these steps may increase the methodological rigor of exercise research, they are not always practical to implement and unlikely to completely prevent study-specific expectations from developing. Thus, researchers should consider measuring expectations to help determine their potential influence on the results.

3.2. Application of measuring expectations

The approach to measuring participant expectations should be guided by several questions. These include, (i) are the needs of the study design addressed by measuring habitual expectations, study-specific expectations, or both?, (ii) what is the required level of specificity needed to answer the research question?, (iii) how will the information be used to guide the interpretation of the study results?, and (iv) do the advantages of using a validated questionnaire or investigator-created questionnaire outweigh the disadvantages? Below we detail several scenarios in which these questions may be considered.

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.

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

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

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

The placebo run-in phase is appealing for conducting clinical exercise trials because reducing placebo responses would presumably help provide a more precise estimation of the true effect of exercise. The absence of a valid exercise placebo prevents the ability to use the placebo run-in approach in exercise studies; however, this concept could be adapted in several ways. One strategy is to measure habitual expectations prior to study enrollment. By screening out participants who endorse changes in psychological outcomes as a habitual expectation of exercise and only including participants with neutral or low expectations about psychological improvements, a more conservative estimate of the true effect of exercise could potentially be acquired (Ojanen, 1994). Conversely, participants who are at-risk for nocebo responses could be screened out by excluding individuals who expect negative psychological consequences of exercise. Considering that placebo run-in trials are also used to decrease placebo or nocebo effects by habituating participants to the placebo prior to baseline testing, another

possibility is to familiarize participants to several acute bouts of exercise before starting the trial. In terms of recruitment, this strategy may be more feasible than screening for expectations because finding individuals with low or negative expectations may be challenging, especially when the trial is focused on an endpoint for which the psychological benefits of exercise are widely publicized such as depression or anxiety.

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

4. EXPERIMENTAL METHODS FOR STUDYING PLACEBO EFFECTS IN PSYCHOLOGICAL RESPONSES TO EXERCISE

Measuring expectations is an important step when the objective is to account for variability in psychological responses within or between groups. Likewise, experimental manipulation of expectations and other potential psychological or contextual causes of placebo effects can provide insight into the magnitude of their contribution to treatment responses and the neurobiological mechanisms through which these processes work. The next section of this review discusses several study designs with

potential to advance the understanding of mechanisms of placebo effects in psychological outcomes of exercise.

4.1. Expectancy modification

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

Various strategies such as verbal suggestion (Arbinaga et al., 2018; Crum & Langer, 2007; Desharnais et al., 1993; Helfer et al., 2014; Lindheimer et al., 2017; McCann & Holmes, 1984), film clips (Flowers et al., 2018; Mothes et al., 2016, 2017), and reading standardized scripts (Kwan et al., 2017) are used to manipulate expectations. In some cases, these modifications have been further enhanced through additional psycho-social and environmental cues (Crum & Langer, 2007; Desharnais et al., 1993) or engagement of conscious mental processes by asking participants to recapitulate and record their expectations (Helfer et al., 2014; Kwan et al., 2017). It is not yet clear which types of modification procedures are most effective for influencing expectations about psychological outcomes of exercise. To help address this gap, studies can incorporate ***manipulation checks*** by measuring and comparing expectations between the experimental and control group to provide insight into why some studies

have been more successful in manipulating expectations (Arbinaga et al., 2018) than others (Lindheimer et al., 2017). To further improve the understanding of how to effectively elicit or minimize nocebo effects, questionnaires that also provide the ability to measure negative expectations should be incorporated in manipulation checks.

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

4.2. Conditioning

Conditioning represents a promising approach to studying placebo effects in exercise, particularly in the study of exercise induced hypoalgesia (EIH), a phenomenon in which pain sensitivity is reduced during or following exercise (Koltyn, 2002). This area of inquiry is especially intriguing because EIH and placebo hypoalgesia appear to involve similar biochemical mechanisms such as the opioid and endocannabinoid systems (Benedetti, Amanzio, Rosato, & Blanchard, 2011; Crombie, Brellenthin, Hillard, & Koltyn, 2018). Yet, despite extensive interest among both exercise and placebo researchers in studying pain, EIH studies are seldom designed to experimentally manipulate psychological mechanisms of placebo or nocebo effects.

A recent investigation by Colloca and colleagues has provided one potential approach to studying placebo and nocebo effects in EIH by adapting a well validated conditioning model to isotonic exercise (Colloca, Corsi, & Fiorio, 2018). During an initial acquisition phase, participants learned to associate three different visual color cues (i.e., green, yellow, red) with three distinct thermal pain stimulus intensities (i.e., low, medium, high) and were led to believe that these same visual color cue-thermal stimulus intensity pairings would be presented during a subsequent test phase. During the test phase, however, a series of trials were administered wherein the presentation of each color cue was followed only by a medium intensity stimulus and participants were asked to rate their perceived pain on a 0-100 visual analog scale. Thus, placebo effects were measured by comparing pain ratings between trials where the medium intensity stimulus followed the expectation of medium pain intensity (i.e., yellow cue-medium stimulus intensity) to trials where the medium intensity stimulus followed the expectation of a low pain intensity (i.e., green cue-medium stimulus intensity). Similarly, nocebo effects were measured by comparing yellow cue-medium stimulus intensity trials to trials where the medium stimulus followed the expectation of high pain intensity (i.e., red cue-medium stimulus intensity).

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

habitual expectations (e.g., is conditioning easier to implement in participants with stronger pre-existing expectations about the effect of exercise on pain?).

There is promise in implementing the conditioning procedures used by Colloca and colleagues to study placebo and nocebo effects, particularly when experimental pain (e.g., tolerance, threshold, ratings of painful stimuli) is the outcome of interest. A far more elusive pursuit concerns conditioned placebo responses to exercise that take place in real world settings and how they affect placebo effects in a controlled laboratory environment. Ostensibly, a greater level of exposure to a given behavioural stimulus is more likely to lead to a conditioned response. Therefore, one potential approach to untangling the influence of conditioning effects that take place outside of the laboratory is to study how conditioned placebo hypoalgesia differs between participants who frequently engage in exercise and sedentary individuals. Demonstrating that conditioned placebo hypoalgesia is greater in active participants would suggest that those who are more familiar with the pain alleviating effects of exercise are more likely to respond positively to exercise and that increasing exercise behaviour in sedentary participants may improve subsequent responses to exercise.

5. FUTURE DIRECTIONS

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

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

measuring and experimentally manipulating these placebo/nocebo mechanisms in exercise based research.

2. The measurement of expectations for psychological outcomes of exercise would be improved by using psychometric instruments that measure study-specific expectations. Rather than using questionnaires with inherent biases toward only measuring expectations for desirable outcomes, we recommend using questionnaires with item phrasing and scales that allow a respondent to indicate expectations for either positive *or* negative changes for neutrally presented psychological outcome. For instance, a study of EIH can ask participants to rate their level of expected changes in pain on a bipolar Likert-type scale with verbal anchors that allow the participant to indicate the expected direction and degree of change (e.g., -3 = “large decrease”, -2 = “moderate decrease”, -1 “slight decrease”, 0 “no change”, 1= “slight increase”, 2= “moderate increase”, 3= “large increase”).
3. Measuring expectations in expectancy modification studies is also encouraged. Verifying the success of the manipulation by measuring expectations would allow researchers to begin cataloging which types of expectancy modification procedures are most effective. This information may be especially valuable for addressing calls to maximize treatment effects in clinical settings by augmenting the contribution of placebo effects (Evers et al., 2018).
4. Conditioning studies are a promising strategy for investigating mechanisms of placebo and nocebo effects, although this approach has only been tested in one study of exercise and experimental pain (Colloca et al., 2018). More work is needed to determine whether conditioning could also be applied to the study of placebo effects in other psychological outcomes of exercise such as mood and cognition.
5. The extant data on nocebo effects and their respective mechanisms in psychological responses to exercise can be traced to two studies (Colloca et al., 2018; Kwan et al., 2017). This line of research

requires further attention and may have particularly important implications for explaining inter-individual variability in how healthy and clinical populations respond negatively to exercise.

6. The question of whether study participants reliably demonstrate placebo responses across different clinical conditions (Kaptchuk et al., 2008) and whether biological or psychological markers can distinguish such individuals from non-responders (Hall, Loscalzo, & Kaptchuk, 2015; Jakši, Aukst-Margeti, & Jakovljevi, 2013) has attracted the attention of placebo researchers and clinical trialists alike. In the absence of having a valid exercise placebo, these concepts may be worthwhile to investigate.
7. That patient-physician interactions can influence placebo effects in a therapeutic setting (Zion and Crum, 2018) opens the possibility that interactions between test administrators and participants can elicit placebo or nocebo effects. Such effects should not be discounted in any research setting. The testing, either observationally or experimentally, of the degree to which personality characteristics and behaviours of study personnel who interact with study participants has a similar effect on treatment responses is a valid line of inquiry.

6. CONCLUSION

Embracing and adopting the notion of studying placebo and nocebo effects without traditional placebo treatments is germane to advancing the understanding of their impact on psychological responses to exercise. Researchers can capitalize on using established psychological mechanisms of placebo effects to better understand how psycho-social context influences psychological responses to exercise in clinical trial and laboratory settings. Measurement of habitual and study-specific expectations can help explain inter-individual variability in positive and negative outcomes of exercise whereas expectancy modification and conditioning can elucidate the neurobiological mechanisms that mediate the influence of placebo and nocebo effects on these responses. These endeavors would make a valuable contribution toward advancing the current standard of knowledge about placebo and nocebo

effects in psychological responses to exercise which in turn may help inform the design of effective exercise interventions in the future.

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Figure legends

Figure 1. Distinguishing treatment effects from placebo effects and non-specific effects requires the inclusion of a placebo and no-treatment control group. Panel A shows what is typically measured in exercise studies, the observed effect of exercise, which is estimated by comparing the change in the exercise group to the control group. Panel B shows the placebo effect, which is estimated by comparing the change in the placebo group to the control group. Panel C shows that the true effect of exercise can be estimated by subtracting the placebo effect from the observed effect of exercise. In a meta-analysis of randomized controlled studies that included an exercise, placebo, and control group, approximately half of the observed effect of exercise on psychological outcomes was attributed to placebo effects (Lindheimer et al., 2015).

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

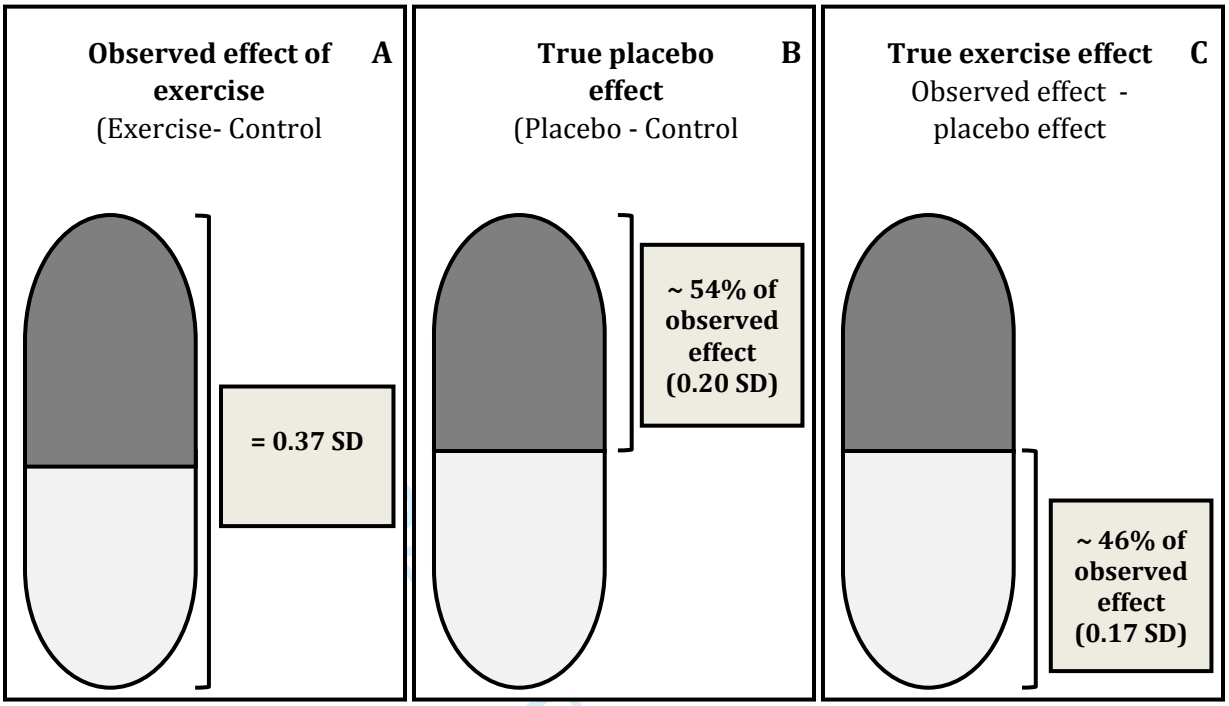

Table 1. Key terms

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.
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