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Placebos and Neurofeedback: A Case for Facilitating and Maximizing Placebo Response in Neurofeedback Treatments

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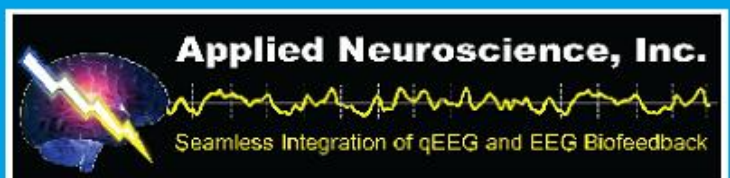
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RESEARCH ARTICLES

PLACEBOS AND NEUROFEEDBACK: A CASE FOR FACILITATING AND MAXIMIZING PLACEBO RESPONSE IN NEUROFEEDBACK TREATMENTS

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This article provides an overview of the nature of placebo responses. A critical review is provided of placebo-controlled psychopharmacology research, demonstrating that a large proportion of the improvements resulting from psychiatric medication treatments is the result of placebo effects. This finding calls into question the degree to which psychiatric treatments are genuinely evidence based. The value, limitations, and ethical problems associated with placebo-controlled research in the field of neurofeedback are then discussed. Placebo effects are an active ingredient in all therapeutic modalities. Rather than being a negative to be controlled, however, clinicians can view placebo responses as actually representing a resource to be encouraged and maximized. Practical examples are offered for creating positive expectancies and for the use of positive suggestions to further enhance neurofeedback treatment outcomes.

INTRODUCTION

Placebo effects are not unitary but represent multifaceted phenomena that have been verified to have a psychobiological basis (Benedetti, Carlino, & Pollo, 2011) but that can involve unique and divergent parts of the brain. A review of literature by Benedetti et al. (2011) suggests that placebo effects may be mediated by a combination of mechanisms including expectations of therapeutic benefit or reward, pavlovian or operant conditioning, and social learning. Genetics and brain integrity, particularly of the prefrontal cortex, also appear to be involved.

Entire volumes have been written about placebo effects, but this article initially provides an introductory overview of research on placebo effects. Then, because the largest body of literature on placebo response associated with treatment is in psychopharmacology, a critical review is provided that documents the incidence of placebo response associated with

medication treatments. It is demonstrated that by far the largest proportion of improvement resulting from psychiatric drug treatment comes from placebo effects. Yet, despite the fact that widely accepted and insurance reimbursed psychiatric treatments are mostly mediated by placebo effects, these treatments are nevertheless regarded as “evidence based.” Implications of these findings for neurofeedback research and practice are then discussed, concluding that neurofeedback practitioners should embrace placebo effects and learn to systematically encourage and maximize placebo components that contribute to positive treatment response.

AN OVERVIEW OF PLACEBO RESPONSE

Kirsch (2002) fascinatingly pointed out that different placebos can have different effects.

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For example, placebo injections are more effective than placebo pills (e.g., Traut & Passarelli, 1957); placebo acupuncture (with sham needles that retract) is more effective than placebo pills; blue-colored placebo pills produce more depressant effects, whereas red placebos produce more stimulant effects; blue placebo pills cause patients to fall asleep more quickly than orange pills; red placebos are more effective pain relievers than green, blue, or white placebos; and placebos provided as tranquilizers have very different effects from the same ones given as stimulants (Frankenhauser, Jarpe, Svan, & Wrangsjö, 1963). Brand name placebos are found to be more effective than generic names (Braithwaite & Cooper, 1981). More expensive placebos are more effective than cheaper ones, and in general placebo pills taken four times a day produce even greater effects than ones taken twice a day (Kirsch, 2010). Verbal suggestions that a treatment is more powerful likewise enhances placebo effects (Vase, Riley, & Price, 2002) and when the placebo involves patient cooperation (such as neurofeedback requires) there are greater placebo effects (Hrobjartsson & Gotzsche, 2001).

The simultaneous administration of a placebo pain medication (which was actually saline solution) along with a narcotic has been found to reduce narcotic pain medication intake 30% for postoperative pain (Pollo et al., 2001). Even surgical procedures are associated with expectancy effects and placebo surgery (e.g., an incision that is simply made and stitched up) have been documented in some cases (angina, arthroscopic knee surgery) to produce roughly comparable effects to the actual surgery (Cobb, Thomas, Dillard, Merendino, & Bruce, 1959; Dimond, Kittle, & Crockett, 1960; Kirkley et al., 2008; Moseley et al., 2002). It has also been shown repeatedly that placebos can induce activation of endogenous opioids and dopamine.

The literature on placebo effects truly demonstrates the power of suggestion in affecting change in emotions, behavior, and physiology. Several examples should suffice. Wolfe (1950) demonstrated that one could

often reverse the effects of medication through suggestion. When subjects were told that ipecac (a drug producing nausea and vomiting) was actually an antinausea drug, he reversed nausea and vomiting associated with pregnancy (hyperemesis gravidarum) and demonstrated a 33% reduction in gastric secretions (the opposite of what would be anticipated). Somewhat similarly, an experiment was done (Ikemi & Nakagawa, 1962) with boys who were hypersensitive to lacquer leaves and who would develop contact dermatitis, much like someone does with poison ivy, from touching them. When they were told their arm was being touched with this leaf (but it was actually a chestnut tree leaf), it induced dermatitis in all 13 boys, but when they were touched with the lacquer leaf on the other arm while being told that it was a lacquer leaf, 11 of 13 reacted by developing dermatitis.

Traut and Passarelli (1957) found a 50% improvement rate in rheumatoid arthritis patients with placebo pills. For individuals not improving with placebo pills, they were switched to receiving placebo injections and the improvement rate increased to 64%, with greatest relief when the placebo was injected close to the area of pain.

Placebo response is dependent on not only the nature of the placebo (e.g., injection vs. pill, color, price and/or dose) being administered but also the condition being treated. Placebo response rates have been found to differ in various diagnostic groups: 30% of migraine patients (Benson, Klemchuk, & Graham, 1974, with a range of 14–50%, and with subcutaneous placebos showing better response than oral placebos); for premenstrual syndrome/premenstrual dysphoric disorder, 20% of placebo responders had sustained improvement, 42% partial improvement (meaning a decrease of at least 50% in the level of symptoms; Freeman & Rickels, 1999); for dyspepsia, 20% (with 10% having complete relief of symptoms; Lanza, Goff, Scowcroft, Jennings, & Greski-Rose, 1994). Andrews (2001) summarized placebo effects in major depression as at least 60%, in generalized

anxiety disorder as 53%, but in obsessive-compulsive disorder as only 23%. One study (Mavissakalian, Jones, & Olson, 1990) found virtually no placebo effects in OCD patients, but compulsive shopping shows a high placebo response rate, whereas it is low with Tourette's and trichotillomania and is low in ADHD (Sangal & Sangal, 2003). Placebo responding is also low in schizophrenia (Quality Assurance Project, 1983) and chronic fatigue syndrome (Cho, Hotopf, & Wessely, 2005), but placebo response rate is high in Parkinson's (Kradin, 2008). Epilepsy also shows significant placebo response, with between 9.3 and 16.6% of patients receiving a placebo reporting a reduction of more than 50% in seizure rate, which represents 20 to 50% of the effect that is obtained with active antiseizure medications (Burneo, Montori, & Faught, 2002). Research has not found evidence of placebo-related effects in alcohol abuse but has shown large placebo effects associated with nicotine and smoking, and Alzheimer's patients show very reduced response to placebo pain medication (Benedetti, 2009). Two thirds of asthma medication effects have been shown to be accounted for by placebo (Sodergren & Hyland, 1999). Further illustrations of placebo effects are presented later as expectancy is discussed.

Placebo Effects in the Brain

It is interesting that neuroimaging studies of improvements in depression resulting from cognitive-behavior therapy (Goldapple et al., 2004) or interpersonal psychotherapy (Brody et al., 2001; Martin, Martin, Rai, Richardson, & Royall, 2001) show that they each result in distinctive changes in the brain, and there are also changes in the brain associated with placebo improvements, which are distinctive from those produced by the psychotherapies. It is interesting that changes in the brain during improvements in depression from these two psychotherapies and from Prozac have been shown to be different (Mayberg et al., 2002; Benedetti, Mayberg, Wager, Stohler, & Zubieta 2005). Placebos and antidepressants were found by Leuchter, Cook, Witte, Morgan, and

Abrams (2002) to produce different changes in the brain, but other studies have found some similar areas were affected by each (Leuchter et al., 2004; Mayberg et al., 2002).

Placebo improvement in pain and in anxiety both show fMRI changes in functioning in the anterior cingulate and the lateral orbitofrontal cortex (Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004), which may indicate that placebo analgesia and placebo improvement in anxiety operate through a similar mechanism. Of interest, not only has placebo been shown to improve insomnia, but Fratello and colleagues (2005) found quantitative EEG (QEEG) changes following placebo administration (increased .4-5 Hz power in non-REM sleep and a decrease in beta frequency during REM sleep at central electrode sites). Research is now documenting that when placebos and when antidepressants each facilitate therapeutic effects, they produce different kinds of changes in the brain (Leuchter et al., 2002; Mayberg et al., 2002; Olfson et al., 2002).

Placebo Response and Research Design Bias in Psychopharmacology Treatments

It should be recognized that the psychiatric/medical community, evidence-based databases, and insurance companies routinely rely on psychiatric treatments as "efficacious" without a preoccupation with whether these treatments involve substantial placebo influences and without apparent consideration of the serious flaws in medication treatment research design, or even the common side effects. A brief review of this literature demonstrates these facts and creates important perspective for evaluating neurofeedback research design.

Some pharmacologic treatment advocates were troubled by the original Kirsch and Sapirstein (1998) review of antidepressant research wherein they suggested that 75% of the response obtained by antidepressants was from the placebo effect, meaning that only 25% was due to a specific medication effect. After psychiatrists (e.g., Klein, 1998) challenged their conclusions, Kirsch, Moore, Scoboria, and

Nicholls (2002) filed a Freedom of Information Act release with the Food and Drug Administration (FDA) compelling them to provide all of the original research on the six most widely prescribed antidepressant medications (Prozac, Paxil, Zoloft, Efexor, Serzone, and Celexa). This was valuable information because the subsequent analysis was free from the usual publication bias wherein drug company research is withheld and never published when it does not show positive effects, which results in an overstatement of the positive effects of antidepressants (Moncrieff, 2003). In fact, it appears that 40% of drug-company-sponsored antidepressant research is never published (Williams et al., 2000), and it has been documented that this publication bias boosts the perceived efficacy of antidepressants and their acceptance as an evidence-based treatment (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008).

When Kirsch et al. (2002) independently analyzed the data obtained from the FDA, they discovered that antidepressants on average had only an 18% effect over and above placebo effects. The difference between antidepressants and placebos represented an only 1.8-point difference on the 51-point Hamilton Depression Rating Scale. This has been referred to as the "dirty little secret" in the pharmaceutical literature and with the FDA (Hollon, DeRubeis, Shelton, & Weiss, 2002). Therefore, 82% of drug response is duplicated by a placebo. Likewise, an independent review of 75 clinical trials of antidepressants by Walsh et al. (2002) found that the active medication treatment group with the highest improvement rate was only 20% better than the mean improvement rate in the placebo groups, supporting the Kirsch findings. Even the largest and most elaborate, \$35 million antidepressant study (STAR*D) found antidepressants to be only marginally efficacious compared to placebos (and without controlling for publication bias; Pigott, Leventhal, Alter, & Boren, 2009). Naturally spontaneous remission, habituation, patient or rater bias, and unidentified simultaneous interventions or effects are also factors that can be involved in the outcomes in addition to placebo response.

Expectation of effectiveness has been shown to be the largest variable in antidepressant improvement—an important fact to remember as we later discuss expectancy and neurofeedback. Krell, Leuchter, Morgan, Cook, and Abrams (2004) asked subjects who were entering a study to rate their expectations of the effectiveness of the study medication. They could rate "not at all effective," "somewhat effective," or "very effective." They discovered that 90% of the patients who expected the medication to be very effective subsequently responded to treatment versus 33.3% of those expecting medication to be "somewhat effective." Similarly, one study (Benkert et al., 1997) found that patient knowledge of increased medication dose (whether it is a placebo or an actual antidepressant) produces identical symptomatic improvements showing that belief and expectancy (placebo effects) are central to medication treatment outcomes.

One of the reasons that these factors are not more widely known is because at least 70% of drug trials are now sponsored by pharmaceutical companies (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999). In other words, they own the data, and the data can be submitted for publication only with their approval, which means that unless drug studies show significant effect, the public, prescribing physicians, and other mental health professionals never see the data (Melandner, Ahlqvist-Rastad, Meijer, & Beermann, 2003). Therefore, when drug-industry-sponsored research does not produce the desired findings, the research is often excluded and negative findings go unpublished. In fact, a meta-analysis (Freemantle, Anderson, & Young, 2000) discovered that the greatest predictor of antidepressant efficacy was the trial sponsor, and Cosgrove (2010) verified that among the authors of 162 randomized, double-blind placebo controlled studies, those who reported positive results were 4.9 times more likely to have financial ties with drug companies. Furthermore, 90% of the authors of guidelines for psychiatric practice for conditions such as bipolar disorder, mood disorders, and schizophrenia have been documented to have

financial links to the drug manufacturers of the medications cited in the guidelines, and yet none of them reported this association and conflict of interest during publication. When Cosgrove examined the interests of members of panels preparing the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.) diagnostic criteria for mood disorders and schizophrenic/psychotic disorders, 100% were found to have financial ties to the drug manufacturers.

There are a variety of systematic research biases present in psychiatric medication research. Moncrieff (2002, 2009) established that recent antidepressant studies have mostly been conducted with outpatients where there may be a greater potential for placebo effects due to their milder levels of depression, and Moncrieff and Kirsch (2005) indicated that “there seems to be little support for the suggestion that recent failure to find marked differences between antidepressants and placebo is due to the recruitment of patients with mild depression, which is less responsive to antidepressants” (p. 156).

There is evidence (Antonuccio et al., 1999; Greenberg & Fisher, 1989) that a majority of double- or single-blind, placebo-controlled medication studies prescreen their subjects in a manner so that those individuals who are identified as placebo responders within the first 1 or 2 weeks of the study, or who show improvement after being taken off a currently used antidepressant medication, are screened out from participation before they are randomly assigned to placebo and treatment groups. This is one of the subtle components in their research that is designed to encourage outcomes in the direction of showing a better response to the study medication in comparison with a placebo. Another component in drug studies is that they often do not control for the effects of discontinuation syndromes in placebo subjects who are associated with the withdrawal effects from their previous medications.

Many drug studies also do not include in their analyses the data from patients who withdrew early from the treatment group, for example, due to side effects. Because from

30 to 60% of patients drop out of medication treatment (30% dropped out of most drug trials reviewed by Kirsch et al., 2002) due to undesirable side effects such as impotence, loss of sexual desire, weight gain, drowsiness, anorexia, and dry mouth, the failure of including this group of patients introduces still another systematic bias favoring positive outcomes of drug treatment. Cosgrove (2010) verified that 47.4% of randomized controlled drug studies failed to report adverse effects, and the severity of adverse side effects from medication were not reported in 27.1% of studies. Zimmerman, Mattia, and Posternak (2002) noted sampling bias in drug studies as well, where antidepressant drug trials represent only a small minority of the patients seen for depression in clinical practice.

Outcome measures that have been commonly used in drug studies are also problematic. As an example, antidepressant studies have relied on the ratings of improvement provided by psychiatrists using the Hamilton Depression Rating Scale, when patient self-reports (e.g., with the Beck Depression Inventory, Minnesota Multiphasic Personality Inventory) have been consistently found to show less positive improvements than psychiatrist ratings (Kirsch, 2010). The Hamilton Scale has been shown to have poor interrater and test-retest reliability, as well as poor content validity, with many items being only slight contributors to the measurement of severity of depression, and with poor replication across samples (Bagby, Ryder, Schuller, & Marshall, 2004). In relation to these recent criticisms, Kirsch et al. (2002) had earlier pointed out that antidepressants have nonspecific effects associated with sedation, reducing agitation, and inducing sleep, masking depressive feelings. However, seven of the 17 items on the Hamilton Depression Scale are associated with sleep disruption and anxiety—all of which can respond to simply nonspecific sedative effects of drugs, thus potentially accounting for the 18% average improvement (which stems from an only 1.8 point difference between groups on a 0–51-point rating scale; Kirsch & Moncrieff, 2007).

Remarkably FDA approval for a new drug only requires two adequately controlled studies showing a statistically significant difference between a medication and placebo—and there is no limit to the number of studies that can be conducted before they come up with those two supportive studies.

Trials showing negative results simply don't count. Furthermore, the clinical significance of the findings is not considered. All that matters is that the results are statistically significant. If enough subjects are run (and in these trials, the number of subjects often runs into hundreds), even tiny differences of no clinical importance can be statistically significant. (Kirsch, 2005, p. 64)

Yet it has been shown that the safety of a new medication treatment cannot be known until it has been on the market for several years, and more than two thirds of new drugs are withdrawn from the market within 3 years of being released (Hollon, 2005).

Another common, yet unperceived, aspect of placebo-controlled drug studies is their use of inert placebos that have no side effects. As a result, many patients and psychiatrist raters correctly discern the group to which they have been assigned, effectively unblinding their “gold standard,” blinded, placebo-controlled studies because informed consent documents have identified possible side effects and many of the patients have a prior history with other antidepressant medications wherein they know that they commonly experience side effects from them. Rabkin et al. (1986) found that 80% of patients in an active antidepressant drug condition broke the blind, realizing that they were receiving the active drug rather than placebo, thus increasing their expectancy of improvement. Indeed the presence of side effects enhances placebo response, and an almost perfect correlation (.96) between side effects and improvement has been found across studies of Prozac (Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994). Likewise, after the drug-placebo differences were adjusted for in the frequency of side effects

in studies of Paxil (Kirsch, 2010), there was no longer found to be a significant difference between the antidepressant and placebos.

In reviews of the older studies where an active placebo (e.g., atropine, which causes anticholinergic side effects) was used, in which we would anticipate producing a greater level of positive expectancy in members of the placebo group, the two reviews (Greenberg, Bornstein, Greenberg, & Fisher, 1992; Moncrieff, Wessely, & Hardy, 1998) found that only one in seven, and two in nine studies, respectively, discovered the antidepressant to be superior to a placebo. This represents an even lower difference between antidepressants and placebos than that found by Kirsch et al. (2002)—only about 10%. This aspect of drug research design has grown in popularity with the drug companies; incorporating active placebos has not been used in antidepressant trials since the 1980s (Moncrieff, 2003). In studies that have a discontinuation design, where antidepressant-treated patients are taken off their prior medications and put on inactive placebos, yet another confound is provided because such patients may mistake their withdrawal syndrome for relapse or become unblinded by the withdrawal syndrome.

We thus see that drug researchers do not design their studies to provide the optimal condition for a placebo response to occur but rather seek to minimize placebo response in the placebo control group, possibly to maximize the likelihood that their drug be shown to have a more robust effect. The problem that neurofeedback professionals are well aware of is, of course, that in the real world it is impossible to eliminate the effects of expectations in virtually every treatment, and adding positive expectations (placebo effect) to effects specific to neurofeedback treatment is actually desirable. This is discussed in more detail shortly.

It should also be noted that comparisons of antidepressants to other drugs (e.g., benzodiazepines, stimulants, neuroleptics, St. John's Wort) have shown that many other drugs demonstrate equal effects to placebos and antidepressants in randomized trials (Moncrieff,

2009). The findings we have discussed led Moncrieff (2009) to conclude,

The SSRI's produce no effects that look likely to be useful in depression. They cause unpleasant agitation in a proportion of patients and, although it is difficult to prove conclusively, an increase in suicidal and violent tendencies may be associated with this effect. Therefore, I can think of no good reason to prescribe them at all. (p. 172)

Moncrieff and Cohen (2005) reached the following conclusions: "The case that psychiatric drugs are specific either to diseases or to pathological processes is far from established" (p. 147). "Research attempting to find independent evidence of the suggested biochemical abnormalities has not, to date, produced conclusive findings in any mental disorder" (p. 148). "Thus, biochemical hypotheses of depression focus on the synthesis, release, metabolism, and/or receptor sites of one or two members of a single neurotransmitter family, whereas antidepressants influence almost all neurotransmitters, most hormones, and many neuropeptides" (p. 148). These conclusions have also been reached by Jackson (2005).

There are similar problems with studies of anxiolytics. For example, a review of the research (Khan, Khan, & Brown, 2002) on 13 anxiety medications found (even without taking into account the inherent methodological biases just noted) that less than half the time (48%) psychopharmacologic treatment was found to be superior to placebo. Recent research (Benedetti, Maggi, et al., 2003; Colloca, Lopiano, Lanotte, & Benedetti, 2004) has shown that when antianxiety medications such as Valium are administered in a covert way, they appear completely ineffective. A review of the drug treatment of obsessive-compulsive disorder (Hammond, 2003) has shown unimpressive results.

Outcome studies of the effectiveness of stimulant medication treatment of attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) are seriously limited because they have followed-up patients only

for an average of 3 weeks. A recent meta-analysis of randomized controlled studies with Ritalin found that they were of poor quality, there was strong evidence of publication bias, side effects were frequent and problematic, short-term effects were inconsistent between different rating scales, and long-term improvements beyond 4 weeks were not demonstrated (Schachter, Pham, King, Langford, & Moher, 2001).

A recent comprehensive review (Drug Effectiveness Review Project, 2005) of medication treatment for ADD/ADHD concluded that there was no evidence on the long-term safety of the medications used in ADD/ADHD treatment and that good quality evidence is lacking that drug treatment improves academic performance or risky behaviors on a long-term basis, in adolescents or adults. The latter conclusions were also reached by Joughin and Zwi (1999). The largest randomized controlled multisite study compared medication treatment, "routine community care," and behavior therapy. Outcome raters were not blinded and introducing a bias, and most subjects in community care were also on medications. In this study, at 14-month follow-up (MTA Cooperative Group, 1999), all groups showed improvements, and medication produced better improvements in attention and hyperactivity (the latter only on parent ratings) but not in aggression, social skills, grades, or parent-child relations. The ratings provided by the only blinded rater (a classroom observer), however, showed no difference between groups, and on 3-year follow-up (Swanson et al., 2007) there was no difference on any outcome measures between groups. These findings were confirmed on 8-year follow-up (Molina et al., 2009). Studies (e.g., Swanson et al., 2007) have confirmed loss of appetite and growth suppression as a side effect of medication treatment, along with other side effects such as increased heart rate and blood pressure, insomnia, loss of emotional responsiveness, dizziness, headache, and stomachache. In the MTA study, 64% of children reported side effects, 11% of them moderately severe and 3% severe.

Readers interested in a more in-depth analysis of the problems in psychopharmacology and biological psychiatry studies are encouraged to read Kirsch (2010), Moncrieff (2009), Jackson (2005), and Wyatt and Midkiff (2006). Extensive discussions of the possibilities that psychiatric medications may increase possibilities for relapse and produce serious long-term adverse effects may be found in Jackson (2009), Whitaker (2010), and Fava (1994, 2003).

IS PLACEBO-CONTROLLED NEUROFEEDBACK RESEARCH ESSENTIAL?

There are many potential problems in utilizing what many persons consider to be the “gold standards” in designing placebo-controlled studies to evaluate the efficacy of neurofeedback. These include controlling for the nuances of therapist–subject interaction in a training paradigm, the lack of genuine feedback reward in utilizing sham feedback, the inherent transparency to an experienced clinician who is coaching neurofeedback when only sham feedback is being provided, the significant number of sessions required in effective neurofeedback treatment, and the issue of experienced versus clinically inexperienced neurotherapists. It could be argued that double-blind placebo controlled studies, therefore, have limited applicability in evaluating neurofeedback outcomes. It seems to the author almost as unrealistic as trying to do placebo-controlled psychotherapy studies.

In addition, the review that has been provided of medication outcome research helps to provide an invaluable perspective that must be kept in mind with regard to the degree in which medical and psychiatric treatments are actually evidence based. From the pharmacology studies just reviewed it can be concluded that medication treatment of anxiety and depression is efficacious and associated with positive outcomes, *but* placebos produce almost identical outcomes and could be considered close to comparably efficacious treatments that have a much lower risk of side effects. Despite the aura that modern

psychiatry and medicine are evidence based, Tricoci, Allen, Kramer, Califf, and Smith (2009) recently revealed in the *Journal of the American Medical Association* that only 11% of 2,711 treatment recommendations in medicine are based on Level A evidence (multiple randomized trials). Of the remaining recommendations, 41% were based on Level B evidence (a single randomized trial or nonrandomized studies), and 48% were based on Level C evidence (expert opinion or case studies). Thus although all scientifically minded neurofeedback practitioners acknowledge a need for additional outcome research, much of current medical and psychiatric treatment is not based on sound scientific evidence.

Criteria have been proposed for evaluating the efficacy of treatments in psychology (Chambless et al., 1998) and in biofeedback (La Vaque et al., 2002). Efficacy refers to the determination from controlled research that there is a positive outcome from using a treatment procedure, such as neurofeedback, with specific clinical problems. The criteria for evaluating the efficacy of biofeedback interventions progresses from anecdotal data; to uncontrolled case studies; historical controls; observational studies; wait list control studies; within-subject and intrasubject-replication design studies; treatment equivalence or treatment superiority studies (comparing the investigational treatment to a known and accepted standard treatment); single-blind, random assignment control design (sham or active) controlled studies; and double-blind control studies (sham or active controls with random assignment).

The levels of evidence of an efficacious treatment have been defined (LaVaque et al., 2002) as follows:

1. Not empirically supported (anecdotal reports and/or case studies in non-peer-reviewed sources).
2. Possibly efficacious (at least one study of sufficient statistical power with well-identified outcome measures but lacking randomized assignment to a control condition internal to the study).

3. Probably efficacious (multiple observational studies, clinical studies, wait list controlled studies, and within-subject and intrasubject replication studies that demonstrate efficacy).
4. Efficacious (found in at least two independent research settings to be equivalent or superior in a comparison with a no-treatment control group or alternative treatment group utilizing randomized assignment, conducted with a population treated for a specific problem with reliable inclusion criteria, valid and clearly specified outcome measures, with procedures that are clearly defined in a manner that permits replication of the study by independent researchers).
5. Efficacious and specific (shown to be statistically superior to a placebo or sham from at least two independent research settings).

Reiterating then, qualifying for the status of an efficacious and specific treatment in either biofeedback or clinical psychology requires placebo-controlled studies. However, medical ethicists (Andrews, 2001; Lurie & Wolfe, 1997; Rothman, 1987), neurofeedback advocates (La Vaque, 2001), and the Declaration of Helsinki (World Medical Association, 2000) have expressed the view that requiring placebo-controlled studies in conditions where there is a known effective treatment already available is considered unethical. Fifteen years ago an Institutional Review Board did, in fact, reject as unethical a proposed placebo-controlled study of neurofeedback with ADHD for the very reason that medication treatments exist already with known effectiveness (Linden, Habib, & Radojevic, 1996).

However, setting aside the design problems reviewed in the first paragraph of this section, and the ethical problem in requiring placebo controls in neurofeedback research, as it has already been pointed out, neurofeedback applications for specific diagnostic conditions can be determined to be “efficacious” when randomized studies have shown equivalence or superiority to a no-treatment control group or an established alternative

treatment—in ADD/ADHD, for example, to Ritalin (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003), or in depression equivalent improvement in comparison with established antidepressant or transcranial magnetic stimulation treatments. As the efficacy research criteria indicate, the efficacy of a treatment can be determined through comparisons to a no-treatment, wait list, or an alternative but established treatment control group. Placebo-controlled research will not tell us if neurofeedback works, but rather such studies tell us how and why it works. Therefore, although academia or the FDA may disregard the ethical concerns just noted and idealize placebo-controlled studies to evaluate psychological influences, in the real world of clinical work we are primarily concerned with determining whether neurofeedback produces positive outcomes that are at least comparable to established treatments. A historical example worth remembering is that of mesmerism, now referred to as hypnosis. The Royal Commission established by Louis XVI investigated mesmerism in 1784 and in surprisingly sophisticated experiments determined that expectancy effects accounted for much of its effectiveness (Gauld, 1992). Consequently mesmerism was disregarded to a considerable degree for a century and a half, whereas today there is a large volume of research supporting its efficacy with many conditions (e.g., Hammond, 2007, 2010; Montgomery, DuHamel, & Redd, 2000).

Some placebo-controlled studies have demonstrated efficacious and specific effects of neurofeedback with learning disabilities (Fernandez et al., 2003), anxiety (Raymond, Varney, Parkinson & Gruzelier, 2005), sleep latency and declarative learning (Hoedlmoser et al., 2008), cognitive enhancement in the elderly (Angelakis et al., 2006), and depression (Choi et al., 2011), whereas a preliminary study (Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2010) did not show these same effects. Certainly animal studies (e.g., Larsen et al., 2006; Serman, 1973) also suggest that neurofeedback has therapeutic effects independent of placebo effects. We would not

anticipate that cats would form positive expectancies about being more seizure resistant simply because an experimenter was putting electrodes on their heads. For clinicians, as contrasted with academics interested in clarifying mechanisms of action, placebo response is our friend and not something to control and rule out. Suggestion effects enhance treatments and psychiatric medication treatments, as already reviewed, have been characterized as consisting mostly of “active placebos” (Kirsch, 2010).

Clinicians using neurofeedback do not believe that it is a placebo, but realistically one must assume that some degree of placebo/psychological effect is operative in neurofeedback, just as it is with virtually all other therapeutic modalities. Although the author strongly believes that there are active effects other than placebo involved with neurofeedback, for purposes of arguing with skeptical academics, let us consider, “What if the majority of the positive effects of neurofeedback treatment were nothing more than placebo effects?” If this were the case it would not be so different from the findings of research documenting that the effects of psychopharmacological medications primarily represent placebo effects. But, if this were the case, the major difference would still be that the risk/benefit and side effect profile appears much better with neurofeedback (the Monastera, 2005, review of neurofeedback with ADD/ADHD estimated side effects to occur in 1–3%). In addition to side effects and withdrawal effects, medication treatments are disempowering because improvements are attributed to the effects of continuing to take the medication, whereas neurofeedback presents treatment effects to the patient as representing an enduring reconditioning of brain patterns or as a self-regulation skill, which increases their sense of self-efficacy and confidence in their ability to cope with future eventualities.

THE POWER OF PRODUCING POSITIVE EXPECTANCY

Expectancy and the power of suggestion are certainly an important component in obtaining

a response from a placebo, and in fact expectancy effects appear to result in activation of dopamine in the nucleus accumbens and reward circuitry of the brain (Scott et al., 2008). Thus acupuncture has been verified to have both specific and placebo effects. It is undoubtedly the same with neurofeedback. In the case of acupuncture, individuals with higher expectations that acupuncture would help them had larger clinical improvements, whether real or sham acupuncture was used. This was verified not only in 8 weeks of treatment but also in a 6 month follow-up (Linde et al., 2007), and research (Pariante, White, Frackowiak, & Lewith, 2005) has shown the mind–body interaction that takes place in pain when placebo activated changes are produced in the dorsolateral prefrontal cortex, anterior cingulate, and midbrain, whereas real acupuncture showed an effect in the insula.

The power of suggestion has been demonstrated in many studies. Kirsch and Weixel (1988) compared response to caffeinated or decaffeinated coffee in a double-blind experiment. At 20 min after administration the group receiving decaffeinated coffee who believed it contained caffeine showed significantly higher systolic blood pressure, a physiological arousal created by expectation. A person’s beliefs about a medication he or she is receiving is so influential that a placebo will even tend to produce the same side effects as the real drug (Pogge, 1963). Placebo effects are directly related to beliefs and expectations.

Two studies (Vase, Robinson, Verne, & Price, 2003; Verne, Robinson, Vase, & Price, 2003) showed that when it was simply suggested that “the agent you have just been given is known to significantly reduce pain in some patients,” this indication was sufficient to increase placebo analgesia to a level equal with an active topical analgesic, and yet it was pointed out that this was a nondeceptive statement, because a placebo is known to decrease pain in some individuals. As cited earlier, 90% of patients who have a higher pre-treatment expectation that an antidepressant medication will be effective respond to treatment in comparison with only 33.3% who

expected medication to be somewhat effective (Krell et al., 2004).

Expectations that the placebo is a tranquilizer/sedative has been found to elicit more symptomatic relief, just as superior effects are obtained from combining medication and with psychotherapy (but not the reverse; Blom et al., 2007; Bockting et al., 2005; Friedman et al., 2004). It is interesting to note that placebos identified as being tranquilizers produce very different effects than the identical placebos identified as stimulants (Frankenhaeuser et al., 1963).

Conditioning has also been shown to enhance placebo effects (Benedetti, Pollo, et al., 2003; Montgomery & Kirsch, 1997; Watson, El-Deredy, Vogt, & Jones, 2007). Thus the author speculates that if a neurofeedback intervention like alpha/theta training, in which one has eyes closed and is engaged in mental imagery, results in increased feelings of calm and relaxation, this may increase a patient's expectations and result in greater outcomes.

It is important for clinicians to realize that general patient personality characteristics do not predict placebo response. It appears that most patients have the capacity to have a placebo response and that therapist warmth, empathy, optimism, confidence, enthusiasm, and positive suggestions can be facilitative of placebo-mediated improvements (Kelley et al., 2009). In a study on the treatment of angina (Benson & McCallie, 1979) a high response rate ranging from 70% to 90% was found with an enthusiastic doctor administering the placebo medication in comparison to a lower response (30–40%) when administered by a skeptical physician. Thomas (1987) compared effects where a physician told patients with diverse symptoms (cold symptoms, pain, tiredness) either (a) that they were being given a prescription but he was not sure if it would have an effect, or (b) that the prescription would certainly make them better. In both cases the patients received a placebo, but 2 weeks later there was a significant difference in recovery depending on the suggestions given. Consider the implications of these findings and of Kelley et al. (2009) for skeptics

who conduct controlled research on neurofeedback.

A variety of variables seem to increase possibilities for the involvement of placebo factors, including showing interest in and concern for the patient, making frequent eye contact, showing empathic understanding and warmth, displaying confidence, appearing competent and trustworthy (e.g., by one's knowledge of literature and diagnostics, through certifications and degrees that are displayed; Hammond, Hepworth, & Smith, 1977; Kaptchuk et al., 2008; Kradin, 2008). Consider the difference between a person administering neurofeedback who seems to have a scientific detachment and whose language implies uncertainty (e.g., "Let's try this and see if it does something'") versus a clinician who seems enthusiastic and says, "Research commonly finds that close to 80% of people obtain significant improvements with this, and I anticipate that within four to five sessions you will begin noticing improvements." Research on expectancy has shown that subtle differences in a health care professional's words can result in a considerably different outcome.

Because of the importance of language (and the interpersonal skills just described) in fostering positive expectancy, the last section of this article provides specific suggestions on the therapeutic use of language in facilitating the additive benefits from placebo response that can magnify improvements obtained strictly from neurofeedback.

PRACTICAL SUGGESTIONS FOR FACILITATING & MAXIMIZING CONTRIBUTIONS FROM PLACEBO EFFECTS

The author has been active in the field of clinical hypnosis for more than three decades. A central focus in hypnosis is giving positive suggestions and fostering positive expectancy. A wide variety of types of suggestions may be utilized to accomplish this (Hammond, 1990). Because expectancy is vitally important to treatment outcome, clinicians need to foster positive expectations. Many patients,

especially with chronic conditions (e.g., depression, head injuries, ADHD) that have been unresponsive to medication and previous treatments, must be offered hope. This may be done by citing neurofeedback research and results of long-term follow-ups (e.g., Lubar, 1995; Monastra, Monastra, & George, 2002) as well as the clinician's experience.

However, creating positive expectancies must also be fostered in an ethical manner (Hammond et al., 2011). Thus informed consent and ethical behavior also require that clinicians temper enthusiasm with accurate portrayals of the improvement rates found in research, potential for side effects, and areas where the use of neurofeedback remains more experimental due to a lack of controlled research but where nonetheless their clinical experience has been positive. The expectations fostered must also be realistic, as unrealistic expectations, for example, about the timetable for experiencing change can backfire, as changes usually occur gradually. It is better that the patient anticipate that change be gradual.

As part of the informed consent process, the author notes to the patient that occasionally a side effect will occur. However, at the same time it is emphasized that when treatment is individualized and based on a scientifically objective pretreatment assessment, such side effects are usually infrequent and that if one occurs and we are immediately informed about it, the treatment protocol can be adjusted to eliminate it. Clinicians must be ethical in the informed consent process, but at the same time we are in somewhat of a double-bind because we do not want to create negative expectancies and overemphasize potential side effects. Studies have shown that patients are informed of the possible side effects (e.g., headaches, gastrointestinal symptoms) associated with a treatment (vs. when they are not informed), this significantly more often elicits patient reports of the side effect symptom (Daniels & Sallie, 1981; Myers, Calms, & Singer, 19087; Reeves, Ladner, Hart, & Burke, 2007). Research (Reidenberg & Lowenthal, 1968) has shown that within the

previous 3 days, 39% of patients (who are not taking any medications) report feeling fatigued, 23% drowsiness, 26% difficulty concentrating, and 14% headache, whereas only 19% report being completely asymptomatic during the 3 days. Another study (Barsky, Saintfort, Rogers, & Borus, 2002) noted that 73% of healthy persons not on medications noted negative symptoms in the previous 3 days. Thus if one suggests too strongly that a patient look for side effects, they may well notice something they interpret as such, and patients with anxiety, depression, and somatization may all be predisposed to nocebo effects.

To encourage positive expectancies of patients with regard to neurofeedback technology the author notes that a patient's brainwave activity is being sampled at more than 1,000 samples per second, while letting them see their brainwave activity on the screen. Also, prior to saving the data, they are allowed to see the screen displaying raw brainwave activity and the activity at different frequencies, and are often shown a display of statistics. Symptom ratings are obtained at the beginning of each session for not only feedback to the therapist and to create an immediate awareness of any potential side effects but also because it conveys the therapist's expectation that the patient will begin noticing changes soon.

Kirsch (1990) recommended,

An important part of any effective treatment is the inclusion of some means by which therapeutic change will be apparent to the client. It does not matter whether the initial change is due to the treatment itself, to expectancies generated by the treatment, or simply to random fluctuations. The important thing is that it be noticed by the client and interpreted as a sign of improvement. Feedback, especially experiential feedback, strengthens the effects of positive expectations. (p. 35)

Such feedback may also come from showing the patient trend graphs, statistics, and raw EEG demonstrating improvement occurring in their EEG activity over the course of a session

of over a number of sessions. When a mild side effect (e.g., feeling fatigued or overstimulated following a session) occurs, it may also actually enhance positive expectancies just as has been noted with medication side effects, and although the therapist should adjust the treatment protocol in response to the side effect, it may nonetheless be interpreted as demonstrating that treatment is producing effects.

A significant amount of the responsiveness to suggestion that is seen in someone who is hypnotized can also occur in response to what have been called waking suggestions. Research has shown that in children suggestibility is maximal between the ages of about 5 to 12 (Olness & Kohen, 1996), and therefore giving positive suggestions to children may be especially productive.

EXAMPLES OF COMMENTS CREATING POSITIVE EXPECTANCY & MAXIMIZING SUGGESTION EFFECTS

The author will often make some of the following suggestions to patients in neurofeedback treatment. "About 80% of the time we find significant and enduring improvements." "Most people begin to notice positive improvements beginning within four to six sessions, and sometimes after just one or two sessions people indicate that they feel calmer or more clear-headed, for example, when they are on their way home." At the conclusion of a session, especially one facilitating calming and relaxation, a patient may be asked, "What do you notice right now?" Note the implication that there may be something to be noticed. Again note the implication of asking, "Do you feel different from when you walked in half an hour ago?" "Many people who have seen their progress plateau or slow down will begin to see improvements again after we shift to this other neurofeedback protocol."

Note the implication of "yet" in asking a patient at the beginning of a second, third, or fourth session, "Are you beginning to notice some changes yet?" "I think you'll be surprised to discover how soon you'll notice differences beginning to occur." "Soon other people will

be surprised at how well you'll be able to concentrate." "Research has shown that students commonly have their IQ scores increase 10 to 15 points after neurofeedback. This is going to let your true self shine through." "It won't be long before you'll be surprised to discover how much better you can read and how well you can focus. You'll even be able to focus better when you're playing video games" (if that is an interest of the child). "Now that you are improving your concentration, you will begin soon to really feel like studying and reading more, and you will begin to feel a new confidence as you study. You will be able to use your study time much more efficiently." "As you study, you'll begin to find yourself concentrating much more easily, and it will be easier to remember what you've learned." After a parent has reported improvements in concentration, a child may be told, "Your concentration is becoming so good that you'll find that when you are studying, your mind will quickly understand what you are studying. Each fact will make a strong impression on you, so that you'll be able to recall the information more easily whenever you need to." "Soon you're going to begin to find that you will be able to concentrate so intently that you will absorb the material like a sponge soaking up water. What your teacher is saying, or what you're reading, will make such a strong impression in your mind so that you'll be able to remember it whenever you need to." "As you're studying, things that used to distract you won't bother you as much. When you study, other things going on around you will seem temporarily more distant and unimportant." A suggestion referred to as a bind of comparable alternatives would be to say, "I wonder where you'll notice the improvements first; if it will be in your concentration or in falling asleep more easily." Suggestions may also be given less directly to patients through sharing patient success stories, for example, as one is hooking up electrodes to the patient.

Positive expectancies may also be accomplished through interspersing other subtle treatment methods with the neurofeedback. An example would be having

anxious patients do slow, smooth diaphragmatic breathing with their eyes closed while electrodes are being attached and during eyes-closed neurofeedback training.

SUMMARY AND CONCLUSIONS

An extensive body of literature has demonstrated the power of positive expectancy and placebo effects. Psychiatric medication treatments are widely regarded as being evidence based. Yet it has been shown that at least 80% of clinical improvement is accounted for by placebo response, and much of medical treatment continues to be based on far-from-robust experimental evidence. Efficacy standards in psychology and biofeedback do not require that a treatment demonstrate superiority to a placebo to be accepted as an efficacious treatment. What is of prime importance is establishing that neurofeedback treatments produce improvements that are at least comparable to accepted and established treatments. It is assumed that neurofeedback effects are due to some combination of expectancy (placebo) effects, and effects specific to the neurofeedback treatment. Therefore, because placebo effects are an active ingredient in virtually every therapeutic modality, they represent a resource that can be maximized for the benefit of patients. Andrews (2001) suggested exactly this to psychiatrists: "The size of the response to placebo might well be a bane to researchers but, properly handled, it is surely a boon to busy clinicians and their patients. . . . Perhaps we should actively strive to potentiate the placebo effect when treating people" (p. 193). Neurofeedback clinicians are encouraged to utilize methods for increasing positive expectations within the limits of ethical informed consent.

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