Toward Understanding the Placebo Effect: Investigating a Possible Retrocausal Factor

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ABSTRACT

Objective: Conventional models of placebo effects assume that all mind–body responses associated with expectation can be explained by ordinary causal processes. This experiment tested whether some placebo effects may also involve retrocausal, or time-reversed, influences.

Design: Slow cortical potentials in the brain were monitored while adult volunteers anticipated either a flash of light or no flash, selected with equal probability by a noise-based random number generator. Data were collected in individual sessions of 100 trials, contributed by 13 female and 7 male adult participants.

Outcome measures: Ensemble median slow cortical potentials 1 second prior to a light flash were compared with the same measures prior to no flash. A nonparametric randomized permutation technique was used to statistically assess the observed difference. Electroencephalographic data were analyzed separately by gender.

Results: Females' slow cortical potentials significantly differentiated before stimulus onset ($z = 2.72$, $p = 0.007$, two-tailed); males showed a suggestive effect in the opposite direction ($z = -1.64$, $p = 0.10$, two-tailed). Examination of alternative explanations indicated that the significant effect in females was not caused by anticipatory strategies, equipment or environmental artifacts, or violation of statistical assumptions.

Conclusions: This experiment, in accordance with previous studies showing similar, unconscious "presentiment" effects in humans, suggests that comprehensive models seeking to explain placebo effects, and in general how expectation affects the mind and body, may require consideration of retrocausal influences.

INTRODUCTION

Norman Cousins' pithy phrase, "belief becomes biology," summarizes the placebo effect's relationship between expectation and physiologic responses.[1,2] Evidence from neuroimaging studies suggests that there may be several varieties of placebo effects associated with different underlying brain circuits, all modulated by expectation. Expectation involves prefrontal cortical and limbic areas of the brain, and activation of those areas is thought to initiate a series of biochemical responses that produce the anticipated physiologic outcome.[3,4] This psychoneuroimmunologic (PNI) explanation takes for granted the assumption that the underlying processes operate in an ordinary causal, mechanistic fashion.[5]

Although the PNI approach is persuasive in some respects, it does not account for anomalously large correlations observed between effect sizes in treatment versus placebo conditions in double-blind experiments.[6] To account for such effects, Wallach has proposed a "Weak Quantum Theory" that postulates macroscopic entanglements among conditions in blinded studies. If Wallach's idea is correct, then explanatory models of placebo effects must include not only PNI considerations, but also nonlocal relationships between treatments and controls. Similar entanglement ideas have been proposed recently by Tiller[7] and by Bengston and Moga.[8]

Here we propose another possible factor that may modulate placebo effects: What if the goal-oriented nature of the placebo effect were understood as a form of *final cause*,

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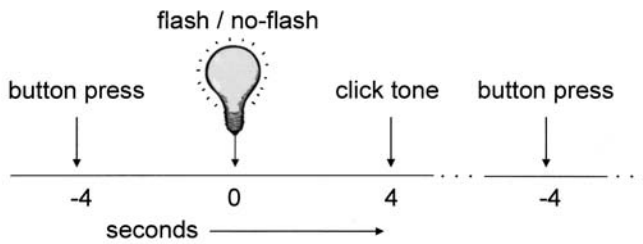
FIG. 1. Experimental design. A computer sampled a truly random number generator circuit immediately before the stimulus to decide whether to flash or not flash the lamp.

(e.g., as a teleological pull from our own future?) Put another way, what if expectation acts to focus our attention on our potential future states, and allows us to "select" favorable future paths to pursue? If gaining information from our future were possible, then in principle we might be able to navigate through potential futures to achieve a desired outcome.[9]

Of course, from a conventional view the teleological patina suggested by the placebo effect is just an illusion, because everyone knows that "our view from the future is based upon our past experiences," and past experiences alone.[10] This assumption is taken as self-evident because the idea of the future influencing the present seems to evoke a causal paradox: the classic example is a son preventing the birth of his own father. Such paradoxes cannot occur in a universe with a single course of history. One way to avoid the paradox is to postulate the existence of parallel universes, which is a respectable idea in physics.[11] Another is to regard "the future" as a probabilistic state that *might* occur rather than one that must occur.

To test whether expectation—a key component of the placebo effect—may be influenced by future information, we conducted an experiment examining unconscious responses to randomly selected future stimuli. Previous experiments of this type have monitored skin conductance level,[12–18*] nonspecific skin conductance response,[19,20] heart rate,[21,22] brain electrical activity,[23,24] and blood oxygenation levels in the brain as measured with functional magnetic resonance imaging.[25] Stimuli have included emotional versus calm pictures, stylized happy versus sad faces, and audio startle tones vs. silence. In some studies participants initiated trials of fixed lengths at will, in others stimuli appeared spontaneously at random times.

We decided to examine slow cortical potentials (SCPs) in the brain because SCPs reflect states of anticipation and expectation,[26,27] and as such, if SCPs were found to respond differentially according to future stimuli, then we could infer that our expectations may be influenced by future events,

and thus that the placebo effect might also be influenced by future events.

METHOD

The concept of presentiment predicts that SCPs will behave differently before a light flash than before a no-flash control. Based on McCraty et al.'s[15] previous results based on a similar design, this differential effect was predicted to become most evident about 1 second before the stimulus. Also, because the anticipated stimulus in our design was simply a light flash, the principal SCP changes were expected to occur in the visual cortex. To provide a design that avoided multivariate complications, a single electroencephalogram (EEG) measurement was taken over the occipital lobe at O_z according to the international 10–20 standard.[28]
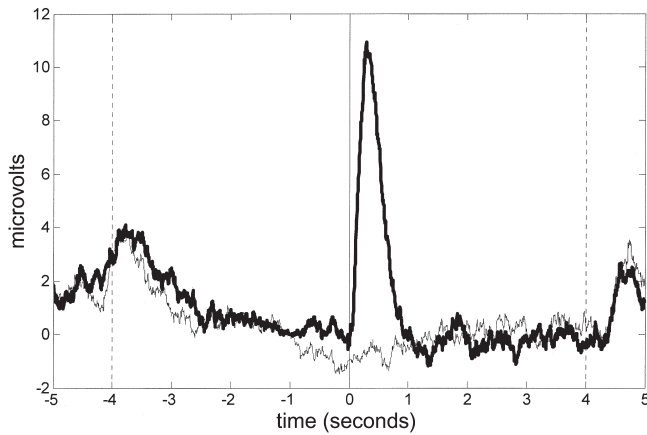
Procedure

Each participant was prepared with three Ag/AgCL electrodes (Biopac Model EL258S, Biopac Systems, Goleta, CA; Omni Prep skin preparation solution and Ten20 Conductive Paste, D. O. Weaver and Co., Aurora, CO).[†] Electrodes were placed at O_z and both earlobes; the left earlobe was used as ground and the right as reference. All connections were tested for impedance (Checktrode® Model 1089e, UFI, Morro Bay, CA), and then connected to a Biopac EEG-100C amplifier (16-bit resolution, 20,000 gain, 0.1–35-Hz
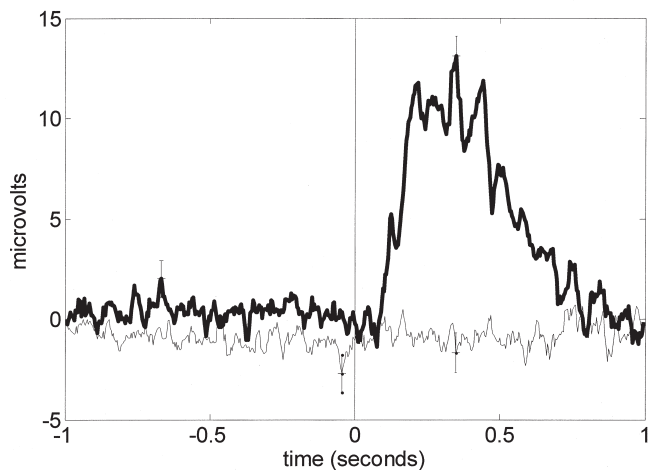
FIG. 2. Median electroencephalographic signals at Oz for the 13 female participants combined, with baseline subtracted 1 second prestimulus (stimulus shown as time 0), and smoothed using a sliding average window of 12 milliseconds. The bold line is the median during flash trials, and the thin line is the no-flash control. Error bars are 1 standard error.

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*Wildey C. Impulse response of biological systems. Master's Thesis, Department of Electrical Engineering, University of Texas at Arlington, 2001.

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†Two sessions were conducted using gold electrodes, which may have affected the SCP signals.

FIG. 3. Median electroencephalographic signals for 13 female participants ±5 seconds from stimulus onset, with baseline subtracted 1 second prestimulus, and smoothed with a sliding average window of 200 milliseconds. The bold line is the median prior to flash stimuli, and the thin line is the no-flash control. These curves differ slightly from those in Figure 3 because of the longer smoothing window used to enhance the curve's clarity.

bandpass, Biopac M-150 system). Digitized EEG data were recorded continuously during each experimental session at 250 Hz and saved to hard disk.

The participant relaxed in a comfortable chair and wore a pair of visual stimulator glasses (Model VSW-3, A/V Stim, San Rafael, CA). Three bright white light-emitting diodes (LEDs) were mounted in these glasses in front of each eye, with one LED positioned laterally toward the outside of the eye, and one above and one below, for a total of six LEDs. The stimulator was controlled by an A-D circuit (Ontrak Control Systems, Sudbury, Ontario, Canada, Model ADR-100), which was in turn connected to a Windows-based computer through a serial port. The controlling program for the experiment was written in Microsoft Visual Basic 6 (Microsoft Corp., Redmond, CA) by the first author.

The participant was asked to hold a computer mouse in his or her dominant hand and press the left button at will. The button press started a timer that waited 4 seconds; then a truly random number generator (RNG; Orion, ICATT Interactive Media, Amsterdam, The Netherlands) was queried by the computer to decide whether to flash the six LEDs for 250 milliseconds or to remain dark, with p(flash) = p(no-flash) = 0.5 (Fig. 1). After the stimulus, the timer waited another 4 seconds and then the computer sounded a short click tone to signal the end of the epoch. The participant then began the next trial at will. Each recording session consisted of 100 trials. Note that during the 4-second prestimulus period, the stimulus was not yet determined. Thus the participant and investigator were not simply blind to the stimulus conditions, but under the null hypothesis, they were *unknowable*.

After confirming that all hardware and software were operating as expected, the experimenter placed a flexible shield around the participant's head to block distractions from ambient lights and movements. Participants were asked to keep their eyes closed throughout the session to reduce eye blink and movement artifacts, and to remain as still as possible during each 8.25-second trial.

Analysis

All analyses were conducted in custom Matlab 7 programs (The Mathworks, Inc., Natick, MA). The following nine steps were used:

1. To reduce high-frequency noise, each test session's EEG record was smoothed with a sliding average window three samples (12 milliseconds) in length (i.e., each smoothed sample s_i consisted of the average of original samples o_{i-2}, o_{i-1}, and o_i.
2. Epochs ±1 second from stimulus onset in each smoothed EEG record were extracted. If the absolute value of any sample during the prestimulus period exceeded ±75 μV, that epoch was considered to contain a potential movement artifact and was eliminated from further analysis. This threshold value was selected based on previous studies investigating SCPs.[29]
3. Each epoch passing the artifact threshold in Step 2 was baseline adjusted by taking the difference between the sample at 1 second prestimulus onset and the remaining 499 samples in each 2-second epoch.
4. An ensemble median was calculated for all flash epochs across all sessions (by gender), and a similar ensemble median curve was calculated for all no-flash epochs. Median was used rather than the mean to provide a nonparametric curve less sensitive to potential outliers.
5. The summed difference between the flash and no-flash median curves determined in Step 4 was calculated for the 1-second period prestimulus onset. Call this value sum_{pre}.
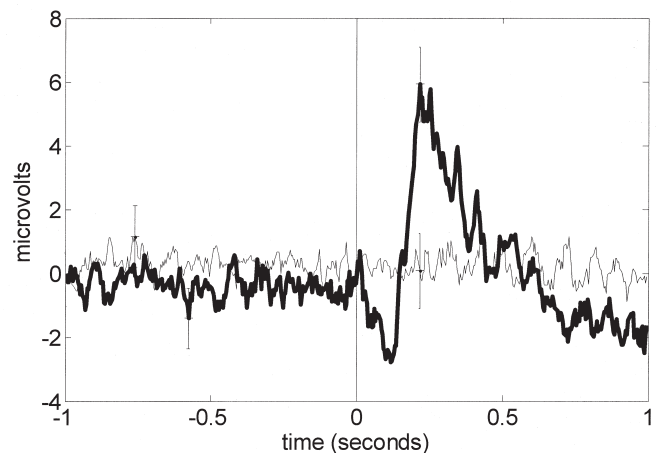
FIG. 4. Median electroencephalographic signals for the 7 male sessions combined.
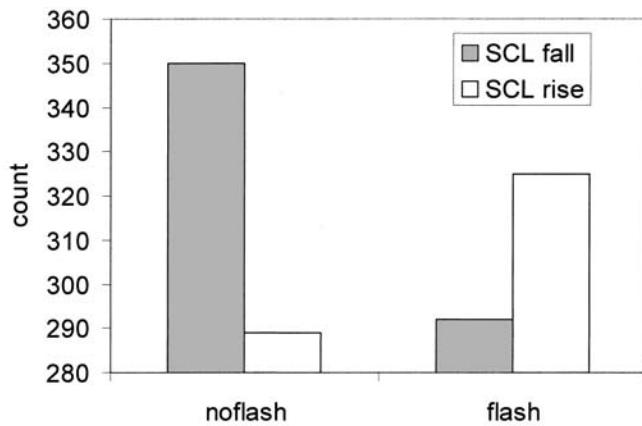
FIG. 5. There were more trials with slow cortical potentials (SCPs) falling when the epoch future condition was a no-flash, and more trials with SCP rising when the future condition was a flash ($p = 0.007$).

6. The original assignment of flash and no-flash conditions was randomly permuted.[30]
7. Steps 4–6 were repeated 10,000 times, building up a distribution of randomly permuted sum_{pre} values. Call these values sum_{pre-r}.
8. The mean (μ) and standard deviation (σ) of the distribution of sum_{pre-r} were calculated, and then $z_{pre} = (sum_{pre} - \mu)\sigma$ was determined. This z score is a normalized measure of prestimulus response.
9. The presentiment concept predicts that z_{pre} would significantly differ from chance expectation; a two-tailed test was used.

A secondary analysis examined the maximum–minimum difference in the prestimulus median curve prior to a flash versus no-flash. A similar permutation method as in steps 7 and 8 was used to create a normalized max–min score, z_{mm}.

Procedural control

To check for systematic electrical or analytical artifacts, after the experimental data were collected a second set of 1000 planned epochs were collected using a "sham brain" (a fresh grapefruit). The original set of electrodes and visual stimulator glasses were used and 10 sessions of 100 trials each were run using the same procedures employed in the experiment, with one addition: A timer was used to generate a random intertrial latency, and then the controlling program automatically ran each successive trial.

RESULTS

A total of 20 sessions of 100 trials each were collected. Participants included 20 adults, 13 females (ages 18–55), and 7 males (ages 48–65), all recruited by convenience. Because of known gender differences in how the brain

processes visual information,[31–33] data were evaluated separately for male and female participants. No attempt was made in this study to collect personality or experiential characteristics of the participants.

Of the 2000 trials collected, 1925 passed the 75-μV artifact rejection criterion; thus, 96% of the data were used in the subsequent analysis. (After the second session, the EEG amplifier gain was adjusted, and in the last 18 sessions 98.9% of the data were usable.) Among all 2000 trials, 1015 were randomly assigned to the no-flash condition and 985 to the flash condition. Stimulus conditions were distributed in accordance with chance expectation ($z = -0.69$ for proportion of flash conditions), as were autocorrelations of the sequence of flash versus no-flash conditions, calculated through lag ±50.

For females, the presentiment hypothesis was supported with $z_{pre} = 2.72, p = 0.007$ (all p values are two-tailed), and $z_{mm} = 3.45, p = 0.0006$. For males, the same analyses were weakly negative, $z_{pre} = -1.64, p = 0.10$, and $z_{mm} = -1.36, p = 0.18$. The gender difference between z_{pre} outcomes was significant, $z = 3.08, p = 0.002$, as was the difference for $z_{mm}, z = 3.40, p = 0.0007$. These significant gender differences warrant future research, but because of the small sample sizes involved in this study, caution is warranted in prematurely generalizing this finding.

Figure 2 shows the median curves for all 13 females for ±1 second around the stimulus onset; Figure 3 shows the same curves ±5 seconds to show the results in context (with 200-millisecond smoothing for the sake of clarity). Figure 4 shows the same analysis for the 7 males. The control test with a sham brain resulted in a nonsignificant difference, $z_{pre} = -1.34$ ($p = 0.18$, with 490 no-flash and 510 flash trials).

To further study these differences, for each trial in each of the two stimulus conditions we examined whether the SCP at -0.5 seconds was positive or negative. Counts within the four resulting categories, evaluated for females in a 2×2 contingency table, resulted in a chi-square =
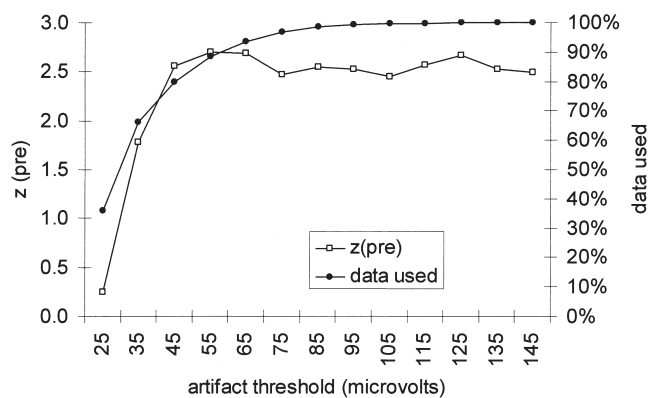
FIG. 6. Statistical results and percentage of retained data across a range of artifact rejection thresholds.
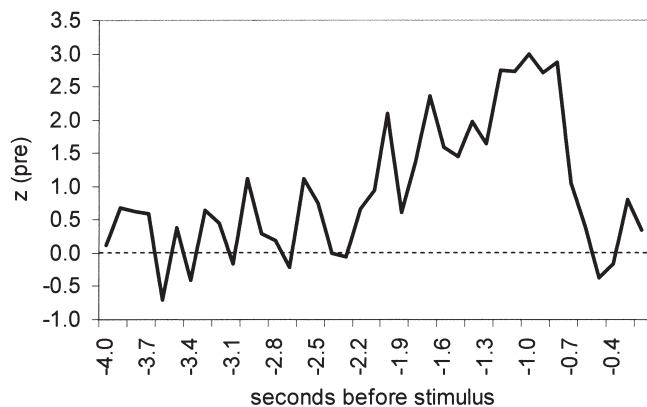
FIG. 7. Results of z-score measure of prestimulus response (z_{pre} score) after clamping the median curves from 4 seconds to 200 milliseconds prestimulus onset. This shows that the peak presentiment effect occurred approximately -1.4 to -0.8 seconds before the stimulus.

7.25, $p = 0.007$ (Fig. 5). The same analysis for males was nonsignificant ($p = 0.51$).

This indicates that in epochs when nothing happened (the no-flash condition), the majority of SCPs in females followed a negative trend; this is consistent with a state of continued anticipation. By contrast, in epochs where the future contained a light flash, then the majority of SCPs showed a rising trend. The larger difference in trends observed in the no-flash condition is intriguing; additional replications will be required to judge whether this is a meaningful difference.

DISCUSSION

This study supports the idea that models of the placebo effect may need to consider not only ordinary causal PNI explanations, or analogs of macroscopic entanglement, but also the possibility of retrocausal influences.

Before considering such a radical suggestion, it is useful to review conventional explanations that might have been responsible for the observed outcomes. Most potential alternatives were avoided by the experimental design and controls, and others could be evaluated analytically. The former included sensory or expectation cues about the future stimuli; the latter included sensitivity of the results to various design parameters.

For example, *sensory cues* were unavailable because the stimuli were generated by a truly random process after the prestimulus period. *Expectation cues* were controlled because a truly random process selected the two conditions with equal probability ($p = 0.5$), and analyses showed no discernible biases in the sequence of actual stimuli. *Procedural artifacts* were tested with the sham brain, and no evidence of systematic bias was observed.

To test whether the outcome might have been sensitive to the artifact rejection threshold of 75 μV, the analysis was repeated (on the female data) using thresholds ranging from 25 μV to 145 μV in steps of 10 μV. As shown in Figure 6, the statistical outcome was stable at $z_{pre} \sim 2.5$ for thresholds at or above 45 μV.

To test the sensitivity of clamping the data 1 second be-

TABLE 1. RESULTS PER SESSION PER INVESTIGATOR, FOR Z_{pre} AND Z_{post}, NUMBER OF SAMPLES
PER SESSION PASSING THE ARTIFACT CRITERION, AND THE PERCENTAGE OF STIMULI IN
THE FLASH CONDITION

Session	Gender	Investigator	Z (pre)	Z (post)	Samples	% Flash
1	F	DR	0.72	3.01	100	48%
2	F	EL	1.18	2.14	100	52%
3	F	EL	2.64	4.67	99	47%
4	F	EL	−2.46	3.67	100	60%
5	F	EL	0.90	1.61	100	48%
6	F	EL	1.95	5.84	98	48%
7	F	EL	1.12	3.79	97	47%
8	F	EL	0.88	1.93	100	45%
9	F	DR	−1.50	0.89	100	50%
10	F	DR	1.15	4.91	94	48%
11	F	DR	−0.32	4.69	100	50%
12	F	DR	2.04	3.55	94	55%
13	F	DR	0.66	4.84	99	51%
1	M	EL	−0.13	1.32	46	52%
2	M	EL	−0.48	4.21	100	48%
3	M	DR	−0.85	0.09	100	43%
4	M	DR	−1.78	2.49	100	49%
5	M	DR	−0.29	−0.80	100	43%
6	M	DR	0.37	2.23	99	43%
7	M	DR	0.74	1.05	100	57%

Note: DR is the first author, EL is the second author.
Z_{pre}, Z-score measure of prestimulus response; Z_{post}, Z-score measure of postimulus response.

fore the stimulus, we reanalyzed the female data by clamping the data from -4 seconds to -0.2 seconds before stimulus onset (in steps of 40 milliseconds), and then recalculating z_{pre} for each of these prestimulus periods. As shown in Figure 7, this showed that the optimal time to detect a presentiment effect was about -1 second before the stimulus, but the effect was already apparent about -2 seconds prestimulus.

In addition, as shown in Table 1, 10 of the 13 female sessions resulted in positive z_{pre} scores, and 6 of the 7 male sessions resulted in negative z_{pre} scores, so the results were not caused by a few participants who produced unusually deviant outcomes, or to dramatic differences between experimenters.

Interpretations

A passive perceptual interpretation of the presentiment effect proposes that some aspect of the mind–brain is sensitive to events that are about to unfold.[34] This requires that the future events exist in some form (determined or probabilistic), otherwise there would be nothing available to perceive in the present. An active interpretation suggests that the act of anticipation alters the probabilities of potential future events.[35] The present experiment was not designed to clearly discriminate between these two possibilities, but the results seem to be more consistent with a perceptual interpretation because the distribution of flash versus no-flash stimuli was in accordance with chance expectation.

The concept of retroaction is taken seriously in physics,[36,37] but the idea that such effects may influence macroscopic systems, including human health and behavior, is rarely considered. This study suggests that our understanding of how belief becomes biology may benefit by reconsidering Aristotle's final cause, and it raises the conceptual bar for developing comprehensive explanatory models of the placebo effect.

ACKNOWLEDGMENTS

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