

Review

Motivation and placebos: do different mechanisms occur in different contexts?

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This paper challenges the common assumption that the mechanisms underlying short-term placebo paradigms (where there is no motivation for health improvement) and long-term placebo paradigms (where patients value improvement in their health) are the same. Three types of motivational theory are reviewed: (i) classical placebo motivation theory that the placebo response results from the desire for therapeutic improvement; (ii) goal activation model that expectancy-driven placebo responses are enhanced when the placebo response satisfies an activated goal; and (iii) motivational concordance model that the placebo response is the consequence of concordance between the placebo ritual and significant intrinsic motives. It is suggested that current data are consistent with the following theory: response expectancy, conditioning and goal activation are responsible for short-term placebo effects but long-term therapeutic change is achieved through the effects of goal satisfaction and affect on the inflammatory response system and hypothalamic–pituitary–adrenal axis. Empirical predictions of this new theory are outlined, including ways in which placebo effects can be combined with other psychologically mediated effects on short-term and long-term psychological and physiological state.

Keywords: placebo; motivation; clinical; expectancy; psychoneuroimmunology; review

1. INTRODUCTION

Response expectancy theory [1] is the dominant theory in placebo research but conditioning effects have also been demonstrated. Response expectancy and conditioning explanations have the same logical structure as that of the conditional ‘if–then’ [2]. To illustrate, *if* this cream is analgesic *then* there will be less pain; *if* this is an asthma bronchodilator, *then* there will be less bronchoconstriction. In the case of response expectancy, the conditional is represented in consciousness and can be communicated by others. In the case of conditioning theory, the conditional is not represented in consciousness and is achieved through direct experience. Numerous studies show that either type of conditional, but particularly those that are consciously mediated, lead to placebo responses [2].

According to the original author of the response expectancy theory, the relationship between expectations and physiological response is unmediated [1] (e.g. not mediated via affect or other physiological response). In a later paper, he suggested that expectation was a parallel and complementary description of an underlying biological event [3]. According to this interpretation, expectations are a form of biological information.

Motivation has been a small but recurrent concept in the history of placebo research. The aim of this paper is, first, to examine three perspectives in which motivation features in placebo research: (i) classical

placebo motivation theory; (ii) goal activation model; and (iii) motivational concordance model. A second aim is to provide a critical evaluation of a common though largely unstated assumption that placebo mechanisms are the same in short-term and long-term placebo contexts. This paper begins with a brief description of motivation theory and its relationship with biological processes relevant to health.

2. MOTIVATION THEORY

Motivation is a psychological construct that is used to explain behaviours that are energized and directed towards a goal. The logical structure of motivational concepts can be represented by a negative feedback or control loop [4] and the several different motivational theories can all be represented in terms of the components of a control system [5]. In a control system, a reference criterion is compared with a perceptual input at a comparator, and the difference activates a behavioural output. The behavioural output then alters the environment which has consequences for the perceptual input. The reference criterion of the control system is analogous to the concept of goal, motive or value that features in motivation theories, and provides the direction for goal-oriented behaviour. The energizing of behaviour is the consequence of the gain (or amplification factor) round the control loop. The words *goal*, *motive* and *value* are used in different motivational theories but are equivalent to the extent that they all refer to a reference criterion.

Expectancy \times value theory is a well-established motivation theory [6]. Expectancy \times value theory

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shows that motivation to perform a task is a function of two variables: expectancy of success and the value of success, where motivation is enhanced by positive expectancies and positively valued outcomes. In this theory, expectancy is a conditional ('if-then') that provides information about the optimum way of achieving a goal. Goals are more easily achieved if expectations of success are high. From a control theory perspective, expectancy influences the way lower level goals are selected to achieve higher level goals. To illustrate, if a person has the higher level goal of 'being happy', then they will engage in daily activities (i.e. lower level goals) only to the extent that they expect those daily activities to make them happy. They will avoid activities that they believe will lead to unhappiness. In sum, expectancy features in motivation theories as a form of information that alters goal-seeking behaviour.

Motivation theorists distinguish between different types of goals, where the goals are hierarchically related. The higher level goals are sometimes referred to as self-defining goals, self-determining goals, values or intrinsic motives [7–9]. Theories of intrinsic motivation focus on the satisfaction of these higher level goals. Lower level goals serve to satisfy the higher level goals, and these lower level goals motivate behaviour to the extent that they are perceived (i.e. expected) to satisfy higher level goals. So, for example, people earn money not because they think money is intrinsically valuable, but because money is perceived to achieve what is intrinsically valuable—such as happiness. Intrinsic motivation refers to the value of engaging in the task for its own sake. For example, an artist paints a picture just for the enjoyment of painting. Extrinsic motivation refers to external valued outcomes that come from performing the task. For example, the artist paints a picture so as to sell it and make money. Money has no intrinsic value, but is valued for what it brings: the ability of the artist to do what he or she likes, namely paint pictures.

Although the biological structure of some motives (i.e. the control loops) are known (e.g. thirst and hunger), those relating to self-defining goals are not, though it is likely they are distributed in the cortex. Nevertheless, modern motivation theories, such as self-determination theory [8], assume that people are biologically predisposed to achieve self-defining goals such as good interpersonal relationships and control of their environment.

Not only are different motives, goals or values associated with intrinsic and extrinsic motivation, but so are different types of expectancy. These differences can be illustrated when the idea of intrinsic and extrinsic motivation is applied to the performance of therapeutic rituals—i.e. the paradigms in which placebo effects are investigated. First, there is *expectancy of health improvement* and the *value of health improvement*. Taken together, these two variables predict the *extrinsic* motivation to engage in a therapeutic task. Not surprisingly, people are more likely to engage in health-promoting behaviour if they expect it to help and they value the help that the behaviour can bring. The expectancy of health improvement can be labelled *response expectancy* as it is this type of expectancy that features in response expectancy theory.

The value of health improvement is not the only extrinsic motivator to engage in therapy—or an experimental task. Money, course credit or to please relatives comprise other extrinsic motivators for engaging in tasks. In these cases, however, expectancy represents a different kind of conditional, e.g. *if I take part, then I will earn money*.

Second, there is the *intrinsic value* of the therapeutic task, and the *expectancy that carrying out the task has intrinsic value*. Again, value and expectancy predict the motivation to engage in a task, but in this case the person is intrinsically motivated to engage in the therapeutic task for its own sake, not because of the health benefits that it brings. In this second instance, the meaning of expectancy is different from response expectancy, and will therefore be called *value expectancy*. Furthermore, *task value* (the intrinsic value of the task) will be distinguished from *outcome value* (the value of the health improvement).

Four points should be noted in relation to the above. First, task value and outcome value vary between different placebo paradigms. Short-term laboratory studies are commonly carried out on student participants who do not report health problems. For example, a placebo pain study might involve inducing pain via a pain stimulator and then observing the effect of the placebo cream. In this study, the student participants are not ill and have not attended for health improvement. Thus, outcome value is small. In addition, they have not attended because they enjoy taking part in psychology studies—typically they attend for course credit or for money. Consequently, task value is also small. Compare such a placebo pain study with the placebo arm of a clinical trial where patients hope the treatment will improve their clinical condition. In a clinical trial, outcome value is high and, depending on whether the study is enjoyable or not, task value may also be high. Patients are more likely to enjoy taking part in the clinical trial if the doctors and nurses are friendly and if the patient is made to feel important. Thus, the values, and consequently the motivation of placebo responding depends crucially on the nature of the paradigm used, and it is therefore reasonable to expect that motivational mechanisms vary between paradigms.

The second point concerns the relationship between the intrinsic value of the therapeutic task, i.e. task value, and the expectancy that the task will have therapeutic benefit, i.e. response expectancy. Tasks that have intrinsic value tend to be perceived as effective. In a study where participants rated therapy vignettes and completed a value survey scale, participants rated a therapy as being more effective if the motivational features of the therapy were related to the individual's own motives [10]. The correlation between response expectancy and task value can be high. Correlations between expectancy of outcome and dispositions that are concordant with the therapy have been shown to vary between 0.39 and 0.58 [11–13]. Therefore, an observed correlation between response expectancy and outcome may be due to a causal relation between task value and outcome, rather than between response expectancy and outcome.

The third point concerns the biological consequences of either achieving or not achieving goal

satisfaction. Theory and research in motivation consistently show that improvements to mental and physical health are gained from goal satisfaction [14–19]. Goal satisfaction is associated with improved affect, which is associated with lower activation of the hypothalamic–pituitary–adrenal (HPA) axis and inflammatory response system [20]. Most major diseases involve an inflammatory component. As goal satisfaction/positive affect is associated with lower levels of non-specific inflammation, goal satisfaction is associated with a reduced predisposition to develop disease [21].

Fourth, theory and research [8] show that it is satisfaction of the higher level, intrinsic or self-determining goals in contrast to the lower, extrinsic goals that lead to happiness, and hence via known mechanisms of psychoneuroimmunology to better health. Indeed, high aspirations and expectancy of material gain (i.e. extrinsic motives) can be associated with lower levels of well-being [22], though there are circumstances under which satisfaction of extrinsic goals can lead to greater happiness [23].

In summary, the relationship between psychological state and somatic disease development has been widely researched in the field of psychoneuroimmunology and elsewhere. There are anticipated psychological and physiological consequences of either achieving or failing to achieve goal satisfaction, particularly those relating to the higher, self-determining goals.

3. CLASSICAL PLACEBO MOTIVATION THEORY

An early hypothesis for the placebo effect was that people who are motivated to get well are more likely to do so. The origin of this hypothesis is not documented but it probably owes its origins to general assumptions about the relationship between positivity and health. No specific mechanism was suggested. In an early study, Totman [24] gave a placebo analgesic ‘injection’ (actually a pin prick), to two groups of participants, one that was paid and the other not paid for participation. On the basis of cognitive dissonance theory, Totman reasoned that those who were not paid to take part would have a greater discrepancy between their cognitions and their behaviour of receiving an injection and so would be more motivated to demonstrate a placebo effect. These predictions were confirmed: those not paid money exhibited a stronger placebo effect. In a later study, Jensen & Karoly [25] manipulated motivation by providing participants with descriptions of two types of personality types, A and B, and where type B was more attractive than type A. Participants in the enhanced motivation condition were told that type B people were more likely to respond to a ‘sedative’ placebo pill, whereas those in the control condition were told that the relationship between personality type and ‘sedative’ response was weak. A manipulation check showed that those in the first group were more motivated to respond. The results showed that the motivation manipulation had a significant effect on outcome in the predicted direction. A similar motivational manipulation was used by Aletky & Carlin [26] except that participants in the motivation condition were informed that their response to a placebo jelly purporting to relieve muscle fatigue indicated good health and

normal muscle tonus. However, although females exhibited the predicted effect of motivation, males did not. On the contrary, males in the motivation-enhanced condition exhibited a reduction in response in the post-treatment condition, indicating that the placebo response was reduced by the manipulation. In a placebo analgesia paradigm, Price *et al.* [27] manipulated the level of desire for pain relief by instructing participants that the pain they receive would either be difficult to endure if the analgesic was not working (high motivation), or of a moderate level and no more than previously experienced (low motivation). The authors also manipulated expectancy by labelling the (placebo) analgesic cream as either being a strong or weak solution. The results showed that expectancy but not desire for pain relief predicted the magnitude of placebo pain relief.

These limited numbers of studies lead to different conclusions: although Price *et al.* [27] found no evidence for an effect of motivation (outcome value) on placebo response, significant effects were obtained by Totman [24] and Jensen & Karoly [25]. The results obtained by Aletky & Carlin [26] provide evidence of a significant effect of sex on the results and sex \times motivation \times placebo interaction. It is possible that the difference in results between these studies is due to differences in the motivational manipulation, or differences in the way the motivational manipulation is perceived by males and females. However, in none of these laboratory analogue studies was there any genuine desire for therapeutic benefit. Clinical trials where patient desire for improvement (outcome value) and expectancy of benefit (response expectancy) are measured independently indicate that both response expectancy and outcome value predict better response [28–30].

4. GOAL ACTIVATION MODEL

The goal activation model [31] of placebo responding is based on the hypothesis that response to expectancy induced placebos is enhanced if that response satisfies other goals. In five studies, participants were divided into two groups [31]. One group was given a cooperative prime, which would therefore enhance the motivation to cooperate. The cooperative prime was achieved by asking participants to engage in a task that involved presentation of terms such as cooperate, helpful and assist. The other group engaged in the same task except that other non-cooperative words were used. After priming, both groups were exposed to a placebo or neutral procedure (i.e. expectancy inducing versus not inducing) and outcome measured. In the series of studies, the researchers varied the type and duration of the placebo procedure (including a laboratory study where participants were told that a caffeine pill would produce a physiological response and an overnight study where participants were told that a mental task before going to bed would improve sleep quality), type of outcome measure (including subjective symptoms and blood pressure), and the method of cooperation priming and expectancy manipulation. The authors demonstrated that unconscious goal activation (i.e. the cooperative prime) moderated the expectancy-induced placebo effect. Geers *et al.* [31] argue that ‘although

expectations are an important determinant of the placebo effect, an individual's currently active goals drives the extent to which the placebo expectation affects somatic experience. If a compatible goal is associated with the placebo expectation, then an individual will extensively engage in processing and behavioral strategies that are likely to yield a placebo effect' (p. 145).

The findings showed that although the cooperative prime enhanced placebo responding, it only did so when there was an expectation of change. Where no expectation was induced, then the cooperative prime did not have an effect. Thus, the goal activation model preserves the idea that expectancy (i.e. response expectancy) drives the placebo response, but adds the idea that this expectancy-driven response is enhanced when the response leads to the satisfaction of other goals. In these studies, the cooperation goal which was enhanced, unconsciously, through the use of priming procedure was consistent with the placebo response and therefore enhanced the placebo response. According to the goal activation model, motivation is important, not because people want to get better, but because responding to an expectation can, under specific circumstances, satisfy currently active goals. Of course, if the currently active goal is to get better, then the goal activation model makes the same prediction as the classical placebo theory: people who are more motivated to improve their health should do so.

5. COMMENT: CLASSICAL PLACEBO MOTIVATION THEORY VERSUS GOAL ACTIVATION

In the laboratory analogue classical placebo studies, the motive for placebo response improvement was linked to other motives: to have a good personality [25], to be healthy [26] or to avoid cognitive dissonance caused by non-payment for taking part in the study [24]. These paradigms therefore share features in common with the paradigm used to support goal activation theory [31], where the placebo response was linked to cooperation. It is therefore unclear whether the introduction of 'other goals' into the paradigm has its effect by increasing motivation for health improvement (classical theory) or because the placebo response is enhanced due to satisfaction of other goals (goal activation). Thus, the results supporting the classical theory can also be explained in terms of the goal activation theory.

6. MOTIVATIONAL CONCORDANCE

Although the goal activation model incorporates the dominant view of response expectancy, the motivational concordance model proposes an alternative to the response expectancy and extrinsic motivation framework. The motivational concordance model derives from research on human motivation showing that the satisfaction of goals, and in particular those goals that are important or self-defining, lead to positive changes in mood. Hyland *et al.* [12] write 'engaging in health-promoting rituals that enhance self-defining or self-actualizing goals provides better outcomes when compared to health-promoting rituals that are not' (p. 332).

In a series of three studies [11–13], advertisements were placed on a university campus and the Internet, advertising free flower essences in return for questionnaire completion. Flower essences can be purchased in pharmacies and on the Internet and purport to treat a variety of minor mental problems, ranging from depression and fatigue through to an excessive tendency to agree with others. Publically available literature, which was made available to participants, suggests that flower essences work through some form of vibrational energy—i.e. a spiritual contextualization of the underlying mechanism. Flower essences are a homoeopathic-like preparation in that they contain no active pharmacological ingredients and have been shown to be no different from placebo [32].

In all three studies, expectancy and dispositional spirituality were measured at baseline, then participants selected their flower essences or essences from a list, and finally improvement in symptoms were measured after three or four weeks. The studies differed in the measures of expectancy and spirituality, the nature and frequency of outcome assessment and the way the flower essences were described. In all three studies, expectancy and dispositional spirituality correlated with outcome.

Because expectancy and task value are correlated, the authors tested whether expectancy or spirituality predicted outcome independently of each other. When added simultaneously into a multiple regression, spirituality but not expectancy predicted outcome in two studies [11,12], and in the third study [13] expectancy failed to predict outcome when effort was added into the multiple regression, but spirituality predicted independently of expectancy and effort. These results suggest that it is not the cognitive factor of expectancy that is having an effect on mood improvement, but rather the behaviour of engaging in an intrinsically satisfying activity. People respond to placebo therapies when the placebo ritual is concordant with the person's motives.

In order to demonstrate that it was the meaning of flower essences that was responsible for the correlation with spirituality, in their final study [13], the researchers varied the meaning of the therapy. Those in the 'spiritual' group were given the written instruction: 'flower essences work best if, while you are taking them, you imagine the essence connecting you to a universal pool of healing and life'. Those in the affirmation group were told: 'flower essences work best if, while you are taking them, you imagine them helping you solve your problems'. Data were collected at seven time points over the next 21 days using an automatic telephone system with verbal questions and keypad response. At the end of each data collection point (i.e. on seven different days), participants were told 'Remember, flower essences work best, if while you are taking them, you imagine—followed by the group specific instruction'. There was also a 'neutral' group with no additional description of flower essences. After accounting for expectancy, the beta of spirituality predicting outcome for the three groups was 0.35 ($p = 0.01$) in the spiritual group, 0.23 ($p = 0.06$) for the neutral group and -0.27 ($p = 0.03$) for the affirmation group. When flower essences were described in an explicitly non-spiritual manner, then the association between spirituality

and outcome, after controlling for expectancy, was actually negative.

7. COMMENT: MOTIVATIONAL CONCORDANCE VERSUS OTHER MOTIVATIONAL THEORIES

There are several possible motives to take part in the flower essence studies (e.g. to improve mood, because it was a cheap deal, or because it seemed a nice thing to do) but these reasons are different from those studies which report that participant recruitment was based on course credit [27,31]. A second distinguishing feature of the motivational concordance studies was that they were of a longer duration, lasting either three or four weeks. The significance of this time difference is clear from the data in the final flower essence study [13], where data were collected at various time points over a period of three weeks. Mood/symptom change after taking flower essence was not immediate. Instead, there was a gradual improvement asymptoting after about 7 days.

The differences in design and findings between the motivational concordance and other studies should alert researchers to the possibility that mechanisms are context-dependent. The importance of context is illustrated by research on the personality of the placebo responder. There is a long history of research trying to establish the nature of a placebo responder. What is notable about this research is not so much the failure to identify a placebo responder, but rather that some studies show significant and sometimes substantial correlations between personality and placebo outcome but these findings are not replicated [33]. A recent example of this inconsistency is found in research from two different research groups, using different research paradigms. Geers *et al.* [34] have found that optimism predicts placebo responding. This correlation can be explained in terms of response expectancy theory: people who are optimistic are more likely to form positive expectancies of outcome, or fail to develop negative expectancies in nocebo contexts. By contrast, in their studies, Hyland and colleagues [12,13] found no evidence of a correlation between optimism and long-term response to a placebo therapy. Thus, although there is no evidence of a generic placebo responding personality, there is evidence of context-specific placebo responding personalities, and hence, by implication, context-specific mechanisms. The research on optimism suggests that response expectancy is less important for long-term therapeutic change.

8. INTEGRATION AND EXPLANATION

There are two approaches to inconsistent research findings. One is to assume that the inconsistencies reflect random variation. A sensible response, therefore, is to conduct a meta-analysis so as to average out the differences between studies. The other is to assume that inconsistencies are due to differences in methodology. If that were the case, a sensible response would be to develop a theoretical rationale that will explain differences between studies. The latter approach is taken in this paper. Existing data are consistent with the hypothesis that placebo responding mechanisms

are context-specific. That is, they are consistent with the hypothesis that the mechanisms occurring in laboratory analogue studies are different from those in long-term therapeutic studies.

9. MECHANISMS IN SHORT-TERM PLACEBO PARADIGMS

The body responds to external events. Under most circumstances, this response is functionally appropriate to those external events, and includes psychological and physiological adjustments to psychologically and biologically mediated inputs. The experience of pain provides an example of a psychologically mediated adjustment. Physical assault causes the psychological experience of pain and which then leads to pain-avoiding behaviour. However, the experience of pain is moderated by other psychological factors, including distraction, coping, mood and expectancy, that make the pain response more appropriate for the current situation. Pain is a psychologically moderated experience. Pain theory shows that pain experience is an output from a neuromatrix that has multiple psychological and physiological inputs, including attention and cultural factors [35]. Short-term placebo pain response can therefore be understood within this standard theory: Expectancy is another input into the neuromatrix. The similarity between placebo pain effects and other psychologically moderated pain effects is supported by research showing that both involve endogenous opioids. In a study of psychological determinants of pain perception, cognitive coping training reduced pain perception but the effect of cognitive training was reduced by the endorphin antagonist, naloxone [36]. Expectancy mediated pain reduction is also mediated by endogenous opioids, and the placebo effect reduced by naloxone [37]. Thus, several different psychological moderators of pain perception employ, in part, the same mechanism, namely, endogenous opioids.

Short-term placebo responses occur not only for psychological responses, such as pain, but also for physiological responses. The placebo response to asthma inhalers provides a useful example of a short-term physiological placebo response [38]. Bronchodilators cause short-term relaxation of the airways that counteract the bronchoconstriction which in asthma is an exaggerated but otherwise normal response to respiratory irritants. Placebo bronchodilator inhalers have a similar but weaker bronchodilator effect when compared with the active drug. However, bronchoconstriction–bronchodilation is also affected by a variety of other psychological factors, including mood [39]. The effect of expectancy on bronchoconstriction is not a unique effect of psychological state on physiology, but one of several different ways in which mental state leads to changes in physiological adaptation, in the case of asthma mediated via the vagal nerve. The adaptation is temporary. Neither the active bronchodilator nor the placebo, nor temporary mood change produces any long-term therapeutic benefit. In both cases there is a temporary change in respiratory function but no change in the underlying inflammatory disease.

In sum, external events are *interpreted* and the interpretation of these events then leads to psychological

and physiological states that are appropriate for that state. According to the present theory, expectancy is just one of several psychological moderators of psychologically mediated physiological and psychological responses that are exhibited in short-term paradigms. The goal activation model demonstrates yet another psychological factor that alters symptom perception and psychological response: people show short-term responses in accordance with their activated goals. This explanation is consistent with the original suggestion that the effect of expectations on physiology is unmediated [1]: the expectation is just one type of biological information.

10. MECHANISMS IN LONG-TERM PLACEBO PARADIGMS

There are several lines of evidence which suggest that the mechanisms underlying long-term placebo change are different from those in short-term studies, and where the latter mechanism is response expectancy. First, expectancy does not predict outcome independently of motivational variables in the clinically relevant, long-term flower essence studies [11–13]. Second optimism predicts outcome in short-term [34], but not long-term studies [12,13], again suggesting that response expectancy is not involved in long-term studies. A contrary argument is that there are several clinical trials where expectancy does predict outcome. However, these results can be explained in terms of motivational concordance: people who expect to get better do so because they place more intrinsic value on the task. Third, in laboratory analogue studies, the placebo effect is rapid and certainly in less than a day. By contrast, outcome in the flower essence studies was gradual—there was little change on the first day after treatment but symptoms gradually improved over the following 7 days [13]. Gradual improvement is also observed in contextual therapies such as massage therapy [40] and also in psychotherapy [41].

In addition to the psychological data cited above, there is physiological evidence that placebo effects in long-term, clinically relevant, contexts involve a different mechanism from those in short-term studies. A study in response to placebo analgesia for pain in irritable bowel syndrome (IBS) showed that psychological factors including desire and expectation affected placebo response, but these responses were not mediated via an endogenous opioid mechanism—i.e. responses were unaffected by naloxone [29]. This finding contrasts with studies where endogenous opioids are shown to be in part responsible for psychologically mediated short-term effects for placebo and psychologically coping pain reduction [36,37]. The authors of this IBS study [29] conclude that the mechanism of pain relief in their clinically relevant study was emotionally mediated, which is consistent with the motivational concordance explanation.

Finally, good clinician–patient relationships are central to the outcome in psychotherapy [41], and, as suggested by self-determination theory [8], the satisfaction of relationship goals is therapeutic. However, an enhanced physician encounter in a laboratory-based placebo bronchodilator study [38] failed to affect

placebo outcome when compared with a physician who was not overtly socially supportive. Thus, the affective bond influences the outcome for long-term therapeutic change but not short-term placebo change. Consistent with the idea that emotional factors are important for long-term therapeutic change, a supportive physician versus non-supportive physician contact reduced medically unexplained symptoms in a long-term, clinical context. However, treatment versus no treatment made no difference to the outcome in this study [42]. As treatment leads to expectancy of improvement, this clinically relevant study suggests that long-term effects are not driven by expectancy—but they are by the emotion generated by an affective bond.

11. THE THEORY THAT PLACEBO MECHANISMS ARE CONTEXT-SPECIFIC

Existing data are consistent with the following new theory. Short-term placebo effects, such as those observed in the laboratory analogue studies, are due to biologically encoded information of the conditional ‘if–then.’ This information is *either* associated with expectations that are conscious, such expectations being influenced by external, psychologically mediated information (i.e. response expectancy theory); *or* the information is represented in a form resulting from direct experience without conscious involvement. In either case, the conditional information is combined with other (biologically encoded) information responsible either for symptom perception or physiological response. The idea of a neuromatrix, suggested in pain theory, is consistent with the additional hypothesis that the various sorts of information are combined through a system that has an underlying network structure and hence is capable of ‘problem-solving’. If the idea of a neuromatrix or network has wider application, then the body is well suited to combining the several different kinds of information that lead either to symptom perception or physiological response, as networks are particularly suited to ‘soft’ decision-making [43]. Along with other incoming information, when the situation described in the ‘if’ of the conditional occurs, then the problem-solving response is that appropriate to the situation. For example, if there is to be less pain, then the appropriate response is that there is less pain. Motivation is not important to this short-term response except insofar as activated motives are relevant to adjustment to the current situations. Social modelling effects demonstrated in nocebo studies provide yet another way in which information is used to produce an adjustment to the current situation [44].

Long-term placebo effects in clinically relevant contexts are the result of motivational processes established elsewhere in motivation research and psychoneuroimmunology. Motivational concordance is the application of self-determination theory and theories of intrinsic motivation to the placebo context. However, although intrinsic motives are the main determinants of improved affect, other extrinsic motives (e.g. the desire for health benefit) may also play a role, though mediated through affect (e.g. hope). In addition, cognitive appraisals have behavioural consequences [45] and it is these

behavioural consequences that have an effect on long-term placebo outcome. The effect of motivational-affective mechanisms on physiology is the same as those identified in psychoneuroimmunology: the satisfaction of higher level goals in particular has affective and immunological consequences. Specifically, well-being achieved through goal satisfaction leads to reduced activation of the inflammatory response system and reduced HPA axis activation [18,19].

Although this theory is plausible and consistent with the existing data, further corroboration is needed through empirical predictions deduced from the theory. The next section provides some of these predictions and new research directions. New theories can also be evaluated in terms of their logical relationship with other theories. Recent research has focused on the special properties conferred on systems that have network structures [43]. It is also possible that the whole body and not just the brain functions as a network system [46]. Networks have the properties of problem-solving and of learning—the former a rapid response and the latter a comparatively slower one [43]. Mechanisms of placebo response in short-term laboratory studies as described above correspond to a network problem-solving response. The psychoneuroimmunological mechanisms of long-term benefit as described above correspond to network learning or self-organizational change. Thus, the distinction between short-term non-therapeutic change and long-term therapeutic change is consistent with network theory [46].

12. EMPIRICAL PREDICTIONS

(a) *Laboratory analogue studies*

The theory presented predicts that the effect of a placebo manipulation on physiological outcome will vary with the extent to which that physiological outcome is affected by other forms of psychological influence (e.g. relaxation, stress). For example, heart rate and blood pressure are homeodynamically controlled variables (i.e. where the reference criterion varies with external conditions) that are influenced by psychological state. Such homeodynamic variables should exhibit greater placebo effects compared with homeostatic variables, such as blood glucose, that are normally unaffected by psychological state. A more specific prediction can be made for bronchodilator response in asthma. Most people with asthma report a worsening of symptoms with triggers, and where the trigger can be due to psychological stress. Those patients reporting psychological triggers should exhibit a greater placebo response than those who do not report psychological state to be a trigger. Psychological triggers are reported by some but not all patients of many chronic diseases (IBS, gastro-oesophageal reflux, multiple sclerosis), so the same prediction of increased placebo response in this subset of patients (i.e. those susceptible to psychological triggers) applies across several diseases. People whose symptoms worsen with psychological triggers should be particularly prone to placebo effects on those—and only those—particular triggers.

If, as suggested here, short-term placebo effects are part of the normal response made by the body for

symptom perception and physiological response, then it would be useful to examine how the body combines different forms of information. Possible research questions include: how does expectancy of pain reduction combine with other psychological manipulations (e.g. distraction or efficacy training)? How does the asthma placebo bronchodilator response combine with other psychologically mediated effects such as mood or with physiologically mediated effects such as an airway irritant. In the absence of any theory of how different types of information are combined, such research would be inductive, at least in the first instance.

(b) *Long-term clinically relevant studies*

According to the theory described above, long-term placebo effects should be mediated by changes to the inflammatory response system and HPA axis brought about by the satisfaction of (mainly) intrinsically important goals. The immune system and psychological states of depression and fatigue are closely related [17,18], and therefore placebos should produce long-term therapeutic benefit for those patients' depression or fatigue. By contrast, there should be minimal long-term placebo effects for diseases that are little influenced by psychological treatments. Attention-deficit/hyperactivity disorder (ADHD) is comparatively insensitive to psychological treatment. In a large pragmatic study, standard community care (of whom 67% received medication) was compared with three treatment strategies that had additional interventions: medication management (involving accurate titration of dose), behavioural management (including a parent-child training camp) and the combination of the last two. The combined treatment was no better than medication management for core ADHD symptoms and nor was the behavioural management compared with the standard community care [47]. Behavioural management did have a small advantage compared with community care on non-core ADHD symptoms, and the benefit of behavioural management was stronger in that subgroup of patients where ADHD was combined with anxiety [48]. These results suggest that the placebo effect in ADHD should be considerably smaller than that of depression and that it should affect primarily the non-core rather than core symptoms.

Although activation of the inflammatory response system is a precursor to major disease, a reduction in non-specific inflammation may not reverse the established disease processes. The theory therefore predicts that long-term placebo effects on physiological morbidity are limited to the extent that disease processes are altered by changes in non-specific inflammatory mediators. Placebo effects on physiological morbidity should be greater in those diseases that exhibit spontaneous remission (Crohn's disease, hypertension) versus those that typically do not (cancer, heart disease), as it is likely that the former are more easily influenced by lifestyle-induced reductions in non-specific inflammation. Meta-analysis of psychological interventions for heart disease suggests that psychological interventions have only a limited influence on mortality for heart disease unless linked with exercise [49]. A systematic review of psychological interventions for

cancer shows that, despite early promise, there is also little evidence of an effect of psychology beyond its effect on clinical management [50]. Nevertheless, a recent study [51] shows that early palliative care for newly diagnosed lung cancer can lead to an increase in survival, which leads to the possibility that it is not so much psychological techniques that are important (to inflammation and hence disease progression) but rather the supportive milieu provided by caring therapists—i.e. a milieu sometimes found in clinical trials. This possibility is consistent with other data showing that it is the therapeutic context (therapeutic bond and engagement with the ritual) rather than the techniques that are important for the outcome in psychotherapy [41].

Estimates of long-term placebo effects obtained by comparing the placebo arm of a clinical trial with natural history should be treated with caution, as such comparisons can confuse true placebo effects with trial effects. Trial effects are biologically mediated effects that occur due to changes in behaviour with regard to preventive medication. For example, in an asthma clinical trial, patients might be randomized to receive an active treatment or placebo, but are commonly maintained on open label preventive treatment (typically an inhaled corticosteroid). As adherence to preventive medicine is low (in asthma about 50%) [52], patients who enter a clinical trial are likely to increase adherence to the open label preventer, leading to biologically mediated improvement in respiratory function.

In addition to trial effects, clinical trials involve a variety of psychological effects on patients beyond that of response expectancy. Positive expectations coupled with the desire for benefit lead to the positive affect of hope; clinical trials involve increased clinician/researcher contact and so help satisfy patients' relationship goals; patients who take part in clinical trials may find intrinsic satisfaction from taking part in important scientific research. In sum, clinical trials, both for the placebo and the active treatment provide a therapeutic milieu which can have biological consequences. The psychology of a clinical trial is more than expectancy, and as this therapeutic milieu is likely to vary between clinical settings, it comes as no surprise that, in multi-centre clinical trials, significant differences between centres are sometimes reported for the placebo arm [53].

13. FUTURE RESEARCH WITH LONG-TERM PLACEBO EFFECTS

Differences in the size of the placebo effect are found between different research centres in multi-centre trials [53]. In addition, the size of the placebo effect in depression studies is highly correlated with the effect size of the active treatment, indicating that placebo effects vary systematically between studies [54]. These results suggest that long-term placebo effects are not constant: They vary as a function of their context. They can therefore be considered a form of contextual or non-specific therapy [41] but where the effectiveness of the context varies. Not all placebos are equal! Several questions remain to be answered. First, what are the characteristics of the context that best promote this long-term therapeutic effect? This question can be investigated in a clinical trial by

varying the context (e.g. enhancing the intrinsic enjoyment of the study) and measuring desire for health improvement and expectancy at baseline and enjoyment shortly after the start of the study, and using these measures as predictors of outcome. Second, do contexts interact with people and diseases? This second question is an extension of the first, but with an emphasis on individual differences and disease differences. Third, can long-term placebo effects be explained in terms of changes in inflammatory mediators? The theory predicts that placebo responses on physical parameters will be greatest for people or diseases with high psychological comorbidity—because such people or diseases have greater scope for reduction in non-specific inflammation. By understanding the answers to these questions, it may be possible to develop placebo therapy so as to become a more effective form of therapy, namely, one which alters the underlying physiology of the body through psychological inputs and lifestyle.

14. CONCLUSIONS

Placebo research to date is largely influenced by a common assumption: The same mechanisms occur in short-term laboratory analogue studies as they do in long-term clinical contexts. This paper has set out an alternative: psychological inputs are biologically encoded and are used in two ways (i) short-term adjustment to the current situation and where relevant inputs include but are not limited to expectancy; (ii) long-term changes that involve mechanisms encountered in the field of psychoneuroimmunology. Both short- and long-term placebo effects need to be placed within a more general theory of the short-term and long-term effects of psychological inputs into a biological system.

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