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

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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 conceptualisation 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

Behaviour; cognition; health; methodology; neuroscience

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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, Carlino, & Pollo, 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 recognising 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 recognised over three decades ago (McCann & Holmes, 1984). However, elucidation of the prevalence, magnitude, and mechanisms of placebo effects in psychological responses to exercise has been relatively slow compared to other scientific fields. Taking into account recent interdisciplinary developments in the conceptualisation 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 concepts and facilitate this discussion, a list of key terms is provided in Table I.

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) as well as other types of constructs (e.g. body image, affect, mood, self-esteem). Additionally, we recognise 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 II).

2. Placebo effects in exercise interventions

Effect size estimates from meta-analytic reviews of randomised 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, O’Connor, & Dishman, 2010; Herring, Puetz, O’Connor, & Dishman, 2012; 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. Characterising 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 (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 randomisation 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 a metaanalysis of nine randomised controlled trials that included an exercise treatment, control, and placebo arm (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, biochemical, or physical mechanism of action according to the current standard of knowledge” (p. 695). After estimating the placebo effect by aggregating the standardised 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 standardised 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).

2.2. Practical issues with characterising 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 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 also unresolved and an early review by Ojanen (1994) argued that "the idea of a placebo group in exercise studies is, in practice, impossible" (p. 63). 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. Importantly, this interpretation is not entirely accurate 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 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 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

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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 behavioural 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 characterising 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 designs in studies of exercise and psychological out-comes 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 et al., 2010; Kirsch, 1997; Price, Finniss, & Benedetti, 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 minimise placebo effects altogether. To help researchers accomplish this goal, we operationalise 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 recognise 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 recognise 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, familiarisation, data collection), whereas habitual expectations are 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 that are generated during research participation but are 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 minimised 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 motorised 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 minimise 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 recognised (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 rigour 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. Moreover, repeated measurement of expectations may also increase the likelihood of reactivity, a behavioural artifact wherein observed changes are confounded by a participant's awareness that a given psychological or behavioural 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 centred around anticipation of negative responses to a given stimulus and are strongly linked to nocebo effects (Benedetti, 2008; Webster et al., 2016). Similar to how the conceptualisation of placebo effects has changed over time, the idea of a nocebo effect has shifted from any negative response that follows the administration of an inert substance (Kennedy, 1961) to the negative responses arising from specific psychological and neurobiological mechanisms (Beedie et al., 2018; Evers et al., 2018). Measuring negative expectations could provide valuable information in terms of understanding why some participants differ in 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 randomised 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 randomisation in order to minimise 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 familiarise participants to several acute

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bouts of exercise before starting the trial. In terms of recruitment, this strategy may be more feasible than screening for expectations because identifying 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 publicised (e.g. depression, 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. On the other hand, 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 a 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 standardised scripts (Kwan et al., 2017) are used to manipulate expectations. In some cases, these modifications have been further enhanced through additional psychosocial 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 minimise 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 tradeoff 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 colour 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 colour 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 colour 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. can conditioned placebo or nocebo effects be studied in the context of aerobic exercise modalities such as cycling or running?), (iii) neurobiological mechanisms (e.g. how would blocking the opioid or endocannabinoid system affect conditioned placebo and nocebo effects during exercise?), and (iv) habitual expectations (e.g. is conditioning easier to implement in participants with stronger preexisting expectations about exercise and pain?).

There is promise in implementing the conditioning procedures used by Colloca and colleagues to study placebo and nocebo effects, particularly in the laboratory setting when experimental pain (e.g. tolerance, threshold, ratings of painful stimuli) is the outcome of interest. A far more elusive pursuit concerns conditioned placebo effects 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 conceptualisation and study of placebo effects in exercise studies. Below we highlight potential next steps to prioritise in future work.

1. As suggested above, the 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 traditional 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 are capable of measuring both positive *and* negative expectations. Rather than using questionnaires with inherent biases toward only measuring expectations for desirable outcomes (e.g. reduced feelings of pain), we recommend using questionnaires with item phrasing and scales that allow a respondent to indicate expectations for either positive *or* negative changes for a 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 maximise 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. The idea that patient-physician interactions can influence placebo effects in a therapeutic setting (Zion & 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. Testing the degree to which personality characteristics and behaviours of study personnel who interact with study participants affect psychological responses to exercise is a valid line of inquiry.

6. Conclusion

Embracing and adopting the notion of studying placebo and nocebo effects without administering traditional placebos may be germane to advancing the understanding of their impact on psychological responses to exercise. Researchers can capitalise on using established psychological mechanisms of placebo and nocebo effects to better understand how psychosocial 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 endeavours 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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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.

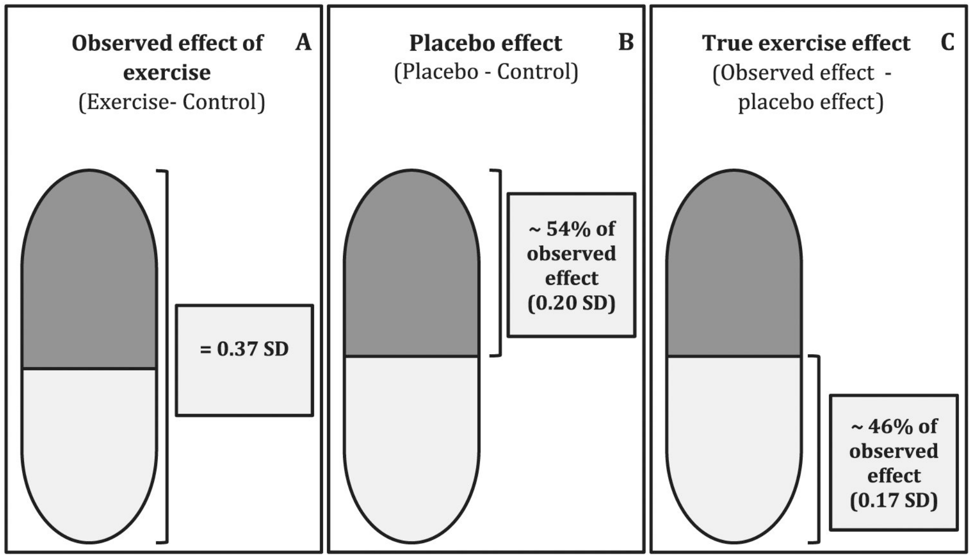

Figure 1.

Distinguishing treatment effects from placebo effects and non-specific effects requires the inclusion of a placebo and no-treatment control group. Panel A shows 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 nine randomised 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).

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Table I.

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 behavioural 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 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 expectation that is formed from experiences that occur during the various phases of a study (e.g. advertisement, recruitment, screening, informed consent, familiarisation, data collection).

Table II.

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

Perceptual/sensory	Mental Health	Cognition	Miscellaneous
Experimental pain	Anxiety	Executive function	Affect
Perceived exertion	Depression	Sustained attention	Body image
Somatic symptoms	Sleep quality	Processing speed	Mood
	Stress	Working memory	Self-esteem