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Review Article

Placebo Effects and Neuromodulation: Ethical Considerations and Recommendations

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ABSTRACT: Placebo-controlled trials are the gold standard of evaluating treatment efficacy in clinical research. Neuromodulation is emerging as an important treatment pathway for many neuropsychiatric conditions, and placebo control arms of these trials require careful design with unique considerations (e.g., sham devices that mimic active stimulation, blinding effectiveness). Inherent to placebo-controlled trials are ethical concerns, such as deception, and potential harm of not receiving the active treatment. In this article, we outline important ethical considerations of placebo-controlled trials across neuromodulation approaches and provide recommendations on how ethical principles can be adhered to going forward. We specifically address issues of autonomy and respect for persons, beneficence, and justice. Within the context of this ethical framework, we also discuss factors influencing placebo effects in neuromodulation, the importance of adequate blinding, and alternative trial designs that could be considered.

RÉSUMÉ : Les effets placebo en lien avec la neuromodulation : considérations éthiques et recommandations. Les essais contrôlés par placebo constituent la norme par excellence de l'évaluation de l'efficacité des traitements en recherche clinique. De son côté, la neuromodulation apparaît comme une avenue de traitement importante pour de nombreuses affections neuropsychiatriques. Les « bras » comparateurs par placebo (*placebo control arms*) de ces essais nécessitent par ailleurs une conception minutieuse avec des considérations uniques (par exemple, des dispositifs fictifs qui imitent la stimulation active, l'efficacité des procédures d'insu). Soulignons enfin que les essais contrôlés par placebo soulèvent des questions éthiques telles que la duperie et le préjudice potentiel lié au fait de ne pas bénéficier d'un traitement actif. Dans cet article, nous souhaitons d'abord mettre en relief les considérations éthiques importantes liées aux essais contrôlés par placebo dans toutes les approches en matière de neuromodulation. Dans un deuxième temps, nous entendons fournir des recommandations sur la façon dont les principes éthiques peuvent être respectés à l'avenir. À cet égard, nous aborderons spécifiquement les questions d'autonomie et de respect des personnes, de bienfaisance et de justice. Finalement, nous nous pencherons également, dans le contexte de ce cadre éthique, sur les facteurs influençant les effets placebo dans la neuromodulation, sur l'importance de procédures d'insu adéquates et sur les conceptions alternatives d'essais pouvant être envisagées.

Keywords: Placebo; Neurotechnology; Clinical trial methodology; Neuromodulation

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Introduction

Placebo effects can be defined as beneficial effects generated by the context surrounding the administration of a treatment rather than due to the specific treatment itself. These effects depend on a complex interaction between internal factors such as the patient's expectations and previous experiences associated with similar medical treatments and external factors such as environmental cues, and the patient–physician relationship. In clinical research trials, placebo responses are observed by participants in the placebo arm that are given an inert treatment, such as a sugar pill or sham device. This overall placebo response includes placebo effects and other nonspecific effects such as spontaneous improvement, regression to the mean, and Hawthorne effects (i.e., differences in performance/behavior by virtue of being observed in a trial).[1] Despite not receiving active treatment, placebo responses can sometimes rival the effect sizes associated with medical treatments for some neuropsychiatric conditions.[2,3,4] While placebo effects have long been viewed as a nuisance for clinical trials, research

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HIGHLIGHT BOX: OPPORTUNITIES FOR ACTION

- Proper care in the trial design of placebo-controlled neuromodulation studies is essential to ensure valid scientific rationale, minimize risk, and properly attain informed consent.
- Although there are challenges with blinding neuromodulation, placebo-controlled studies must have adequate blinding with sham devices and procedures.
- To maximally combat challenges, adopt standardized methods and acquire blinding validity assessments.
- In the future, placebo effects may be better defined through using alternative placebo-informed trial designs.

Table 1: Summary of common misconceptions of placebo effects and countering evidence

Misconception	Evidence Against	References
Placebo effects are not therapeutically meaningful	Considerable improvement of symptoms is often seen in the placebo arm of trials for a variety of medical disorders. This includes psychiatric disorders (e.g., depression or anxiety), neurological disorders (e.g., Parkinson's disease, migraine), and other medical conditions (e.g., asthma, IBS)	Goetz et al., 2008;[2] Polich et al., 2018[3]
	Placebo effects may alter activity in brain regions that process expectation, reward prediction, and hope	Burke et al., 2021;[7] Lidstone et al., 2010[11]
The placebo-control group is the only group deriving benefits of placebo effects	It is often forgotten that overall effect seen in the active treatment arm is actually a combination of specific treatment effects and the placebo response (placebo effects and other nonspecific effects)	Benedetti et al., 2003;[12] Enck et al., 2013[13]
	Furthermore, open-hidden paradigms whereby active treatment is delivered devoid of expectation and other contextual cues substantially lower the efficacy of the active treatment	Pollo et al., 2001[14]
Patients will no longer benefit if told they are receiving placebo	Placebo response may persist even in the absence of deception, as seen in OLP trials for IBS, back pain, and cancer-related fatigue	Kaptchuk et al 2010;[15] Carvalho et al 2016;[16] Hoenemeyer et al 2018;[18] Kleine-Borgmann et al 2019;[19] Zhou et al 2018;[20] Kaptchuk 2018[20]
Placebo effects are transient and short-lived	While the durability of placebo effects remains a topic with relatively limited research, some studies from patients receiving sham surgery have demonstrated benefits that persist at 1-year follow-up	Marks et al., 2010;[22] McRae et al., 2004[22]

IBS = irritable bowel syndrome; OLP = open-label placebo.

demonstrating activation of brain regions and networks by placebo effects has opened up a new line of scientific inquiry.[5] This includes reconceptualizing placebo effects as a powerful neurobiological phenomenon that can be harnessed for clinical therapeutic applications. Furthermore, the evolving understanding of placebo effects has critical implications for trial design in clinical research, particularly with regard to neuromodulation.[5,6,7]

Historically, the ethics of placebo groups in research trial design has been controversial due to concern of infringing upon patient autonomy by way of deception and by inadvertently posing harm due to not receiving the bona fide test treatment.[8] Ethical considerations may differ depending on technological considerations, invasiveness, and other factors that may impact the trial design placebo group. Neuromodulation is a prime example of a field where trials cannot be properly blinded with a simple sugar pill and instead often require the development of elaborate sham devices or procedures for the placebo group. Neuromodulation approaches, such as transcranial direct current stimulation (TDCS), transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT) and magnetic seizure therapy (MST), vagus nerve stimulation (VNS), focused ultrasound (FUS), and deep brain stimulation (DBS), are becoming increasingly researched and used in the care pathways of many complex, and often treatment refractory, neuropsychiatric illnesses.[9]

Previous discussion on the intersection of placebo effects and neuromodulation has primarily focused on blinding considerations for sham devices and has been limited in scope.[10] In this article, we begin by reviewing the potential ethical issues that may arise in placebo-controlled research and apply these considerations toward neuromodulation treatment trials. We then discuss the unique aspects of placebo effects in neuromodulation that are important to be aware of, with an extended discussion on the importance of blinding effectiveness, and considerations of alternative trial designs. Finally, while an extended discussion on the mechanisms of placebo effects is beyond the scope of this review, we have briefly highlighted common misconceptions associated with placebo effects (Table 1). A summary of strengths and limitations of study designs for neuromodulation trials with a focus on placebo effects is also included (Table 2). Ethical considerations neurotechnology more broadly (e.g., neural interfaces, assistive technologies) is beyond the scope of this review and will not be discussed.

Case Study

Neuromodulation Research

Placebo-Control Group

Three overarching ethical principles govern clinical research: 1) autonomy and respect for persons, 2) beneficence, and 3) justice.[24] Incorporation of a placebo-control group has been an essential component of advancing clinical research to determine effective treatments, and as such the methodology of neuromodulation trials with placebo/sham intervention must adhere to these ethical principles to minimize potential harm to patients.

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Table 2: Strengths and limitations of study designs for neuromodulation trials with a focus on placebo effects

Study design	Strengths	Limitations
Randomized sham-controlled trial		
Active treatment versus sham control group	Considered gold standard in evaluating effectiveness of active treatment	Requires careful design of sham technology to replicate the experience of active stimulation protocols, as well as assessment of blinding integrity
Placebo run-in trial		
All participants receive placebo prior to trial initiation	Potential to exclude patients with high placebo responsiveness in an attempt to increase the ability to find significant differences between active and placebo groups	Greater risks of unblinding and decreased external validity[63] Recently found to be no more effective in finding differences between drug and placebo groups than trials without placebo run-in periods for antidepressants[65]
Three-arm trial with no-treatment control		
Active treatment versus sham control versus no treatment	Would help delineate the magnitude of placebo effects from the magnitude of other nonspecific effects in placebo trial arms (e.g., spontaneous changes, regression to the mean, elevation bias, Hawthorne effects)	More cumbersome trial design that may impact statistical power Ethical concerns regarding beneficence given those assigned to no-treatment control would potentially be exposed to relatively more harms than active treatment or placebo control
Non-inferiority trial		
A new intervention is compared with an established treatment as opposed to placebo control	Allows more ethical evaluation of treatment effectiveness for patients with more severe illness (e.g., acute suicidality) as participants would not be randomized to a placebo group. Bypasses need to develop sham stimulation that would replicate complex protocols (e.g., MST, FUS)	In order to achieve sufficient power, the sample size may need to be larger, and this would influence the costs associated with a trial. Provides no data on placebo response magnitude (placebo effects could drive improvement in both groups)
Open-label placebo		
Participants are truthfully told they will be receiving placebo, typically in comparison to a no-treatment control	Used for studying the efficacy of placebo effects, while avoiding the need for deception	Has not been used for evaluating the efficacy of neuromodulation interventions Requires careful controlling to ensure the effect measured is attributable to taking a placebo, rather than elements of the study design[66] Non-standardized script with potential to alter expectations of a positive response Cannot blind investigator delivering the script OLP research remains in its early stages

FUS = focused ultrasound; MST = magnetic seizure therapy; OLP = open-label placebo.

Autonomy and respect for persons: Aspects of placebo-controlled research that may infringe upon autonomy and respect for persons include deception and an inadequate consent process.[24] Patients randomized to placebo groups and discover they are not getting the test treatment could be disappointed or angered, and this may in turn undermine patient–doctor trust and cause undue influence on overall trial results.[25,26] Ways that deception can be minimized and deemed ethically justifiable are if patients are clearly advised in advance that they may be randomized into either active treatment or a placebo group, coupled with a protocol to debrief them as soon as their own individual participation is complete.[26] Another potential strategy to mitigate deception in research focused specifically on placebo effects is to use an open-label placebo (OLP) trial design (discussed in more detail below), whereby patients are truthfully told they will be receiving placebo.[21] In all scenarios, each patient is owed a robust consent process outlining the risks of receiving placebo/sham intervention, such as forgoing active and potentially more effective treatment, periprocedural risks for more invasive neuromodulation (e.g., VNS, DBS) that still occur as part of the sham procedures, or both.[25,27] Importantly, for certain vulnerable populations (e.g., children, intellectual disability, cognitive impairment), additional efforts to communicate placebo randomization and possible risks are required.

Beneficence: The goal of maximizing benefit and minimizing or eliminating harm is an essential principle guiding ethically justifiable research and medical practice. One ethical argument against placebo arms of trials is the perceived withholding of treatment to the patient, thus exposing them to harms of an untreated illness.[26,28] For conditions with increasing severity and risk of mortality, such as refractory anorexia nervosa or acute suicidality, the implications of untreated illness would certainly be weighed differently.[28] However, inclusion criteria for neuromodulation interventions (particularly the more invasive interventions) typically require a level of treatment resistance, whereby several standard lines of intervention have been tried and failed.[28,29] Another important consideration is that active treatment, particularly with surgical intervention, carries its own risks and adverse effects that need to be clearly communicated.[28]

Use of a sham stimulation control group to evaluate efficacy of neuromodulation against serious conditions (e.g., acute suicidality) could be deemed ethically justifiable if appropriate monitoring (e.g., inpatient unit) and alternative treatment offered for non-responders are clearly outlined and offered, such as with recent

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trials of ketamine for acute suicidality.[30] However, in some circumstances it may be more appropriate to use an equivalency, or non-inferiority trial design, whereby a new intervention is compared with an established treatment as opposed to placebo control, such as comparing the emerging MST with eECT,[31] or FUS with DBS.[32] Also, methodology for certain neuromodulation trials (e.g., TMS) may suggest a washout period for medications in order to evaluate the true effect of the intervention.[33] In these instances, special care must be taken with close follow-up in place and a contingency plan in the event of acute clinical deterioration either before or during the intervention in order to minimize harms.

Arguments against the use of placebo as control in randomized trials primarily suggest that a breach of clinical equipoise may be occurring, and that comparing new interventions for conditions that have an established or standard treatment with placebo results in substandard, and thus unethical care.[34] However, clinical practice for individual patients often differs from the goals of research, which is to determine safety, therapeutic efficacy, and potential generalizability of proposed interventions.[25,29] Furthermore, given findings of robust placebo responses for disorders such as treatment-resistant depression (large, pooled effect size [$g = 1.05$])[4] and in many neuromodulation trials more broadly,[6] being randomized to receive a placebo intervention would not be equivalent to having an illness be entirely untreated in a research trial. Although there would be important ethical considerations, a no-treatment group would help to better understand the magnitude of placebo effects in neuromodulation studies, which is important for determining the true efficacy of the active intervention.[6] A three-arm trial with active, placebo, and no-treatment control may thus be better suited for less invasive interventions with relatively lower disease severity so as to minimize the harms of the no-treatment group. Following a clear consent process and thoughtful trial design, patients randomized to no-treatment control should be offered active intervention after the shortest duration of time possible. Active treatment should also be offered to those randomized to the placebo group if found to be more effective.

Another important consideration pertaining to beneficence in placebo-controlled trial design is the "lessebo effect," whereby there is a reduction in the magnitude of treatment effect in the active intervention group that is associated with the presence of a placebo group in the trial.[35,36] This phenomenon may be due to the negative expectations associated with potentially being randomized to a placebo group.[26] To our knowledge, the lessebo effect has not been thoroughly evaluated in neuromodulation trials. The potential risk that the lessebo effect carries would be a Type II error (i.e., a failure to detect a significant difference between active and placebo intervention groups when one actually exists).[26] Whether, or how, this phenomenon impacts neuromodulation trials is unclear at this time and is a topic that necessitates further research.

Justice: As an ethical principle in clinical research, justice serves to uphold trust at the patient–doctor–-researcher interface and demands that all people receive equal and fair treatment.[24] Recruitment for research trials must be without undue influence, and participants need to know they can withdraw without their medical care being affected. Given the potential for harms outlined above, particularly with more invasive neuromodulation interventions, it is imperative that the research question addressed is clinically important and will potentially result in a significant difference to clinical practice.[28] Furthermore, results of any publicly funded research must be disseminated and shared with not only the participants or subjects in the trial but also all of society, even if the results are those not expected or hoped for.[24] Ensuring that appropriate and diverse groups are recruited in trials is an important tenet of justice in research design, as certain populations may be underrepresented. For example, indigenous or rural/remote communities often experience enormous systemic barriers accessing standard medical care. Unfortunately, neuromodulation trials mostly take place at tertiary academic care centers, which would result in underrepresentation of these populations and represents an important inequity to work toward overcoming in future trial designs.

Summary: For a randomized controlled trial (RCT) using neuromodulation with a sham stimulation group to be ethically justifiable, the trial must: 1) have a valid scientific rationale with clinical relevance, 2) ensure that potential risks do not outweigh potential benefits, and 3) involve informed consent with sufficient disclosure of information so that misconception of the purpose of the trial is avoided and the potential risks of being randomized to a placebo intervention group are clear and transparent (see Figure 1).[25,26,28,29]

Placebo Effects

Many contextual factors modulate the magnitude of placebo effects. These factors can relate to the intensiveness of treatment, elaborate or innovative clinical settings, practitioner–patient relationships, societal perceptions (i.e., hype), and many other variables.[37] Many of these factors are heightened in the setting of neuromodulation studies, which may inadvertently magnify placebo effects. For example, neuromodulation interventions are often inherently complex; they have lengthy procedures involving screening and calibration, sophisticated and expensive technology, and elaborate equipment requiring specialized technicians. The studies are often conducted in academic hospitals or laboratories filled with various credibility cues such as institutional logos, lab coats, and medical paraphernalia. The studies can involve lengthy discussions with physicians and researchers about the benefits and risks of the intervention, which provide the opportunity for positive and warm therapeutic relationships. Patients may even have developed positive expectations about the neuromodulation from seeing it featured in the media.

All of these factors combined can enhance placebo effects in the setting of therapeutic neuromodulation.[6,38] To build on themes introduced above, elaborate and complex treatments tend to produce stronger placebo effects than simpler ones. Studies have shown that treatments involving acupuncture or medical devices tend to produce stronger effects than inert pills.[39,40,41] Similarly, placebo procedures that appear more costly tend to be more effective.[42,43] The various objects in the physical setting as well as the experimenter's behavior can demonstrate cues of credibility and competence, which additionally can promote placebo effects.[44,45] Lengthy discussions about the procedure can allow physicians to develop a connection with patients and demonstrate engagement and warmth, further boosting these effects.[45,46] Also, expectations about the effectiveness of high-profile neuromodulation intervention can be modulated in participants who observe improvements of other patients.[38,47,48]

An additional complicating factor on this topic concerns the implications of potential shared neurobiological mechanisms between how placebo effects modulate the brain and how neuromodulation modulates the brain. A recent neuroimaging meta-analysis by Burke and colleagues identified a common set of brain regions demonstrating changes in activity when healthy individuals and patient populations experience placebo effects.[7] This included activation of the left dorsolateral prefrontal cortex and the subgenual anterior cingulate cortex. They then showed that

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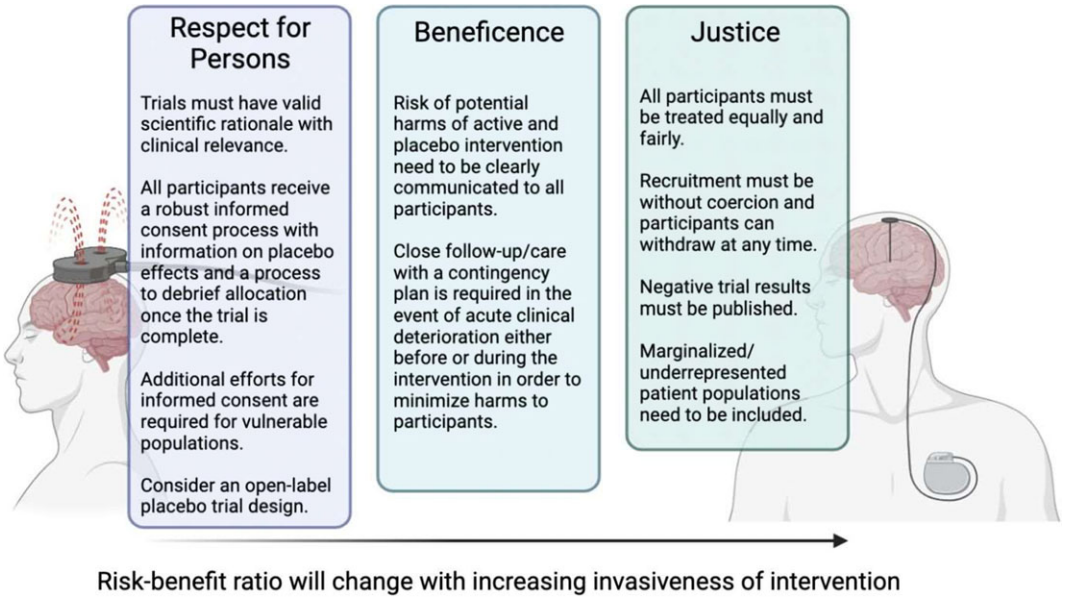

Figure 1: Ethical principles for the use of placebo controls in neuromodulation research trials. This figure was created using BioRender.

these activation clusters overlap with regions that are targeted by TMS and DBS to treat depression. There are many implications of the potential shared mechanism on conventional measurements of efficacy, and models of these impacts may help explain some of the variability in trial results that have been observed. For example, if placebo effects are particularly high (e.g., due to factors described above), the effect that TMS has on activating the dorsolateral prefrontal cortex brain target may effectively be stolen by placebo effects, which have already activated that brain circuit making it hard to show the incremental specific effect of TMS.

Blinding in placebo-controlled neuromodulation trials: Achieving satisfactory blinding in placebo-controlled neuromodulation trials is essential for proper assessment of placebo and treatment effects. Poor blinding may lead patients randomized to the placebo group to have decreased placebo effects by lowering participants' expectations of a positive outcome.[50] Conversely, poor blinding can also lead those randomized to the active group to have elevated placebo effects as they may have increased confidence and expectation that they are indeed receiving the active intervention.[51] This unequal distribution of placebo effects across trial arms can lead to major issues with interpreting clinical trial efficacy.[51] However, determining what constitutes adequate blinding in such trials is complex and varies by intervention studied. In the gold standard double-blind RCT, both participant and investigator are blinded to whether the participant is in the active or placebo arm. As most neurostimulation interventions are elaborate in nature (i.e., exposing patients to advanced machinery and complicated procedures), intricate sham controls are required to achieve even single blinding of the participant.

For noninvasive neurostimulation techniques including TMS, TDCS, and noninvasive vagus nerve stimulation (nVNS), blinded trials generally involve a sham control arm where the active treatment environment (e.g., appearance, sound, sensation) is mimicked, but little or no meaningful stimulation is received. For example, in TMS, specific sham coils have been developed that look indistinguishable from the active coil and make similar clicking sounds.[10,52] In TDCS, pruritis under scalp electrodes may occur with stimulation onset or, less often, throughout treatment.[10,53] Sham controls may therefore involve brief activations of current to cause a similar feeling and pattern of itchiness.[53,54] However, current sham TDCS protocols are heterogenous and may be confounded by separate neurobiological mechanisms enacted by seemingly inert brief activations from the electrodes, and further research is required to improve quality of sham procedures for TDCS.[55] Active TDCS can also lead to local vasodilation and scalp redness that could be observed by raters, although sham stimulation over 30 seconds may also cause redness.[56] To further improve blinding, many trials may rightfully exclude patients who have received previous treatment with a given neuromodulation as they will likely be able to note the difference of the sham procedures and experience.

Despite progress, there remain significant challenges to maintaining blinding integrity in neurostimulation trials. For instance, it can be challenging to reproduce the unpleasant scalp sensation and facial twitching that may occur with repetitive TMS.[10] There has also been debate whether tilting active coils off the scalp (a sham technique used in many early TMS studies) may be more susceptible to unblinding than sham controls.[10] To improve blinding, many trials may rightfully exclude patients who have received previous treatment with a given neuromodulation as they will likely be able to note the difference of the sham procedures. Along similar lines, conventional crossover design studies are generally discouraged as patients receiving active first may then be aware of the switch to sham. A final complicating factor is that in instances where the sham protocol involves low-dose stimulation, it could be argued whether the stimulation itself exerts an effect, a documented issue in previous nVNS trials.[57] In addition, operator blinding is generally very challenging, as the administrators must be familiar with the treatment protocols they are giving. Though novel protocols are trying to mitigate the impacts of this, it is important to have device administrators who are not involved in outcome evaluation. The lack of standardization and methodological heterogeneity sham protocols can impede assessment and meta-analyses of placebo responses across studies and between different treatment modalities.[4]

Invasive neuromodulation techniques, such as DBS and VNS, also employ sham stimulation controls. While historically best medical treatment was commonly used as a control in DBS trials,[58] it would not control for the greater placebo responses expected in the DBS arm due to the elaborate nature of the intervention. In

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sham stimulation trials, the medical device being studied is inserted in both treatment and sham groups, but stimulation is only activated to therapeutic levels in the treatment group. This allows treatment crossover to occur, which largely circumvents ethical concerns associated with having an invasive sham surgery control. Blinding of a sham surgery would be additionally difficult in DBS, as patients are awake during the procedure. One challenge with the sham stimulation approach in DBS is the lesion effect, whereby clinical changes are derived from the lesion created by DBS lead placement itself. This can lead to a temporary physiologic effect in the sham group, as well as difficulty distinguishing stimulation benefit from the lesion effect. A strategy to combat this is by providing a washout period after device implantation where neither group is stimulated, thereby allowing time for the lesion effect to diminish. However, lesion effects are not entirely predictable; they have been shown to last months and likely vary depending on location and target symptoms.[58] Given the wide variety of illnesses under study for treatment with DBS and VNS, there are unique considerations for each condition that can impact blinding integrity. For instance, in trials of DBS for Parkinson's disease, patients may require down-titration of anti-parkinsonian medications alongside DBS adjustments.[58] This could alert the patient to positive treatment response, unless a placebo pill is substituted.

The combination of elevated placebo effects and inherent challenges for blinding neuromodulation makes it critical to measure blinding validity in clinical trials. If blinding is inadequate, placebo effects can be erroneously attributed to the specific effects of the intervention and muddle the interpretation of trial results. Blinding validity is typically measured by determining whether participants and assessors can accurately deduce treatment allocation more often than by chance.[59] Assessing the success of blinding in placebo-controlled trials is a key step in evaluating internal validity that is frequently overlooked. For instance, a study by Fergusson et al. found that only 2% of RCTs reviewed in their analysis (of 191 trials) reported blinding validity in both participants and assessors/investigators.[50] Unfortunately, in 2010, international clinical trial guidelines (CONSORT) removed requirements to measure blinding validity. Reasoning behind this decision included that such measures may rely on hunches on side effects or efficacy and even that patients may not answer truthfully.[60] This remains a controversial topic with many who oppose this position.[61]

Consistent evaluation and reporting of blinding success are critical to the proper evaluation of neuromodulation in clinical trial settings.

Placebo-informed trial designs for neuromodulation studies: In order to better characterize placebo effects in neuromodulation studies, alternative trial designs should be considered (see Table 2). Few prospective studies have been designed to research the potential differential placebo effects between types of treatment modalities, and none to our knowledge have done so in sham-controlled trials of neuromodulation.[6] Such a trial would include an active arm, sham stimulation arm, and additional placebo arm (e.g., an inert placebo pill). While this added placebo pill control would help characterize differential placebo responses, a no-treatment control group would be needed to delineate other nonspecific effects in placebo trial arms, including spontaneous changes, regression to the mean, elevation bias (whereby symptom severity is overreported at initial assessment),[62] and the Hawthorne effect.[63] Though imperfect, the difference between responses in the placebo-control and no-treatment control would represent the magnitude of placebo effects distinct from the overall placebo response.

A potential strategy for reducing the large placebo effects observed in neuromodulation trials is by using a placebo run-in period. A placebo run-in includes a period at study onset where all participants receive a placebo, prior to randomization to active or placebo groups. The goal is to detect participants with high placebo responsiveness and exclude them from the trial. However, there are significant potential pitfalls of placebo run-ins, including risk of unblinding and decreased external validity.[64] Furthermore, run-in trial design for antidepressants was recently found to be no more effective for finding differences between drug and placebo groups than trials without placebo run-in periods, and the authors advocated for cessation of run-in trial design in RCTs for antidepressants.[65] Use of this debated protocol in neuromodulation trials should therefore be considered with caution.

As previously mentioned, an ethical consideration frequently encountered in the study of placebo effects is that of participant deception. This issue can be avoided in trials that use the OLP design. Emerging evidence from small randomized trials suggests placebo responses may persist even in the absence of deception, as seen in OLP trials for IBS,[15] back pain,[16,19] and cancer-related fatigue.[18,20] Several recent reviews have addressed the current status of OLP studies in detail.[20,65-68] Briefly, the mechanism responsible for benefits seen in honestly administered placebos is poorly understood. Kaptchuk et al suggest that commonly proposed mechanisms of OLP response (e.g., expectation and conditioning) provide insufficient explanation, and that OLPs may act through disrupting central sensitization, abnormal signaling, and/or principles of the Bayesian brain.[68] There are several challenges to designing and evaluating OLPs. Careful controlling must occur to ensure the effect measured is attributable to taking a placebo, rather than elements of the study design (e.g., patient–provider interaction time).[67] The script that explains the OLP concept to trial participants is not standardized, and different wording may alter expectations of a positive response. In addition, the investigator or clinician delivering the script cannot be blinded. Nonetheless, OLP research remains in its early stages and further investigation is warranted. To the best of our knowledge, OLP designs have not been used in neuromodulation studies. This could be a future direction for expanding the scope of OLPs studied.

Challenges and Opportunities

For placebo-controlled neuromodulation studies, care must be taken in trial design to ensure that the study has valid scientific rationale with clinical relevance, that steps are taken to prevent exposure to excessive risk, and that researchers provide informed consent with disclosure of information. Placebo responses in neuromodulation trials can be robust and efforts must be taken to try to ensure adequate blinding with sham devices and procedures. Given inherent challenges of blinding neuromodulation, standardized methods should be used, and blinding validity should be assessed to ensure proper interpretation of clinical trial results. Looking forward, alternative placebo-informed trial designs, such as the addition of a no-treatment control group, will better delineate the magnitude of placebo effects from other nonspecific effects in neuromodulation trials.

Conclusion

Considerations related to placebo effects have many important implications for the study and development of neuromodulation. Ethical justifiability of placebo-control groups in advancing neuromodulation research is contingent on adherence to three principles

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of ethical research: autonomy and respect for persons, beneficence, and justice. Vulnerability, trust, and meaningfulness of different procedures add a layer of complexity to an already complex ethical landscape, particularly when considering the need to incorporate marginalized and underrepresented populations in neuromodulation studies. Moreover, the risk-benefit ratio for different trial participants will change based on severity of illness and the invasiveness of the interventions.

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References

1. Colloca L, Barsky AJ. Placebo and nocebo effects. N Engl J Med. 2020;382:554–61. DOI 10.1056/NEJMra1907805.
2. Goetz CG, Wuu J, McDermott MP, et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. Mov Disord. 2008;23:690–9. DOI 10.1002/mds.21894.
3. Polich G, Iaccarino MA, Kaptchuk TJ, Morales-Quezada L, Zafonte R. Placebo effects in traumatic brain injury. J Neurotrauma. 2018;35:1205–12. DOI 10.1089/neu.2017.5506.
4. Jones BDM, Razza LB, Weissman CR, et al. Magnitude of the placebo response across treatment modalities used for treatment-resistant depression in adults: a systematic review and meta-analysis. JAMA Netw Open. 2021;4:e2125531. DOI 10.1001/jamanetworkopen.2021.25531.
5. Benedetti F, Carlino E, Pollo A. How placebos change the patient's brain. Neuropsychopharmacology. 2011;36:339–354. DOI 10.1038/npp.2010.81.
6. Burke MJ, Kaptchuk TJ, Pascual-Leone A. Challenges of differential placebo effects in contemporary medicine: the example of brain stimulation. Ann Neurol. 2019;85:12–20. DOI 10.1002/ana.25387.
7. Burke MJ, Romanella SM, Mencarelli L, et al. Placebo effects and neuromodulation for depression: a meta-analysis and evaluation of shared mechanisms. Mol Psychiatry. 2021;14:1–9. DOI 10.1038/s41380-021-01397-3.
8. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials—a middle ground. N Engl J Med. 2001;345:915–9. DOI 10.1056/NEJM200109203451211.
9. Williams NR, Taylor JJ, Snipes JM, Short EB, Kantor EM, George MS. Interventional psychiatry: how should psychiatric educators incorporate neuromodulation into training? Acad Psychiatry. 2014;38:168–76. DOI 10.1007/s40596-014-0050-x.
10. Davis NJ, Gold E, Pascual-Leone A, Bracewell RM. Challenges of proper placebo-control for non-invasive brain stimulation in clinical and experimental applications. Eur J Neurosci. 2013;38:2973–7. DOI 10.1111/ejn.12307.
11. Lidstone SC, Schulzer M, Dinelle K, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen Psychiatry. 2010;67:857–65. DOI 10.1001/archgenpsychiatry.2010.88.
12. Benedetti F, Maggi G, Lopiano L, et al. Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome. Prev Treat. 2003;6:1a. DOI 10.1037/1522-3736.6.1.61A.
13. Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov. 2013;12:191–204. DOI 10.1038/nrd3923.
14. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. Pain. 2001;93:77–84. DOI 10.1016/S0304-3959(01)00296-2.
15. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One. 2010;5:e15591. DOI 10.1371/journal.pone.0015591.
16. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain. 2016;157:2766–72. DOI 10.1097/j.pain.0000000000000700.
17. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Sci Rep. 2018;8:1–8. DOI 10.1038/s41598-018-20993-y.
18. Kleine-Borgmann J, Schmidt K, Hellmann A, Bingel U. Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: a randomized controlled trial. Pain. 2019;160:2891–7. DOI 10.1097/j.pain.0000000000001683.
19. Zhou ES, Hall KT, Michaud AL, Blackmon JE, Partridge AH, Recklitis CJ. Open-label placebo reduces fatigue in cancer survivors: a randomized trial. Support Care Cancer. 2019;27:2179–87. DOI 10.1007/s00520-018-4477-6.
20. Kaptchuk TJ, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? BMJ. 2018;363:k3889. DOI 10.1136/bmj.k3889.
21. Marks WJ Jr, Bartus RT, Siffert J, et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurol. 2010;9:1164–72. DOI 10.1016/S1474-4422(10)70254-4.
22. McRae C, Cherin E, Yamazaki TG, et al. Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Gen Psychiatry. 2004;61:412–20. DOI 10.1001/archpsyc.61.4.412.
23. Miracle VA. The belmont report: the triple crown of research ethics. Dimens Crit Care Nurs. 2016;35:223–8. DOI 10.1097/DCC.0000000000000186.
24. Miller FG, Crouch RA. The ethics of placebo-controlled trials. In: Emanuel EJ, Grady CC, Lie RK, Miller FG, Wendler DW, editors. The Oxford handbook of clinical research ethics. New York: Oxford University Press; 2008, pp. 261–272.
25. Stoessl AJ. Deception and the ethics of placebo. Int Rev Neurobiol. 2020;153:147–63. DOI 10.1016/bs.irn.2020.03.030.
26. Pugh J, Kahane G, Maslen H, Savulescu J. Lay attitudes toward deception in medicine: theoretical considerations and empirical evidence. AJOB Empir Bioeth. 2016;7:31–8. DOI 10.1080/23294515.2015.1021494.
27. Pugh J, Maslen H, Savulescu J. Ethical surgical placebo-controlled trials of deep brain stimulation for treatment-resistant anorexia nervosa. Lancet Psychiatry. 2017;4:441–2. DOI 10.1016/S2215-0366(17)30154-2.
28. Annoni M. The ethics of placebo effects in clinical practice and research. Int Rev Neurobiol. 2018;139:463–84. DOI 10.1016/bs.irn.2018.07.031.
29. Burger J, Capobianco M, Lovern R, et al. A double-blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. Mil Med. 2016;181:1195–9. DOI 10.7205/MILMED-D-15-00431.
30. Fitzgerald PB, Hoy KE, Elliot D, et al. A pilot study of the comparative efficacy of 100 Hz magnetic seizure therapy and electroconvulsive therapy in persistent depression. Depress Anxiety. 2018;35:393–401. DOI 10.1002/da.22715.
31. Krishna V, Sammartino F, Rezai A. A review of the current therapies, challenges, and future directions of transcranial focused ultrasound technology: advances in diagnosis and treatment. JAMA Neurol. 2018;75:246–54. DOI 10.1001/jamaneurol.2017.3129.
32. Lefaucheur JP, André-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125:2150–206. DOI 10.1016/j.clinph.2014.05.021.
33. Freedman B. Equipoise and the ethics of clinical research. New Engl J Med. 1987;317:141–5. DOI 10.1056/NEJM198707163170304.
34. Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials?. Results from pooled and meta-analyses. J Clin Psychiatry. 2010;71:270–9. DOI 10.4088/JCP.08r04516blu.
35. Mestre TA, Shah P, Marras C, Tomlinson G, Lang AE. Another face of placebo: the lessebo effect in Parkinson disease: meta-analyses. Neurology. 2014;82:1402–9. DOI 10.1212/wnl.0000000000000340.
36. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med. 2002;136:817–25. DOI 10.7326/0003-4819-136-11-200206040-00011.
37. Olson JA, Lifshitz M, Raz A, Veissière SPL. Super placebos: a feasibility study combining contextual factors to promote placebo effects. Front Psychiatry. 2021;12:644825. DOI 10.3389/fpsyt.2021.644825.
38. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? J Clin Epidemiol. 2000;53:786–92. DOI 10.1016/s0895-4356(00)00206-7.

39. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. BMJ. 2006;332:391–7. DOI 10.1136/bmj.38726.603310.55.
40. Meissner K, Fässler M, Rücker G, et al. Differential effectiveness of placebo treatments. JAMA Intern Med. 2013;173:1941. DOI 10.1001/jamainternmed.2013.10391.
41. Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic. JAMA. 2008;299:1016–7. DOI 10.1001/jama.299.9.1016.
42. Espay AJ, Norris MM, Eliassen JC, et al. Placebo effect of medication cost in Parkinson disease: a randomized double-blind study. Neurology. 2015;84:794–802. DOI 10.1212/WNL.0000000000001282.
43. Bernstein MH, Locher C, Kube T, Buergler S, Stewart-Ferrer S, Blease C. Putting the 'Art' into the 'Art of medicine': the under-explored role of artifacts in placebo studies. Front Psychol. 2020;11:1354. DOI 10.3389/fpsyg.2020.01354.
44. Howe LC, Leibowitz KA, Crum AJ. When your doctor "Gets It" and "Gets You". Front Psychiatry. 2019;10:475. DOI 10.3389/fpsyt.2019.00475.
45. Howe LC, Goyer JP, Crum AJ. Harnessing the placebo effect: exploring the influence of physician characteristics on placebo response. Health Psychol. 2017;36:1074–82. DOI 10.1037/hea0000499.
46. Faasse K, Grey A, Jordan R, Garland S, Petrie KJ. Seeing is believing: impact of social modeling on placebo and nocebo responding. Health Psychol. 2015;34:880–5. DOI 10.1037/hea0000199.
47. Faasse K, Porsius JT, Faasse J, Martin LR. Bad news: the influence of news coverage and google searches on gardasil adverse event reporting. Vaccine. 2017;35:6872–8. DOI 10.1016/j.vaccine.2017.10.004.
48. Holtzheimer PE, Husain MM, Lisanby SH, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. Lancet Psychiatry. 2017;4:839–49. DOI 10.1016/s2215-0366(17)30371-1.
49. Fergusson D, Glass KC, Waring D, Shapiro S. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo-controlled trials. BMJ (Clin Research ed.). 2004;328:432–0. DOI 10.1136/bmj.37952.631667.EE.
50. Burke MJ, Blumberger DM. Caution at psychiatry's psychedelic frontier. Nat Med. 2021;27:1687–8. DOI 10.1038/s41591-021-01524-1.
51. Herwig U, Cardenas-Morales L, Connemann BJ, Kammer T, Schönfeldt-Lecuona C. Sham or real–post hoc estimation of stimulation condition in a randomized transcranial magnetic stimulation trial. Neurosci Lett. 2010;471:30–3. DOI 10.1016/j.neulet.2010.01.003.
52. Ambrus GG, Paulus W, Antal A. Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol. 2010;121:1908–14. DOI 10.1016/j.clinph.2010.04.020.
53. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in–short stimulation–fade out approach to sham tDCS–reliable at 1 mA for naïve and experienced subjects, but not investigators. Brain Stimul. 2012;5:499–504. DOI 10.1016/j.brs.2011.12.001.
54. Fonteneau C, Mondino M, Arns M, et al. Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul. 2019;12:668–73.
55. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5:175–95. DOI 10.1016/j.brs.2011.03.002.
56. Schroeder CF, Möller M, May A. nVNS sham significantly affects the trigeminal-autonomic reflex: a randomized controlled study. Neurology. 2019;93:e518–e521. DOI 10.1212/WNL.0000000000007857.
57. Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: placebo, nocebo, lessebo, and lesion effects. Mov Disord. 2016;31:290–8.
58. Bang H, Flaherty SP, Kolahi J, Park J. Blinding assessment in clinical trials: a review of statistical methods and a proposal of blinding assessment protocol. Clin Res Regul Aff. 2010;27:42–51. DOI 10.3109/10601331003777444.
59. Schulz KF, Altman DG, Moher D, Fergusson D. CONSORT 2010 changes and testing blindness in RCTs. Lancet. 2010;375:1144–6. DOI 10.1016/S0140-6736(10)60413-8.
60. Colagiuri B, Benedetti F. Testing for blinding is the only way to determine whether a trial is blind. BMJ. 2010;340:c332–c332. DOI 10.1136/bmj.c332.
61. Shrout PE, Stadler G, Lane SP, et al. Initial elevation bias in subjective reports. Proc Natl Acad Sci U S A. 2018;115:E15–E23. DOI 10.1073/pnas.1712277115.
62. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol. 2014;67:267–77. DOI 10.1016/j.jclinepi.2013.08.015.
63. Laursen D, Paludan-Müller AS, Hróbjartsson A. Randomized clinical trials with run-in periods: frequency, characteristics and reporting. Clin Epidemiol. 2019;11:169–84. DOI 10.2147/CLEP.S188752.
64. Scott AJ, Sharpe L, Quinn V, Colagiuri B. Association of single-blind placebo run-in periods with the placebo response in randomized clinical trials of antidepressants: a systematic review and meta-analysis. JAMA Psychiat. 2021;79:42. DOI 10.1001/jamapsychiatry.2021.3204.
65. von Wernsdorff M, Loef M, Tuschen-Caffier B, Schmidt S. Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. Sci Rep. 2021;11:3855. DOI 10.1038/s41598-021-83148-6.
66. Blease CR, Bernstein MH, Locher C. Open-label placebo clinical trials: is it the rationale, the interaction or the pill? BMJ Evid Based Med. 2020;25:159–65. DOI 10.1136/bmjebm-2019-111209.
67. Kaptchuk TJ. Open-label placebo: reflections on a research agenda. Perspect Biol Med. 2018;61:311–34. DOI 10.1353/pbm.2018.0045.
68. Colloca L, Howick J. Placebos without deception: outcomes, mechanisms, and ethics. Int Rev Neurobiol. 2018;138:219–40. DOI 10.1016/bs.irn.2018.01.005.

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