Perspectives on Placebo: The Psychology of Neurofeedback

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Abstract

The application of operant conditioning with EEG variables to produce changes in behavior has been gaining increasing interest in research and application areas. However, the methodology has come under scrutiny and criticism for its potential placebo effects. This article will examine those issues from the traditional methodologies of demonstrating effectiveness (control group, sham treatments) as well as examine the possible biochemical and electrophysiological effects of a placebo response. Specifically, the role of endorphins and dopamine and their relationship to the alpha and beta frequency in the placebo response will be examined. The research addressing the diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) correlates of the intervention will be examined.

Keywords: neurotherapy; EEG biofeedback; placebo; alpha; endorphins; dopamine

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Definitions of Placebo and Effects

The common thread of varying definitions is that a placebo has (a) a positive effect on the patient's perception and self-report; and (b) does not have any physical beneficial effects on the illness for which it is prescribed.

Thibault and Raz (2017) conclude that "EEG-nf works, but it likely relies heavily on placebo phenomena" (p. 683). They further argue that "mental health professionals stand to benefit from studying the ubiquitous placebo influences that likely drive these treatment outcomes" (p. 679). "EEG-nf studies largely neglect investigating treatment mechanisms that rely on participant motivation, belief in the treatment administered, interacting with a practitioner, level of positive feedback, and sense of control of their brain signal" (p. 684). This paper will investigate the logic and evidence regarding the potential placebo effect in the neurotherapy (NT) situation.

In order to demonstrate a placebo effect, a research project must meet the following criteria document: (a) the expectation of the subject or study characteristics which encourage such an expectation; (b) the concomitant biological correlates (neurochemical, EEG, fMRI, DTI correlates of the expectation); and (c) the lack of a relationship between the biological correlates of the placebo and the biological correlates of the illness in question. To document that the effect is a real, substantive effect, (d) the results must distinguish between the effects of the intervention which have no measurable physical effect on the problem in question (a placebo) and those interventions which have a direct measurable physical effect on the problem.

It is clear that there is a real physiological effect from a placebo. The mechanism is not the pill or the treatment but rather the subject's perception that there is a value (positive/negative) in the pill or treatment. It is this belief that creates a change in the physiology of the brain and thus underlies the

perceived changes in symptoms. It is the goal of this paper to understand the relationship between the perception of change and the underlying electrophysiology and biochemistry of that change. We will address what is known/unknown about this relationship. If NT is a placebo response, then it is necessary to document the physiology of placebo response and its relationship to reported changes obtained with NT.

There is some inherent ambiguity built into the question of whether NT is a placebo in the traditional sense. It should be noted that the placebo argument originated in drug research addressing physical conditions, thus a physical intervention (pill, etc.) addressing a physical condition. NT is not a pill addressing a physical condition but an operant conditioning method to change the EEG signal which is related to behavior (such as attention). In both situations, however, the concern is whether the subject's subjective response is influencing the results which are tied to the relevant behavior issue (attention, etc.) and how much. In the case of attention-deficit disorder (ADD), if the "illness" is excessive theta activity and deficient beta and a placebo or NT changes the theta and beta values and relevant behavior, then the question is: Has a "cure" occurred? It is not assumed that the theta/beta issues are the sole physical issue in the attention-deficit/hyperactivity disorder (ADHD) subject.

This paper will examine research on the physical/physiological effects related to the placebo response (endorphins, dopamine, EEG signal) and determine if it is credible to account for the NT effects as a placebo.

Placebos work on patient's perceptions
Hróbjartsson and Gøtzsche (2010) reviewed the literature on placebos for 60 clinical conditions and concluded that there was a placebo effect in the clinical conditions of pain, nausea, asthma, and phobia but no effect in smoking, dementia, depression, obesity, hypertension, insomnia, and anxiety. Thus, only 7% of the conditions studied had a documented placebo effect. The perception of pain condition appears to be most responsive to the placebo effect (approximately 30 to 60 percent of people report a positive effect; Cherry, 2018).

In addition, not all subjects respond to the placebo effect. Beecher (1955) reviewed 26 studies and found on average 32% of the patients responded to placebo. In addition, it appears that some subjects are not responsive to the placebo effect due to

genetics. "Predisposition to respond to placebo treatment may be in part a stable heritable trait" (Hall, Loscalzo, & Kaptchuk, 2015, p. 20).

Rossi (1986) concluded that "placebo is about 55–60% as effective as active medications irrespective of the potency of these active medications." Rossi also mentions that "in a study of morphine, there was a 50% pain reduction in 75% of the patients treated. The placebo group had a 50% pain reduction in 36% of the patients" (WRF, n.d.)

Kaptchuk et al. (2010) studied two groups of irritable bowel syndrome (IBS) patients. One group did not receive any treatment, while the other group was provided with pills labeled placebo and were told they were "fake, inert drugs" and that the "placebo pills, something like sugar pills, have been shown in rigorous clinical testing to produce significant mind-body self-healing processes'' (Kaptchuk et al., 2010). The group receiving the fake placebo drugs reported twice as much symptom relief as the no treatment group and comparable to the best real medicine for IBS. According to Feinberg (2013), Kaptchuk's interest is "not if, but how, placebo effects work," as Kaptchuk argues that "sham treatment won't shrink tumors or cure viruses" (p. 36).

Wechsler, Kelley, and Kaptchuk (2011) studied 40 asthma patients with four different interventions. They found that only the real treatment showed results. However, there was no difference between the patient's subjective response to the real versus sham treatments. The patient's subjective response was not consistent with the objective measures. Thus, the placebo does not cure the problem but does result in a patient's perception of change.

The argument that NT is solely a placebo effect for all of the participants who have been involved in the treatment must be understood in the context that the placebo effect has only been documented in 7% of the conditions, by 32% of the patients, is determined, in part, by genetics and is about half as effective as morphine (in terms of patient response rates). Thus, the "ubiquitous placebo influences" are not found everywhere.

Placebo's Physical Effects on the Body and Brain

The placebo's physical effects on activity in brain structures has been documented in Parkinson disease (Benedetti et al., 2004; de la Fuente-Fernández et al., 2001), pain (Eippert et al., 2009;

Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004; Zubieta et al., 2005), depression (Leuchter, Cook, Witte, Morgan, & Abrams, 2002), and anxiety (Furmark et al., 2008; Petrovic et al., 2005). The anxiety and depression results are in contradiction to the Hróbjartsson and Gøtzsche Cochrane review. The hypothesis resulting from these studies suggest a prefrontal control mechanism that effects activity and neurotransmitters. A full understanding of the structural, functional, biochemical, and electrophysiological effects is required.

"Researchers have found that placebo treatments—interventions with no active drug ingredients—can stimulate real physiological responses, from changes in heart rate and blood pressure to chemical activity in the brain, in cases involving pain, depression, anxiety, fatigue, and even some symptoms of Parkinson's" (Feinberg, 2013).

Endorphins

Levine, Gordon, Jones, and Fields (1978) first reported that blocking the release of endorphins (chemically) by opioid antagonist naloxone would stop the placebo effect. Endorphins are the brain's natural pain relievers and are similar to morphine and opiates.

Benedetti et al. (2004) concluded that "there is ample evidence that expectancy-based placebo effects are mediated by endogenous opioids." Levine et al. (1978) noted that naloxone blocks the brain's ability to soak up endorphins. Volavka, James, Reker, and Cho (1979) showed that "naloxone elicited a significant slowing of the average alpha frequency" (p. 1267). This slowing effect would most likely be manifested in the lowering of the peak frequency of alpha. Thus, the alpha frequency appears to be involved in the placebo/endorphin response. The interrelationships between different measures of the alpha frequency (magnivolts, relative power, peak frequency) pose a complex problem, which is beyond the scope of this paper.

Lipman et al. (1990) reported that, in chronic pain subjects, the placebo responders had higher concentrations of endorphins in the cerebrospinal fluid than the placebo non-responders. Wager, Scott, and Zubieta (2007) concluded that placebo effects involve opioid activation in opioid receptor rich regions including "periaqueductal gray and nearby dorsal raphe and nucleus cuneiformis, amygdala, orbitofrontal cortex, insula, rostral anterior cingulate, and lateral prefrontal cortex" (p. 11056). Thus, the placebo effects involve a similar activity or results

suggest that endogenous opioid release in core affective "brain regions is an integral part of the mechanism whereby expectancies regulate affective and nociceptive circuits" (p. 11056).

However, it has also been reported that the placebo effect can occur without the involvement of opioids and naloxone can only partially inhibit the placebo analgesia effect in some situations (Amanzio & Benedetti, 1999; Gracely, Dubner, Wolskee, & Deeter, 1983; Grevert, Albert, & Goldstein, 1983).

The relationship between endorphins and the EEG has not been studied directly. However, there is indirect evidence that the endorphins increase the level of alpha magnitudes. Mimasa et al. (1996) "found that the larger the changes in beta-endorphin following exercise, the higher the appearance rate of the alpha wave in EEG. There was a positive and significant correlation ($r = .563$, $p < .05$) between the increase in alpha wave component and that of the plasma beta-endorphin." It is unclear whether the increase was a magnitude or relative power increase. Thornton (2016) reported a positive correlation ($r = .66$, $p < .05$) between magnitude and relative power measures of alpha. However, Crabbe and Dishman (2004) were able to document that exercise results in increased alpha magnitudes. Pfefferbaum et al. (1979) found that "beta-endorphin and morphine produced similar increases in alpha power within 5 to 15 minutes after injection."

Peniston and Kulkosky (1989) compared a nonalcoholic control group, a traditionally treated alcoholic control group, and alcoholics receiving brainwave training (BWT). The BWT group showed significant increases in percentages of EEG record in alpha and theta rhythms (the focus of the intervention), increased alpha rhythm amplitudes, and improved outcome compared to the other two groups.

However, the alcoholics receiving abstinence, group psychotherapy, or antidepressants showed a significant elevation in serum beta-endorphin levels at the conclusion of the experiment. "This neuropeptide is an index of stress and a stimulant of caloric (e.g., ethanol) intake" (Peniston & Kulkosky, 1989, p.271). "Beta-endorphins play a role in certain behavioral patterns (stress, alcoholism), in obesity, diabetes, and psychiatric diseases" (Peniston & Kulkosky, 1989). Dalayeun, Norès, and Bergal (1993) application of brainwave treatment, a relaxation therapy, appears to counteract the increase in circulating beta-endorphin levels seen in the control

group of alcoholics. This partially explained result stands in contrast to the expected increases in alpha associated with increases in endorphin levels.

It appears that the placebo effect involves endorphins and alpha magnitudes, relative power and peak frequency. Thus, when a subject believes an intervention is going to be successful, the endorphins increase and the magnitudes of alpha increase, as well as probably other frequencies. It remains unclear whether the increase in alpha magnitudes is a result of the placebo effect or NT. Even an increase in the alpha and theta magnitudes during a session or treatment period is not an argument against a placebo effect as the argument could be made that the placebo's effect increases during the session gains or as more sessions are employed.

Dopamine

De la Fuente-Fernández et al. (2001) found that placebo-induced expectation of motor improvement activates endogenous dopamine in the striatum of Parkinsonian patients. Additional studies have pointed to dopamine involvement in the placebo response in pain conditions (Scott et al., 2008; Zubieta et al., 2005; Zubieta & Stohler, 2009).

Hall et al. (2012) stated that "Catechol-O-methyltransferase (COMT), an important enzyme in dopamine catabolism, plays a key role in processes associated with the placebo effect such as reward, pain, memory, and learning." As "COMT activity decreased, theoretically making more dopamine available in the prefrontal cortex, placebo responses increased in a linear fashion…associated with a positive outcome only in groups given a placebo (and not in the waitlist control group) is of particular importance, as it indicates that it is a predictor of the placebo effect, not just improvement in general" (Hall et al., 2012).

Dopamine has been shown to be part of the ADHD condition. An increase in psychostimulants should result in increases in dopamine levels and increases in EEG arousal frequencies (alpha and beta) and decreases in lower frequencies (delta and theta). "Methylphenidate: Ritalin produces a decrease in delta and theta, with a more pronounced posterior alpha increase and an increase in low beta, with effects delayed up to 6 hours, compared to the rapid effects of the amphetamines" (Gunkleman, 2009, p. 4). "Medication resulted in normalization of theta power, but, after medication, increased relative beta was also apparent in the female ADHD group" (Clarke, Barry, McCarthy, Selikowitz, & Johnstone,

2007). This result was also obtained in adults Bresnahan, Barry, Clarke, and Johnstone (2006), who reported that following medication, there was a "significant reduction in slow wave activity in the ADHD adult group to levels similar to those in the control group."

However, these findings have not been without contrary evidence. Lubar, Swartwood, Swartwood, and Timmermann (1996) failed to show increases in qEEG indicators of cortical arousal with methylphenidate. Other researchers (Barkley, 1998; Ernst et al., 1994; Matochik et al., 1994) have failed to demonstrate the neurophysiological effects of Ritalin at the cortical level.

There is solid research in the efficacy of operant conditioning (Staddon & Cerutti, 2003). The research has documented that NT can increase beta magnitudes and decrease theta magnitudes as well as increase alpha (Lubar et al., 1996; Sherlin, Arns, Lubar, & Sokhadze, 2010). The effect can be maintained up to 2 years (Gani, Birbaumer, & Strehl, 2008; Leins et al., 2007) and is maintained after cessation of medication (Monastra, Monastra, & George, 2002). Endorphins and dopamine have short-term effects. Foley et al. (1979) reported the half-life of beta-endorphin was 37 to 93 minutes. "The half-life of dopamine effect is 2 min" (ADHB, 2018). It is conceptually challenging to understand how it is possible that the placebo effect could be manifested 2 years later.

In conclusion, activation of an endorphin response appears tied to the alpha frequency, while dopamine's effects are predominantly in the beta frequency. NT and medications appear to break apart the naturally positive relationships between the magnitudes of the theta, alpha, and beta frequencies.

Neurotherapy and Structural/Functional Changes on fMRI, MRI, and DTI

Lévesque, Beauregard, and Mensour (2006) studied twenty ADHD unmedicated children who were divided between the experimental group (EXP; $N = 15$) and control (CON; $N = 5$) and baseline measure were obtained on two cognitive measures (Digit Span, Integrated Visual and Auditory [IVA] Continuous Performance Test [CPT]) and two questionnaire variables (Conners Parent Rating Scale, inattention and hyperactivity component). Following 40 sessions of NT, inhibiting theta microvolts (4–7 Hz) and rewarding beta microvolts (12–15 Hz, 15–18 Hz) at Cz, there were significant improvements in the EXP

group on the two cognitive and two questionnaire variables. In addition, a repeat fMRI scan was conducted while they (EXP and CON) performed a Counting Stroop task. The initial evaluation indicated significant increases in both groups in the left superior parietal location (Brodmann area 7). Postintervention fMRI scan revealed that the EXP group had increased activation of BA 24b-c and 32, which involve the anterior cingulate cortex, known to be involved in attentional issues (Bush et al., 1999). The CON group "did not receive an attentional training lasting the same time duration than the NT received by EXP subjects," which the authors suggested needs to be further evaluated (Lévesque et al., (2006). Thus, the NT intervention showed positive behavioral attentional and relevant fMRI results, with some qualifications regarding the CON group intervention.

In this study, the posttreatment Counting Stroop task requested the subjects to indicate the number of words presented (neutral condition) and then provided with an interference condition, during which the words *one*, *two*, *three*, and *four* were presented. The analysis compared the interference condition to the neutral condition. For both the EXP and CON groups, there was a significant locus of activation in the left superior parietal lobule (BA 7; fMRI) at both time periods. For the EXP group, at time 2, there were significant activations in the right BA 32 and left the caudate nucleus. Banich et al. (2000) reported that the anterior cingulate cortex is employed in selecting an appropriate response and allocate attentional resources. BA 32 is located in the anterior cingulate cortex. The caudate nucleus is involved in the inhibitory control of action (Nestler, Hyman, & Malenka, (2009). Thus, NT interventions appear to have an additional and relevant effect on brain structures that were not present for the CON group. Criteria #4, presented in this article, argues that if a treatment results in relevant change then it is real and not a placebo result. The NT intervention appears to have met that criteria, apart from the CON group intervention qualification.

Ghaziri et al. (2013) examined white matter (WM) and grey matter volume (GMV) in a sample of 30 participants under EXP, sham, and CON group conditions. They employed NT rewarding 15–18 Hz at F4 and P4 for 40 sessions (30 min each). Pre- and posttreatment data were available for the Integrated Visual and Auditory (IVA) test. The EXP and sham treatment showed significant increases on the IVA, while the sham group showed significant increases in the visual attention measure. The CON showed no significant improvements on either measure. The

areas of interest for the structural magnetic resonance imaging (MRI) study and the fractional anisotropy (FA) measure of DTI involved the cingulum bundle (CB), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), and the splenium of the corpus callosum (SCC).

For the EXP group, there were significant increases in fractional anisotropy (FA) in the right and left CB, right anterior corona radiata and SCC as was as left SLF and ILF. "These WM pathways are known to be associated with sustained attention" (Ghaziri et al., 2013, p. 269).

This result satisfies criteria (d) mentioned at the beginning of this paper which states "must distinguish between the effects of the intervention which have no measurable physical effect on the problem in question (a placebo) and those interventions have a direct measurable physical effect on the problem." In this case, the EXP group had a direct measurable physical effect on the problem of attention, as the affected "WM pathways are known to be associated with sustained attention." Thus, the intervention must be viewed not as a placebo but a valid, relevant intervention on the "cause" of the problem—WM pathways.

The visual attention performance correlated with the FA measures in the left SLF and left ALIC (left anterior limb of the internal capsule). In the sham and CON conditions, there were no significant FA increases at posttesting.

For the EXP group, the GMV measures showed increases in Brodmann areas 9, 20, 19, 6, 47, 22 and 7 while the sham group showed increases in BA 10, 6, and 18. Thus, the EXP group activated BA areas 9, 19, 20, 22, and 47 that the sham group did not. The sham group received training "for approximately 20 hours, participants in the SHAM group had to undergo a perceptual-cognitive 'training', consisting of staring at the computer screen and staying focused with respect to the animation displayed on that screen. The members of this group also received hours of personal coaching to pay attention visually" (Ghaziri et al., 2013, p. 269). This coaching, perhaps, explains their improvement on the visual attention IVA. Thus, the sham group did not result in increased communication patterns (increases in FA values) but did result in increased GMV in frontal areas (BA areas 10 and 6) while the EXP group increased frontal GMV in BA 9 and 47. The study was the "first empirical demonstration that NT can lead to microstructural changes in white and gray matter" (Ghaziri et al.,

2013). This study had the sham group engaged in training which addressed the problem in the Lévesque et al. (2006) study with the control group.

The lack of significant FA increases in the sham condition presents a serious challenge to the NT as placebo argument. This result indicates that the NT intervention is resulting in a substantive change in the physical functioning (FA) of the brain while the sham intervention does not. This is evident in both the communication measure (FA) and different GMV increases, reflecting that the NT approach is fundamentally changing. The presence of a sham condition argues definitively against a placebo effect.

Gevensleben, Holl, Albrecht, Schlamp, et al. (2009) and Gevensleben, Holl, Albrecht, Vogel, et al. (2009) studied 94 ADHD children with a randomization approach involving multicenters and a sham condition (a computerized attention skills training). The NT intervention involved decreasing theta (4–8 Hz) and increasing beta (13–20 Hz). The post-qEEG data showed reduced theta power, demonstrating efficacy and specificity. Gevensleben et al. (2010) conducted a 6-month follow-up on the 2009 study and found that the improvements in the NT group were comparable to the effects at the end of the training period (effect size of .71), employing parent rating scales. Thus, the maintenance of effect at the 6-month time period is problematic for a placebo explanation in addition to the reduction of theta magnitudes which is not concurrent with a reduction in beta magnitudes, the naturally occurring pattern.

Clinical Conditions

We will examine the different clinical conditions to determine if the NT effects can justifiably be called a placebo effect.

ADD

The ADD condition has been the subject of many investigations with modern medical imaging technology. Initial research focused on the theta/beta values. Eyes-closed, resting EEG data indicated that higher relative power of theta and reduced relative power of alpha and beta, as well as elevated theta/alpha and theta/beta ratios being associated with ADD/ADHD (Barry, Clarke, & Johnstone, 2003). There are other studies supporting this pattern (Chabot & Serfontein, 1996; Matsuura et al.,1993). Several EEG research reports have shown that beta activity is related to sustained attention (Arruda, Zhang, Amoss, Coburn, & Aue, 2009; Molteni,

Bianchi, Butti, Reni, & Zucca, 2007), thus relevant to the ADHD's problem in attention.

NT approaches (combined theta/beta training with the training of slow cortical potentials, SCPs) obtained a reduction of theta activity (Gevensleben et al., 2010). Improvements on the EEG measures was associated with improvements on an ADHD rating scale. Similarly, Monastra et al. (2002) reported a decrease of the theta/beta quotient in a group of children with ADHD with an initially enhanced theta/beta quotient. The clinical value of the theta/beta ratio resides in its high correlation (r = .99) and age-related changes in the ADHD behavioral symptomatology (Snyder & Hall, 2006).

More recently, the research has focused on deficits in white matter tracts (Hamilton et al., 2008; Konrad et al., 2012; Niogi, Mukherjee, Ghajar, & McCandliss, 2010; Pavuluri et al., 2009; Qiu et al., 2011). Niogi, Mukherjee, Ghajar, and McCandliss (2010) conducted a DTI study (healthy participants) and showed a positive correlation between FA values in the anterior limb of the internal capsule and performance on a sustained attention task.

Kong et al. (2006) has reported DTI research on ADHD which reported significantly lower FA values in the left hemisphere involving the frontoparietal networks (SLF, ILF, and CB), or are implicated in interhemispheric processing within parietal areas (SCC). Van Ewijk, Heslenfeld, Zwiers, Buitelaar, and Oosterlaan (2012) conducted a meta review of the DTI area and ADHD and concluded that "alterations in white matter integrity were found in widespread areas, most consistently in right anterior corona radiata, right forceps minor, bilateral internal capsule, and left cerebellum."

Thus, the ADHD pattern is one of elevated theta, reduced beta activity, and decreased FA values. The decreased FA values would imply lowered coherence and phase values. Treatment approaches have indicated the ability of NT to decrease theta and increase beta levels. Specific interventions on coherence and phase values in the ADHD subject has not been published to the best of the author's knowledge.

If the placebo effect of alpha magnitude increase was occurring during the NT intervention, one would expect an increase in theta and beta1 magnitudes and thus no significant change in the theta/beta ratios. Yet the research (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Monastra et al., 2002)

report decreases in theta magnitudes and changes in theta/beta ratios which employ magnitude values.

Drug abuse

Peniston and Kulkosky (1989) studied alcoholics receiving BWT and showed a gradual increase in alpha and theta brain "rhythms" across the 15 experimental sessions. It is assumed that *rhythms* means *amplitudes*. The reason for the intervention was the previous research which hypothesized a decreased alpha level in alcoholics (Gabrielli et al., 1982). Saletu, Anderer, Saletu-Zyhlarz, Arnold, and Pascual-Marqui (2002) documented with qEEG and LORETA mapping studies of detoxified alcohol-dependent patients, as compared with normal controls, higher values of absolute and relative beta power, and lower values in alpha and delta/theta power for the alcohol patients.

Sokhadze, Cannon, and Trudeau (2008) reviewed the research on substance use disorders and biofeedback and concluded that "alpha theta training—either alone for alcoholism or in combination with beta training for stimulant and mixed substance abuse and combined with residential treatment programs, is probably efficacious…. Based on the guidelines jointly established by the Association for Applied Psychophysiology and Biofeedback (AAPB) and the International Society for Neurofeedback and Research (ISNR)" (p. 1). The NT intervention used most frequently was the rewarding of alpha (8–13 Hz) and theta (4–8 Hz) in eyes-closed condition. The Scott, Kaiser, Othmer, and Sideroff (2005) modification involved initially rewarding C3-FPZ and C4-PZ SMR (12–15 Hz) and beta (15–18 Hz) while inhibiting theta (2–7 Hz) and high beta (22–30 Hz), and then followed up with the Peniston protocol (reward alpha and theta). Abstinence was obtained for 77% of the EXP subjects and 44% for the controls at 1 year after intervention. The controls were involved in the Minnesota Model 12-step-oriented program as well as additional time in treatment which equaled the EXP time in treatment.

There remains the possibility of a placebo effect with endorphins and dopamine affecting the alpha and beta frequencies. However, the endorphins and dopamine would be increasing alpha and beta. The authors did not report the changes in the frequencies. However, the results were better than most rehabilitation programs and the 1-year time reassessment is a long time to expect a placebo effect to last.

Depression

There are numerous studies that report decreases in depression on the Minnesota Multiphasic Personality Inventory (MMPI) and other measures following NT, typically involving alpha/theta protocols (Cheon, Koo, & Choi, 2016; Grin-Yatsenko et al., 2018; Hammond, 2005; Raymond, Varney, Parkinson, & Gruzelier, 2005; Wang et al., 2016). Scott et al. (2005) reported improvements on the MMPI which included the experimental group's changes and exhibited a significant improvement compared with the changes in the control subjects on the Hypochondriasis, Depression, Conversion Hysteria, Schizophrenia, and Social Introversion scales.

As with the other clinical conditions, the possible placebo effect of increased endorphins or dopamine related to increases in alpha and beta remains a possibility. Contrary to that possibility, Sokhadze and Daniels (2016) reported on changes in self-perception of positive emotional state following 12 sessions of NT involving increasing the prefrontal relative power of 35–45 Hz EEG band at Fpz (middle of forehead). The NT training resulted in a significant linear increase of the relative power of the 35–45 Hz gamma measure and increase in self-report of happiness scores. Follow-up at 3.9 months showed maintenance of gains in happiness measure as well as MicroCog and IVA+Plus neurocognitive tests. The foundation for the research was raised in three previous publications (Cowan, & Albers, 2009; Cowan & Sokhadze, 2010, 2011). In addition, there is no research that the author is aware of which ties increases in the gamma frequency to a placebo effect.

Anxiety

Walker (2009) studied 19 PTSD patients with alpha/theta NT and obtained significant reductions in anxiety, while the control group (*N* = 4) did not show any reductions in anxiety. A decline in alpha activity has been reported in anxiety disorders using the qEEG (Buchsbaum et al., 1985; Heller, Nitschke, Etienne, & Miller, 1997).

The qEEG abnormalities in 100 anxious patients were reported by Gurnee (2003). He described six qEEG subtypes—high beta, high alpha, low alpha, cingulate dysfunction, high mean frequency beta, and high mean frequency alpha. Interventions directed towards these problems were generally effective in reducing anxiety. The placebo effect (alpha increase) could be employed to account for some of these improvements. However, the explanation of a sole alpha placebo effect across these diverse EEG

conditions faces the same problem previously discussed of alpha increases related to general magnitude increases across the different frequencies.

Cognitive – Memory

Thornton and Carmody (2013) reported on significant improvements in cognitive function in a group of 79 participants, including normal individuals, traumatic brain-injured, and specific learning disabilities (children, adult). Table 1 presents the results of the 2013 article as well as two previous articles (Thornton & Carmody, 2005, 2008).

Table 1
Treatment Effects of NT.

	Auditory Memory SD Effect	Auditory % Effect	Reading Memory SD Effect	Reading % Effect
Normal (*n* = 12)	1.66	59%	1.29	101%
TBI (*N* = 36)	2.3 (*N* = 36)		1.85 (*N* = 13)	143%
Adult SLD (*N* = 17)	1.42	86%	1.71	219%
Child SDL (*n* = 14)	1.28	74%	1.38	225%
Total (average; *N* = 79)	**1.67**	**73%**	**1.56**	**172%**

The following definitions of the qEEG variables are as follows:
- **RP:** Relative Magnitude/Microvolt or Relative Power: the relative magnitude of a band defined as the absolute microvolt of the particular band divided by the total microvolt generated at a particular location across all bands
- **M:** Absolute Magnitude*:* the average absolute magnitude (as defined in microvolts) of a band over the entire epoch (one second)
- **PA:** Peak Amplitude: the peak amplitude of a band during an epoch (defined in microvolts)
- **PF:** Peak Frequency: the peak frequency of a band during an epoch (defined in frequency)

Connectivity Measures
- **Spectral Correlation Coefficient (SCC)**: spectral morphology comparison correlation between two channels using the formula $(\sum |X||Y|)^2 / (\sum |X|^2 \sum |Y|^2)$ expressed in percent, where X and Y represent the Fourier series of the two channels and $\sum$ represents the summation within a band's frequency range.

- **Phase:** peak amplitude phase difference between two channels using the formula $100(1 - |\theta_1 - \theta_2| / \pi)$. A value of 100 percent represents zero degrees out of phase and a value of zero percent represents 180 degrees out of phase.

The bandwidths were grouped according to the following divisions: delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta1 (13–32 Hz), beta2 (32–64 Hz).

An analysis of the changes in the relative power values of the different frequencies showed that the relative power of beta2 (32–64 Hz) was the only frequency that showed significant improvements when analyzed using confidence intervals. The relative power of beta2 was a main focus of the interventions. Thus, a placebo's effect on the relative power value of beta2 seems unlikely, given the previous discussion, as the placebo response is focused on the alpha and lower beta frequencies.

The correlation between % improvement in relative power of beta2 was most evident in the TBI group (+.46) and adult specific learning disability (+.77) in the auditory memory condition.

The conclusion for the coherence values was that "the average raw value of the Spectral Correlation Coefficient (SCC) change for alpha was 6.1 points (2.09 *SD*), for SCC beta1 (13–32 Hz) 6.53 points (1.81 *SD*), and for beta2 (32–64 Hz) 7.5 points (1.77 *SD*)."

Thus, the NT interventions were able to obtain significant increases in the relative power of beta2 and coherence values from alpha to beta2, across all subjects.

As previously noted, the placebo's effect is in the alpha or beta frequency and not the gamma frequency. In addition, alpha values are generally negatively related to the gamma frequency values (Thornton, 2016). Thus, it appears implausible that the placebo effect could account for these changes as there is no evidence to support the effect of placebos on relative power of beta2 (32–64 Hz) or any changes in the coherence and phase values of the beta1 of beta2 frequencies, which are critical to successful cognitive functioning (Thornton, 2016).

Discussion / Conclusions

Thibault and Raz (2017) make the argument that "placebo effects dominate EEG-nf outcomes. Whereas most neurofeedback experts acquiesce to this insight" (p. 684). The support for this statement resides in following quotes from experts:

It would be naïve to believe that neurofeedback offers an adequate and sufficient treatment for any disorder (Joel Lubar, personal communication, 2016).…"It would be foolish to conclude that a foundation of knowledge has been realized enabling textbooks to be written [on EEG- nf]" (Gruzelier, 2014, p. 178).…Niels Birbaumer proposed that the cumulative evidence in favor of EEG-nf is preliminary and we stand to benefit from more controlled evidence to confirm that genuine feedback is a necessary component to achieve positive treatment outcomes (personal communication, 2016). (p. 688)

These direct quotes do not mention placebo effects, so it is difficult to discern how the authors came to that conclusion.

Thibault and Raz (2017) further state that "in light of the comparable benefits of veritable-versus-sham feedback, conflicts of interest, and a weak theoretical underpinning, advocating for EEG-nf poses a conundrum…Sparse evidence supports the idea that humans can reliably modulate EEG-nf signals" (p. 684). This conclusion is in stark contrast to the Thornton and Carmody (2013) and Thornton (2006) research study of cognitive changes, which consistently documented the ability of the approach to change the EEG signals along a number of measures and across different subjects.

A "weak theoretical underpinning" is a grossly inaccurate way to characterize operant conditioning, a concept Skinner proposed in 1938 (Skinner, 1938). The research cited in this article does show the effectiveness of NT over sham treatment, thus providing research support for its effectiveness which effectively addresses criticisms. In addition, the NT as a placebo argument has considerable problems as:

1) It claims "ubiquitous placebo influences" of NT (Thibault & Raz, 2017). This statement is not consistent with research on placebo effects, which show only 7% overall effectiveness across different clinical conditions, only 32% of patients respond to placebos, a genetic predisposition, and a lower percentage of patient responsiveness than an effective drug (for pain).

2) The biochemical effect of the endorphins and dopamine levels of a placebo are not sufficient to explain the short-term and long-term effects, given their half-lives. However, this criticism requires qualification as some patients show the placebo effect long after the half-lives of the endorphins and dopamine have passed. A possible answer is that the patient is continuing to produce these neurotransmitters by continuing to affect the alpha frequency. If this is the case, then we are still left with the problem of the cause. Is the continuing alpha activity the result of a placebo effect or effective operant conditioning? Since both the biofeedback typical program addresses alpha and the biochemical effect appears to be in the alpha frequency, it appears that the data presently available is unable to directly address that question.

3) The relationship of the biochemical effects on the alpha and beta frequencies appear to possibly explain the NT results. However, the gamma responsivity is inconsistent with the biochemical hypothesis as there is no evidence of a biochemical effect on this frequency.

4) Occam's razor states that among competing hypotheses, the one with the fewest assumptions should be selected. NT as a placebo has considerable problems in its explanation of the research findings. It is simpler to assume and more consistent with the literature that operant conditioning is the effective operant rather than some inconsistent and intermittent placebo effect.

5) This article has presented empirical evidence that humans can have an effect on the EEG signal. The relationship between the qEEG variables and cognitive performance is a complex one. It is difficult to assert that the placebo's effect is on all/most of the variables that relate to performance. If we reward a qEEG variable that has an empirical relationship to performance (memory) and the variable and memory performance improve, it is logical to conclude that the

intervention is not a placebo. To assert that a placebo knows what qEEG variable relates to performance and increases the values of those specific variables (among the 2,000+ available) is a difficult position to defend.

In conclusion, the effect of a placebo or subject's expectation can be linked to biochemical and electrophysiological activity. However, the relationship is a complex one and the ability of a placebo to explain all the effects is not credible, given the evidence reviewed. The alternate explanation that operant conditioning is causing the changes in the EEG signals is a more plausible and simpler one.

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