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The Placebo Effect and Its Implications

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Often regarded simply as a nuisance in clinical drug trials in which the aim is to separate drug response from placebo response in a statistically significant manner, the placebo response has important implications. These implications relate to the nature of illness, the study of non-specific factors in the treatment setting that are related to clinical improvement, methods of enhancing these non-specific sources of benefit, and the neurobiology that is associated with the placebo response. Specific sources of clinical improvement in medical and psychological treatment generally consist of drugs or clear interventions (e.g., surgery, specific therapeutic modalities) that appear to directly contribute to the desired treatment. Non-specific factors, on the other hand, include the clinician–patient relationship, installation of hope, relationship with authority, and other such factors that are more implicit to treatment and may contribute to the placebo response. Our understanding of how these non-specific aspects of treatment relate to clinical improvement and ways of enhancing these non-pharmacological elements of therapy may form important aspects of treatment. Furthermore, an important, albeit potentially overlooked element of the placebo response are clinical-trial designs and methodologies, themselves. Specific neurobiological changes also appear to be associated with the placebo response in at least some cases. Finally, it is suggested that the placebo response may in some instances represent a type of brain plasticity in which expectation and desire — agency — can result in specific changes in brain function that either may mirror or differ from the effects of certain drugs.

Keywords: placebo, placebo effect, placebo response

Simply put, the placebo effect or response is a response to an inert substance or procedure (Piercy, Sramek, Kurtz, and Cutler, 1996; Wickramasekera, 1980). Latin for "I shall please," placebo is associated with what is often considered clinical improvement across a variety of medical and psychological conditions. It also potentially offers a means for an enhanced understanding of the relationship between non-specific factors such as expectation of change and clinical improvement. Furthermore, placebo effects have impor-

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tant implications that concern the evaluation of new drugs, as the placebo response can mask true clinical improvement related to specific drugs under investigation (Heeg, Deutsch, and Deutsch, 1997). However, a response that occurs while a person is taking a placebo is not necessarily the same as a placebo response, as clinical improvement can occur from spontaneous recovery, regression toward the mean (Kirsch, 2002), politeness of the patient, and variation in symptoms (Kienle and Kiene, 1997), making an awareness of these factors integral to an understanding of both placebo and clinical responses in general, as these factors may be confused with a placebo response or improvement from active treatment.

Despite the difficulties in interpreting the placebo response, many diseases and medical conditions, themselves, have been associated with a placebo effect (de la Fuente–Fernández and Stoessl, 2004). For example, it has been suggested that 50 to 75% of the apparent efficacy of antidepressant medication in major depression is actually due to a placebo effect (Leuchter, Cook, Witte, Morgan, and Abrams, 2002). Conversely, placebos also are associated with adverse effects (Bystritsky and Waikar, 1994). *Nocebos*, in fact, are placebos that produce adverse effects (Barsky, Saintfort, Rogers, and Borus, 2002).

It is sometimes assumed that improvement from placebo indicates that there is no associated biological pathology for what the individual is experiencing (Heeg et al., 1997). Such an interpretation, unfortunately, often leaves the placebo response associated with somewhat of a stigma, which suggests that the experience of change is merely fabricated by the individual. If this were not the case, as this perhaps inferential leap in logic goes, an inert substance would not work. However, as just one example, pain from a variety of causes including arthritis and bone metastases, which have clearly identified associated biological pathologies, appears to respond to placebo (Heeg et al., 1997). Furthermore, there appear to be neurobiological changes associated with the placebo response (de la Fuentes–Fernández and Stoessl, 2004). Arguing against the notion that the experience of change from a placebo is merely a fabrication, such findings suggest a complex relationship between disorders, placebo, and clinical response. Findings such as these also suggest that the placebo response, far from being irrelevant to the study of disease and behavior and just a nuisance to be minimized (Kwekkeboom, 1997) in controlled clinical drug trials, deserves careful scrutiny. Furthermore, these findings raise essential questions about illnesses that are associated with placebo responses, the importance of non-specific factors such as motivation, empathy, and genuiness in the study of disease treatment, and how these non-specific factors can be understood and enhanced to contribute more to clinical improvement. Finally, there appear to be neurobiological changes that are associated with the placebo response (de la Fuente–

Fernández and Stoessl, 2004), findings that offer additional insight into the meaning of the placebo response and the conditions under which it may occur. To further develop and understand the placebo effect and its implications, this paper reviews some of the conditions that are associated with a placebo response, non-specific factors that are implicated in the clinical response, methods of potentially enhancing the placebo response, and the neurobiological findings associated with the placebo response. Finally, this paper offers the suggestion that the neurobiological changes associated with the placebo response may represent a form of brain plasticity in which expectation and desire can result in specific brain changes and associated improvement in clinical condition.

Placebo Response of Medical Conditions

Depression. Placebos and the placebo response are integral in understanding how new antidepressants are approved for clinical use. Until approximately 1981, in order to gain approval for marketing, potential antidepressants did not have to show superiority to placebo in clinical drug trials but only had to demonstrate that they were no worse than an already marketed antidepressant (Healy, 2004). However, because of concerns that it could be possible that neither the new drug nor the established antidepressant had antidepressant efficacy, new antidepressants after 1981 had to show that they improved depression better than did placebo. Since 1981, therefore, considerable evidence from placebo-controlled trials exists that enables the comparison of antidepressant medication and placebos in the treatment of depression.

Using data from comparisons of active treatments with placebos, several studies strongly suggest that much of the apparent response to antidepressant medication in depressive disorders is due to the placebo effect (Kirsch, Moore, Scoboria, and Nicholls, 2002; Kirsch and Sapirstein, 1999). Moreover, using a meta-analysis population chosen specifically for homogeneity to diminish bias associated with poorly defined study populations, Stolk, ten Berg, Hemels, and Einarson (2003) also found high placebo rates in clinical trials of depression. Quitkin, Rabkin, Gerald, Davis, and Klein (2000) cite data suggesting that response rates for antidepressants are approximately 50%, compared to approximately 32% for placebo. In their analysis of antidepressant data submitted to the United States Food and Drug Administration for the six most widely prescribed antidepressants approved between 1987 and 1999, Kirsch et al. (2002) reported that approximately 80% of the drugs' antidepressant effects were duplicated by placebo. Put another way, there was on average a less than two-point difference between drug and placebo in these clinical trials, even though the difference between drug and placebo in this analysis was statistically significant. Regardless of the exact

number of placebo responders in depression, it is clear that there is a placebo response of some magnitude. That is, some proportion, possibly substantial, of people with major depression have clinical improvement while on placebo.

Furthermore, placebo response rates in major depression appear to be increasing (Walsh, Seidman, Sysko, and Gould, 2002), a phenomenon known as placebo drift, at a rate of approximately 7% per decade. Although the cause of increasing placebo rates in clinical trials of depression is unknown, placebo drift could be due simply to less severely ill participants being included in the more recent clinical trials and showing a higher rate of placebo response than earlier, more severely ill populations (Stolk et al., 2003; Walsh et al., 2002). However, in a meta-analytic population chosen for similar levels of depression, Stolk et al. (2003) still found an increasing placebo response rate. Not only is there a substantial placebo response in clinical trials of depression, but the rate of response appears to be increasing for reasons that are as yet unexplained.

To better understand the placebo response rate and the placebo drift found in antidepressant clinical trials, factors that may impact the validity and confound the interpretation of clinical trials require consideration, particularly as some of these have the potential to artificially increase response-rate difference between active drugs and placebos (Moncrieff, 2001). Many clinical trials of antidepressants, for example, use what is known as placebo washout. In placebo washout, all participants take placebo in a single-blind fashion (that is, the researcher knows that the participants are on placebo, but the participants do not know whether they are on placebo or active drug) for a certain period. Those participants who respond to placebo at this stage of the study are dropped from the study (Piercy et al., 1996). Allowing time for any prior antidepressants to be eliminated, the placebo-washout period also provides a highly selected group of participants who enter into the placebo-controlled, double-blind portion of the study. That is, the group that enters the double-blind stage of the trial is less representative of the general population than the total group that originally entered into the placebo-washout phase and would be expected to have a much lower placebo response than the original group as some placebo responders have already been eliminated from further study. In contrast, Walsh et al. (2002) found no difference in placebo-response rates between studies using and not using a placebo-washout phase, suggesting that placebo washout may have a smaller than anticipated effect on the placebo-response rate in depression.

Several other factors also complicate the interpretation of randomized, placebo-controlled, double-blind antidepressant trials. As drugs have associated adverse effects while inert substances presumably do not, adverse effects could allow for the investigator to penetrate the blind of a double-blind,

placebo-controlled trial. That is, the blind during randomized, placebo-controlled studies could be weakened because the adverse effects may signal to both the clinical rater and the research participant as to what drug the person is taking (Leber and Davis, 1998). Indeed, patients and clinicians appear able in many cases to determine whether a patient is on placebo or active medication (Bystritsky and Waikar, 1994). That the blindability of a clinical trial has important implications for pharmacological research is illustrated by findings that in trials of tricyclic antidepressants, the drug–placebo response difference is lessened when so-called active placebos (drugs having no specific antidepressant properties but that have adverse effects similar to the drug being tested) are used (Bystritsky and Waikar, 1994). In other words, drug–placebo differences are less pronounced when the adverse effects of the drug in question are matched by those of an active placebo. In view of the problems associated with blindability, some techniques may *diminish*, though not necessarily eliminate, the transparency of the blind. For example, the potential for adverse effects to break the blind may be less in clinical trial designs in which the participant is exposed to only one treatment compared to designs in which every participant is exposed to every treatment arm (Leber and Davis, 1998) as the participants in such trials have experience with only one treatment and cannot compare their experiences with different treatments. However, this is only true if the participants have had no prior experience with antidepressant medications, even experience antedating the clinical trial. Finally, as the previous point suggests, the transparency of the blind may be increased, regardless of the design used, in those cases in which the participants have had any prior experience with antidepressant medications.

Another factor requiring consideration when interpreting antidepressant clinical trial data is that many antidepressant trials use the Hamilton Depression Scale to monitor clinical response. Despite the widespread use of the Hamilton Depression Scale to monitor clinical change during an antidepressant trial, however, this scale has only one item that directly addresses mood. Furthermore, the one item that is designed to evaluate mood is interpreted by the clinician, and self-assessment scales are never the primary outcome of antidepressant trials. That is, the primary endpoints of most clinical trials are based upon the rater's inference of the participant's state of depression and not on the participant's own assessment. Because clinical raters may not be truly blinded secondary to adverse effects caused by the active drug (Bystritsky and Waikar, 1994), investigator-rated scales may provide an inaccurate measure of the clinical status of the trial participant. An additional problem with the Hamilton Depression Rating Scale is that it contains several items addressing sleep and anxiety. A drug with sedative properties, therefore, could be expected to show a reduction in the total score of the

Hamilton Depression Rating Scale and increase any drug–placebo differences on that basis alone (Moncrieff, 2001). An additional concern with the Hamilton Depression Rating Scale is that it is administered by a clinician. Studies using clinician-administered scales tend to show higher drug–placebo differences than do those studies that rely on patient self-ratings (Moncrieff, 2001).

Perhaps one reason for the higher drug–placebo differences in clinician-administered scales than in patient self-ratings is that many investigators, with clinical training, also have a funding incentive to discover and report positive findings for their drug trials. That is, there have been frequent reports of strong ties between medical researchers and the pharmaceutical industry (Angell, 2000; Healy, 2004; Valenstein, 1998). Perhaps these ties relate to the more positive outcomes discovered through clinician-administered scales. This possibility gains further support with the discovery that study sponsor is one of the major, if not the main, predictor of positive trial findings (Baker, Johnsrud, Crismon, Rosenheck, and Woods, 2003; Freemantle and Mason, 1997; Moncrieff, 2001).

In addition to placebo washout, unblinding, measurement problems, and ties to pharmaceutical industry, several other factors may impact the validity of double-blind, placebo-controlled clinical trials. Data analysis that includes only trial completers may show higher response rates than do analyses that evaluate the intent-to-treat population (Moncrieff, 2001), in which all participants initially randomized and for whom there is analyzable data are evaluated. Likewise, publication bias wherein so-called negative trials are less likely to be published also may inflate the perception of drug–placebo differences (Moncrieff, 2001), suggesting that reviews that utilize unpublished data from pharmaceutical companies and make use of statistics designed to detect publication bias (Whitehead, 2002) are required to more fully evaluate drug–placebo differences. In her review, Moncrieff (2001) also points out the potentially confounding effects of antidepressant withdrawal symptoms in that they may be misinterpreted as relapse and increase drug–placebo differences.

There are considerable public health implications to assertions that much of the antidepressant response in clinical trials is due to placebo. For example, a belief that antidepressants are no more effective than placebo could persuade people to avoid drug treatment for depression. If, however, antidepressants do, in fact, treat depression or some types of depression, people may be unnecessarily deprived of an effective treatment further contributing to a proposed undertreatment of depression (Hirschfeld et al., 1997). In part because of such public health implications, studies questioning the efficacy of antidepressants require careful scrutiny themselves to more fully characterize the placebo response in depression. Along these lines, Quitkin et al. (2000) pro-

vide data suggesting that the response rate to active placebos is actually similar to that of inactive placebos and challenge the notion that investigators are reliably able to determine which participants are on drug and which are on placebo. Quitkin et al. (2000) suggest that response rates do not differ between active placebos and placebos without adverse effects and thus validate clinical trial data that have not used active placebos. Moreover, they argue that transparent blinds may not be a critical problem in clinical trials. However, with these limitations and controversies in mind, the main point here is that there is still a substantial placebo response rate in depression.

Anxiety disorders. Much as the findings in the treatment of depression, certain anxiety disorders are associated with relatively high placebo response rates. One study, for example, reported seven out of 17 (41%) participants treated for panic disorder responded to placebo and five out of 10 (50%) responded to clonazepam, a drug with anti-panic properties (Baker, Khaykin, Devins, Dorian, Shapiro, and Newman, 2003). Generalized anxiety disorder may also respond to placebo. In fact, generalized anxiety disorder and panic disorder tend to have a more robust placebo response than do social anxiety disorder and obsessive–compulsive disorder (Piercy et al., 1996), demonstrating the heterogeneity of the placebo response across even seemingly related mental disorders.

Panic disorder illustrates further the finding that some disorders may have a differential response to active drugs and placebos. For example, panic disorder is associated with sleep abnormalities and low heart-rate variability. Baker et al. (2003) in a placebo-controlled study of panic disorder found that while changes in heart-rate variability were associated with clonazepam use but not with therapeutic response, sleep abnormalities normalized with therapeutic response from both clonazepam and placebo. These findings suggest a therapeutic split in which placebo improved some but not all of the manifestations of panic disorder but nevertheless resulted in a therapeutic response.

Pain. That pain responds to placebo is well demonstrated (de la Fuente–Fernández and Stoessl, 2004). In fact, the alleviation of pain from numerous causes is associated with a placebo response in which anywhere from approximately one-third to two-thirds of pain patients respond to placebo. For example, bone pain from metastatic cancer, headache, and third-molar extraction can remit with placebo use (Heeg et al., 1997).

Parkinson's disease. Even though it has a well described pathophysiology, the motor deficits in Parkinson's disease are subject to the placebo response (de la Fuente–Fernández and Stoessl, 2004). Furthermore, in a double-blind sham surgery versus implantation of embryonic dopamine neurons in the brains of patients with advanced Parkinson's disease, the patients who believed that they had received implantation as opposed to sham surgery reported better quality of life after approximately one year of double-blind conditions.

Based on the findings of reported increased improvement in the group believing that they had received implantation, the authors of this study concluded that expectation alone of clinical improvement had a statistically significant effect on emotional and motor functioning and that a strong placebo effect was present (McRae et al., 2004).

Other disorders associated with a placebo response. In addition to depression, panic disorder, pain, and Parkinson's disease, many other disorders appear to be associated with a placebo response. For example, Tourette's syndrome, tardive dyskinesia, restless leg syndrome, and multiple sclerosis may respond to placebo (de la Fuente–Fernández et al., 2002), as does generalized anxiety disorder (Schweizer and Rickels, 1997). There appear to be placebo effects also in hypertension, angina, and congestive heart failure (Bienenfeld, Frishman, and Glasser, 1996). Conversely, a review found that while placebo may be associated with some improvement in pain and appetite in cancer patients, they had little effect on tumors themselves (Chvetzoff and Tannock, 2003).

Non-Specific Factors and Sources of the Placebo Response

Non-specific factors have been hypothesized to contribute to the placebo effect (Heeg et al., 1997). Underscoring the importance of non-specific factors in the placebo response, Mayberg et al. (2002) argue that "it is therefore emphasized that administration of placebo is not the absence of treatment, just an absence of active medication" (p. 732). Likewise, in response to Kirsch and Sapirstein's (1998) findings that much of the response to antidepressants can be accounted for by placebo, Beutler (1998) contends that Kirsch and Sapirstein also "demonstrate that . . . antidepressant effects are about equivalent to the effects of credible but non-antidepressant drugs — *another form of the Do-Do bird verdict* . . . " (online citation, emphasis added). Beutler is referring to the "Do-Do bird verdict" from the classic novel, *Alice in Wonderland*. This verdict, "Everybody has one, and all must have prizes," has frequently been used in the common factors or non-specific factors research in psychotherapy. That is, there is an indication, from a long history of research, that all therapies yield essentially equivalent outcomes, with client variables — perhaps including the placebo effect under its auspices — far outweighing specific treatment variables in the outcome of psychotherapy (Lambert and Bergin, 1994; Luborsky, Singer, and Luborsky, 1975; Rosenzweig, 1936; Smith and Glass, 1977; Wampold, 2001). By using this analogy in response to the findings of Kirsch and Sapirstein (1998), Beutler is making an equally strong and perhaps as controversial statement about this research indicating that all treatments are the same in terms of treatment of psychopathology, including psychopharmacological agents. From Beutler's per-

spective, it is the "common factors" or "non-specific factors," perhaps implicated in the placebo response, that are responsible for and important for understanding the effects of *any* treatment of psychopathology.

Roberts, Kewman, Mercier, and Hovell (1993) concluded in their study of non-specific factors under conditions in which both physicians and patients incorrectly believed a treatment to be effective, that non-specific factors such as patient and physician expectation lead to improvement in nearly 70% of the cases. Furthermore, although no personality type has been reliably linked to the placebo response (Heeg et al., 1997), certain personality variables such as acquiescence and suggestibility are hypothesized to be associated with a placebo response. Particularly germane for clinical trials is the possibility that people who volunteer for participation in clinical trials may be highly motivated for clinical improvement and be compliant with treatment, characteristics that may contribute to the placebo response. Expectation for clinical improvement on the part of the patient also may contribute to the placebo response (Heeg et al., 1997; Piercy et al., 1996).

Variables associated with the treatment setting such as the atmosphere of the clinic and behavior of the staff also can influence the placebo response (Piercy et al., 1996). Factors that may be present in many clinical settings (Heeg et al., 1997), the attitudes, level of enthusiasm, and expectations of the clinician also appear to affect the placebo response (Heeg et al., 1997; Piercy et al., 1996), as can the therapeutic relationship itself (de la Fuente–Fernández and Stoessl, 2004). Although arguing that the dichotomy between non-specific and specific factors in psychotherapy is unhelpful, Butler and Strupp (1986) discuss several additional non-specific factors in the therapeutic relationship that may be relevant for the placebo response such as empathy, acceptance, and even the clinician's status.

Finally, the type of illness itself may be an important variable in placebo response. Certain illnesses, for instance, appear to have a relatively high placebo response rate while others are associated with a much lower placebo response, or no placebo response at all (Kirsch, 2002). For example, as mentioned above, placebo response rates for panic disorder are substantially higher than those for social phobia (Piercy et al., 1996), even though these two disorders are both classified as anxiety disorders and clinically may appear quite similar.

Theories of Placebo Response

In an attempt to account for or to understand the psychology of the placebo response moving beyond non-specific factors associated with the response, researchers and theorists have outlined general mechanisms by which clinical improvement to placebos may occur. Response expectancy, for

example, appears to be an important aspect of the placebo effect (Kirsch, 1997) and relates to a person's expectation of change in response to a drug or other therapeutic intervention. The expectation of the response is believed to lead to a change in experience (Kirsch, 1997), that is, clinical improvement. Response expectancy is supported by the finding that the expected potency of a treatment appears to affect the placebo response. Sham surgery, or an injection of placebo, for instance, has a greater placebo response than an oral placebo (de la Fuente–Fernández and Stoessl, 2004). Not only does response expectancy appear to affect clinical outcome in drug trials, it also may be an important aspect of improvement in the cognitive–behavioral treatment of depression (Kirsch, 1997). The improvement, therefore, during cognitive–behavioral treatment could be due not to the specific mode of therapy but instead due to the expectancy of change from the treatment. Further complicating the assessment of placebo response, response expectation can also be enhanced by subtle clues from clinicians and researchers (Heeg et al., 1997). Exposure to a placebo alone, therefore, does not elicit a placebo response. Rather, it is the expectation of change that seems crucial for the generation of the placebo effect (de la Fuente–Fernández, Schulzer, and Stoessl, 2002).

In another approach, the placebo response has been conceptualized as being essentially due to classical conditioning in which the placebo elicits the classically conditioned response of clinical improvement (Heeg et al., 1997), possibly via response expectancy (Kirsch, 1997), as previous experience with an active drug may prime a person to respond to a placebo given for a similar condition. Neutral stimuli (i.e., placebos) through association with specific treatments can then elicit a response themselves (Voudouris, Peck, and Coleman, 1990; Wickramasekera, 1980); for example, conditioned placebos have been shown to produce pain (Voudouris et al., 1990). The classical-conditioning approach to understanding the placebo invokes response expectancy based upon previous experience with an active drug. Despite the similarity between the response-expectancy and classical-conditioning models, a major difference between the two is that prior experience with the placebo (stimulus) is required for the latter, whereas prior experience with the placebo is not necessary for the former, as no classical conditioning occurs but the person's expectations alone lead to a placebo response. Additional evidence suggests that in some situations, previous association with an active treatment may be more effective, for example, for pain reduction, than expectation alone (Voudouris et al., 1990).

A third general approach evaluates the placebo response in the context of signal detection theory (Allan and Siegel, 2002). In this approach, the patient must determine whether clinical improvement occurred. If the patient determines that improvement occurred under placebo conditions, the

result is a false positive, or placebo response. In this case, the benefits, for example, of pleasing the physician or shortening the time in treatment (a false-positive judgment) outweigh the costs of making the correct assessment (i.e., that no improvement occurred). An important implication of signal detection theory applied to the placebo response is that no actual changes, such as analgesia, occur; instead, there is only a change in the labeling of a particular symptom according to a cost–benefit analysis. However, well-documented biological changes associated with some placebo responses (see below) argue against a simple acceptance of signal detection theory applied to placebos.

Still another general approach to understanding the placebo response labels the placebo response, alternatively, as the "meaning response" (Moerman, 2003; Moerman and Jonas, 2002). A "meaning response" can be considered "the physiologic or psychological effects of meaning in the origins or treatment of illness" (Moerman and Jonas, 2002, p. 472). Arguing that placebos are inert and, as such, cannot be associated with anything, Moerman and Jonas suggest that a more appropriate way to look at this phenomenon is in terms of meaning. The ways in which the people being treated experience (e.g., the meanings they have in) the practice of treatment is what is important in what has been labeled the placebo response. Such meaning responses may include but are not limited to the clinician's overall style, way of dressing, use of language, manner of treatment, and even the diagnosis and prognosis offered. Moerman and Jonas are also careful to differentiate the meaning response from both nonspecific factors and expectancy, arguing that even though the meaning response may seem nonspecific, many elements of the meaning response are actually quite specific (especially to each clinician). Alternatively, the meaning response differs from expectancy in that meaning response can be based on tacit knowledge and, therefore, engenders no (conscious) expectation.

Enhancement of the Placebo Response

Although considerable efforts are placed in minimizing the placebo response in clinical trials to increase the chances of obtaining a significant drug–placebo difference in outcome, an alternative approach is to acknowledge the placebo effect and integrate it into research and treatment. The variability in placebo response rates even from trial to trial (Kupfer and Frank, 2002) suggests that as yet poorly described factors can considerably influence response rates. Additional research focusing on the placebo response itself may elucidate means by which the placebo response may be enhanced. Based on their findings of greater pain reduction associated with previous pairing with an active treatment than expectancy alone, for example, Voudouris et

al. (1990) suggest that when using placebos for pain reduction, placebo effects may be enhanced if there has been an initial pairing of the placebo with an active treatment.

Efforts to enhance the placebo response also could focus on the therapeutic relationship — what aspects, for instance, of this relationship are associated with the placebo response (Antonnucio, Burns, and Danton, 2002). Similarly, Kwekkeboom (1997) argues that a clinical setting of warmth, empathy, and interest in the patient can contribute to the placebo effect. The findings of Walsh et al. (2002) of an apparently increasing response rate to placebo in trials of depression requires further consideration for insight into the causes of this increase. Finally, therapeutic techniques that mobilize the expectation of clinical improvement associated with placebos but without the inherent deceptions of placebos need additional research. For example, the facilitation of a greater perception of personal efficacy on the part of the patient might lead to an improved clinical response.

Neurobiological Findings Associated with Placebo Response

Adding additional insights into the placebo response are offered by the neurobiological changes that may be associated with the placebo response, as, indeed, evidence suggests that at least some placebo effects are associated with specific neurobiological changes. Placebo caffeine, for example, is associated with blood pressure and psychomotor performance changes (Kirsch, 1997). Providing evidence of more specific neurobiological activity, placebo analgesia appears to activate the opioid system and can be blocked by the opiate antagonist naloxone (de la Fuente–Fernández and Stoessl, 2004) — findings that show the importance of the brain's pain-modulating pathways in the placebo response. The expectancy of a response itself can activate these pathways. Investigating, by positron emission tomography, brain regions involved in pain responses to an opiate and to a placebo, Petrovic, Kalso, Petersson, and Ingvar (2002) found similarly increased blood flow in opiate and placebo conditions in the anterior cingulate cortex. In addition, they observed increased blood flow in the orbitofrontal cortex to placebo and speculated that the orbitofrontal cortex may be one component of a neural system linking cognitive cues to the brain's opioid system.

Not all of the pain relief associated with placebo, however, is necessarily mediated by the opioid system. For example, after a dental procedure, placebo-associated pain reduction is not blocked by an infusion of the opioid antagonist naloxone, implying that mechanisms in addition to the opioid system may be involved in some placebo responses in pain (Gracely, Dubner, Wolskee, and Deeter, 1983). Similarly, dopamine and cholecystokinin also are associated with placebo analgesia (de le Fuente–Fernández and Stoessl,

2004), and thus placebos may elicit neurobiological changes in more than one brain system.

As noted above, patients with Parkinson's disease also respond to placebo. In contrast to the opiate activation observed with placebo analgesia, the improvement in motor function in Parkinson's disease from placebo is associated with increased dopamine in the striatum (de la Fuente–Fernández and Stoessl, 2004), mirroring effects that occur from dopamine-enhancing drugs that are used to treat Parkinson's disease.

Given the high placebo response rates associated with depression, surprisingly few studies are available that investigate the neurobiology of the placebo response to depression, possibly due in part to the lack of a unified theory of the biology of depression (Wong and Licinio, 2001). Nevertheless, an emerging but still tentative neurobiology is associated with the placebo response of depression. An important caveat to the interpretation of this nascent literature is that evidence suggests that there may be an advantage for drug treatment over placebo in the long-term treatment of depression as long as the subjects remain on medication (Mayberg, Silva, Brannan, Tekell, Mahurin, McGinnis, and Jerabek, 2002). Nevertheless, in a small (15 subjects completing the trial) study comparing brain metabolic changes in depressed participants in which 50% of the responders received fluoxetine and 50% placebo, similar patterns of clinical improvement and brain metabolic changes were seen in both drug and placebo responders. In the placebo responders, significant increases in metabolism were observed in the prefrontal and posterior cingulate cortex, among others, with decreases in metabolism occurring in the hypothalamus, among other regions. Similar findings were present in the fluoxetine responders, with the further findings of additional changes in brain metabolism in the drug group. The magnitude of metabolic changes also was greater in the fluoxetine responders compared to the placebo responders. It is unclear what the differences between placebo and drug mean, but they do not appear to be associated with adverse drug effects. Despite the differences observed between the placebo responders and the drug responders, the overall pattern of metabolic changes were still quite similar between the two groups, indicating, based on this preliminary evidence, that placebo response in depression elicits neurobiological changes similar to changes seen in fluoxetine responders, a finding that parallels the changes associated with the placebo response to pain and Parkinson's disease.

Alternatively, an additional study using quantitative electroencephalography to monitor brain function during treatment with venlafaxine, fluoxetine, or placebo in depression (52% of drug responders met criteria for response compared to 38% for placebo) found that the placebo responders showed different changes in brain function from those observed in the drug responders (Leuchter, Cook, Witte, Morgan, and Abrams, 2002). Specifically,

although both drug treatment and placebo affected the prefrontal cortex in responders, placebo increased prefrontal cordance [cordance is a quantitative electroencephalographic measure correlated with regional blood perfusion (Cook and Leuchter, 2001)] while drug treatment decreased cordance. The authors of this study emphasized that the placebo group showed significant neurobiological changes compared to baseline and compared to the drug group. Despite the uncertainties of the research concerning the neurobiological changes associated with placebo, the evidence strongly suggests that the placebo response is associated with significant changes in brain chemistry and function.

Implications of the Placebo Response

The placebo response in several conditions including major depression, the neurobiological changes associated with placebos, and the on-going debate over the proper use of placebos in clinical trials of major depression (Kupfer and Frank, 2002), point to the need for an enhanced understanding of the placebo phenomenon. At a minimum, the placebo response suggests a complex relationship between pathology (be it a medical disease or psychological disorder), the perception of symptoms such as pain or depression, the patient's prior experience with an active treatment, and the patient's expectations. Remarkably, placebos in some conditions may affect a condition's underlying pathology, as in the case of dopamine release in Parkinson's disease (de la Fuente–Fernández and Stoessl, 2004). In other cases, such as panic disorder (Baker, Khaykin et al., 2003), placebo may affect some of the manifestations of a disorder but not all. In other words, inert chemicals under certain conditions of patient expectation and previous experience with medications appear to activate specific neurobiological responses seen from the use of specific drugs, suggesting that expectation and other so-called non-specific factors have a tremendous impact on modifying neurobiological pathways, at least for some conditions. The neurobiological changes associated with analgesic placebo may be inconsistent with the assertion from the signal detection theory of placebo that no actual analgesia occurs.

Functional brain-imaging techniques enable a unique methodology for understanding the biological changes associated with the placebo effect. Carefully designed studies could demonstrate which non-specific factors are associated with which alterations in neurobiology and allow for additional comparisons with those changes elicited from active pharmacological interventions. A limiting factor in the study of neurobiological changes associated with the placebo response is simply the paucity of available studies. Although some evidence exists for associated neurobiological changes with the placebo

response in Parkinson's disease and even more for that of pain, the study of placebo-associated neurobiological changes in depression and anxiety is in its infancy, making it difficult to draw any conclusions with certainty. Additional studies similar to those of Leuchter et al. (2002) and Mayberg et al. (2002) detailing the neurobiological changes associated with the double-blind administration of a drug or placebo are necessary to better understand the placebo response. Similar work is indicated in trials of psychotherapy and placebo. Also, it is necessary to study whether placebo-driven changes in neurobiology are maintained or whether they are present only for limited periods and eventually diverge from changes produced pharmacologically. For example, the observation by Leuchter et al. (2002) that placebo responders in depression have increased prefrontal cordance while drug responders show decreased prefrontal cordance suggests that treatment response in depression may be associated with different neurobiological pathways. Moncrieff (2002) similarly suggested that treatment response in depression may not be through any one specific neurobiological modality, as many substances not considered antidepressants, such as antipsychotics and barbiturates, as well as psychotherapy, appear to have antidepressant efficacy. As such, the differential placebo response rate across some disorders (e.g., panic disorder and social anxiety disorder) and across time (e.g., the placebo drift observed in clinical trials of major depression) may provide additional insights into the placebo effect. What disorder-specific factors are associated with a high placebo response rate, and what factors could account for the placebo drift? Unfortunately, these issues have been little explored thus far.

The possible high rate of placebo response in conditions such as depression and some anxiety disorders requires careful consideration as to the nature of these disorders. Are these disorders that require a specific pharmacological intervention or do they represent a much more complex situation wherein they may respond at least in part to hope and expectation and thus require the instillation of such factors for optimum treatment? Because the phenomena of depression and anxiety have been classified as inherently biological, it is easy to see them as solely biological entities and ignore their other dimensions. The relatively high placebo response rate in depression and anxiety suggests that there are other aspects that require consideration for an enhanced understanding of these disorders. Similarly, although the portion of improvement in depression due to placebo effects may be lower than the 75% reported by Kirsch and Sapirstein (1998), any substantial clinical improvement due to placebo lessens the amount of improvement due to a drug and challenges the support that pharmacology provides to strictly medical interpretations of depression and anxiety. As the placebo response implies, other factors in addition to biology are relevant to treatment.

Despite the considerable limitations in placebo-response research, the finding that the placebo response is associated with specific neurobiological changes requires additional discussion. Brain plasticity can be conceived of as brain reorganization in response to injury and learning (Elbert and Rockstroh, 2004). In this context, the neurobiological changes associated with the placebo response, be they activation of opioid pathways due to pain, increased striatal dopamine in Parkinson's disease, or increased prefrontal metabolism in depression, could be understood in terms of brain plasticity in which specific neurobiological changes result from, in this case, the expectation and desire for change associated with placebo. The mental activity related to the expectation of and desire for change alone appear by mechanisms as yet undescribed to be capable of inducing tangible and measurable changes in brain function — in effect, neuroplasticity.

Moreover, viewing the placebo response as an aspect of brain plasticity has implications for the relationship between mind and brain. In this case, functions that can be considered mind are affecting the function of the brain, challenging the notion that mind is merely an epiphenomenon of brain (Schwartz and Begley, 2002) and pointing the way for novel methods of understanding the mind–brain relationship (see Slife and Hopkins, 2005 for an example). Another implication of the effects of placebo on brain function, as pointed out by Schwartz and Begley (2002) in the context of neuroplasticity driven by consciousness, is that thought can alter the physical function of the brain, ushering in volition as possibly a crucial factor in neurobiology. If neurobiological function indeed can be remodeled by expectation and desire, as appears to be the case in some conditions, it is possible also that treatment of certain conditions could use techniques that facilitate the mind's ability to affect the brain. The placebo effect, therefore, requires a new paradigm in which the facilitation of expectation and desire become integral to treatment.

Consistent with the hypothesis that the placebo response is a form of neuroplasticity, the placebo response could be viewed as increased attention on the part of patients to their own condition, similar to the proposed heightened attention associated with hypnotism (Rossi, 2000). In the case of placebo though, the increased attention is elicited by the clinician, the placebo, and the expectation and desire for change, and not of course from the hypnotic process. However, the process of hypnosis and the expectation of placebo may be similar to each other in the generation and focus of attention. Such an hypothesized similarity between the placebo response and hypnosis may provide additional avenues for placebo research by suggesting methods that are independent of the deception inherent in the use of placebos.

Conclusion

To conclude, the placebo response appears to occur across a variety of clinical conditions and seems to depend upon expectation to elicit its effects. Findings of neurobiological changes that mirror, to some extent, those changes associated with active medication place the placebo phenomenon well within the context of not only psychotherapy and neuroscience but also that of understanding the relation between mind and brain. Far from an embarrassing finding to be swept away with hushed discussions of effect sizes, power, and statistical significance, the placebo effect, as pointed out by Kupfer and Frank (2002) "may be nature's way of providing clues to fundamental aspects of the healing process . . ." (p. 1854) and integral to a comprehensive understanding of disorder and disease.

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