EXPECTATIONS MEDIATE OBJECTIVE PHYSIOLOGICAL PLACEBO EFFECTS

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ABSTRACT

Purpose – *A placebo effect is a (positive) change in health outcomes that is due to a (positive) change in beliefs about the value of a treatment. Placebo effects might be "behavioral," in the sense that revised beliefs lead to behavioral changes or new actions that in turn yield changes in health outcomes. Placebo effects might also include a "physiological" component, which refers broadly to non-behavioral, brain-modulated mechanisms by which new beliefs cause changes in health outcomes. Nearly all formal economic models of human behavior are consistent with behavioral placebo effects, but strongly inconsistent with their physiological counterparts. The reason is that the latter effects can imply that expectations enter, rather than multiply, state-contingent preferences. It is therefore unfortunate that little evidence exists on physiological placebo effects. We report data from novel clinical experiments with caffeine that seek to provide such evidence.*

Methods – *Subjects visit the clinic on multiple occasions. On each visit they ingest either a placebo or caffeine pill. Subjects only know the probability with which the pill includes caffeine. We obtain physiological measurements prior to ingestion and at 30, 60, and 90 min after ingestion.*

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Importantly, we constrain subjects to remain seated and read pre-selected magazines during the interval between treatment and outcome measurement.

Findings – *Our design provides particularly clean inference because it (i) eliminates the possibility of behavioral confounds; (ii) provides for measurements at the individual level; (iii) manipulates beliefs without deception; and (iv) uses salient rewards. We find evidence for the existence of physiological placebo effects mediated by expectations.*

Implications – *Our results are consistent with the possibility that the prefrontal cortex provides external, top-down control that modulates physiological outcomes, and make a case for the importance of research geared toward developing appropriate and tractable frameworks that accommodate non-linear relationships between expectations and preferences.*

1. INTRODUCTION

A placebo effect is a (positive) change in health outcomes that is due to a positive) change in beliefs about the value of a treatment.[1] Placebo effects might be "behavioral," in the sense that revised beliefs lead to behavioral changes or new actions that in turn yield changes in health outcomes. Placebo effects might also include a "physiological" component, which refers broadly to non-behavioral, brain-modulated mechanisms by which new beliefs cause changes in health outcomes. Nearly all formal economic models of human behavior are consistent with behavioral placebo effects, but strongly inconsistent with their physiological counterpart. The reason is that the latter effects can imply that expectations enter, rather than multiply, state-contingent preferences. It is therefore unfortunate that little evidence exists on physiological placebo effects. We report data from novel clinical experiments with caffeine that seek to provide such evidence.

Placebo effects are clearly important to the field of medicine and health policy more generally. For example, in a situation where the placebo effects of an inert pill and the pharmacological effect of active treatment are similar, it may be more cost-effective for the healthcare system to encourage physicians to induce positive expectations about the cheap inert substance instead of prescribing the more expensive active medication (Talbot, 2000). Also, to the extent that patients are indeed affected by independently

acquired scientific information about the intervention to which they have been subjected (e.g., in adherence to treatment), healthcare policy-makers should surely be interested in placebo effects.

Placebo effects have recently received attention in the economics literature. For example, Malani (2006) suggested that physiological placebo effects may cause a violation of the independence axiom in the context of blinded clinical trials. Here different treatments correspond to different states of the world. Because patients do not know their actual treatment assignment, placebo effects in any given state will depend on the subject's expected treatment assignment. Therefore, beliefs about treatment states to which a patient was not actually assigned could influence the patient's health outcomes and thus influence utility.

Building on the insight that placebo effects in blinded trials depend on potential rather than actual treatment assignments, Malani (2006) suggested that placebo effects could be estimated by manipulating the probability of assignment to different treatments while holding the subject's actual treatment constant. Specifically, Malani argued that if a treatment is subject to placebo effects, outcomes on that treatment should be improved when the probability of being assigned to the treatment (as opposed to an inferior control) is increased. To test this, Malani examined trials of medications for non-gastric ulcer and for hypercholesterolemia. When he compared the treatment group in trials offering a higher probability of assignment to treatment groups in trials with a lower probability of treatment, he found that the former had better outcomes than the latter, controlling for the actual treatment that subjects received. In addition, he found that expectations about bad outcomes also affect patient response, i.e., a nocebo effect, which we shall discuss later.

Another study that highlights the connection between beliefs and outcomes was reported by Shiv, Carmon, and Ariely (2005). They investigated placebo effects in marketing, with particular focus on whether prices can alter the realized efficacy of products to which they are applied. In a series of three experiments, it was shown that consumers who paid a discounted price for a product (an energy drink thought to increase mental acuity) derive less actual benefit (they are able to solve fewer puzzles) than consumers who purchased the same product at a regular price. The explanation was that subjects who paid a lower price inferred that the drink was of lower quality and this inference led to the subjects' completing fewer puzzles.

A limitation of both Malani (2006) and Shiv et al. (2005) is that they are unable to distinguish between physiological and behavioral placebos.

Because the clinical trials Malani examined did not either hold constant subjects' behavioral response or measure every aspect of subjects' behavioral responses to changes in the probability of assignment to treatment, he was unable to rule out that differences in subjects' expectations are responsible for differences in subjects' behavior, which in turn explain differences in subjects' outcomes. Perhaps, as Malani (2008) suggests, subjects in trials with a high probability of assignment to treatment (versus control) might be more willing to comply with treatment protocols because there is a greater likelihood compliance will have an effect on outcomes. Shiv et al. has a similar problem in tracing the chain of causation from beliefs to outcomes. There are two possible explanations for why subjects who inferred lower quality from lower price completed fewer puzzles. One explanation is that their cognitive function was lower; the other is that they did not attempt as many puzzles. Shiv et al. could not distinguish between these explanations, perhaps because it is impossible to do so.

Because behaviorally mediated placebo effects fit neatly into current economic models, while physiological placebo effects do not, it is important – when possible – to distinguish between behavioral and physiological response to expectations. That is the motivation for the laboratory study we report below. The primary goal of that experiment is to rule out the possibility of behaviorally mediated placebo effects by constraining subject behavior. The secondary purposes of the study are to (i) manipulate subjects' expectations without using deception; and (ii) measure treatment and outcomes at an individual level (as Shiv et al., 2005 do, but Malani, 2006 does not). We find compelling evidence supporting physiological placebo effects mediated by expectations.

2. BACKGROUND

2.1. Expectations and Placebo Effect

Over the past five decades, placebos and the placebo effect have been the subject of pioneering research efforts by Beecher (1955), Lasagna, Mosteller, Von Felsinger, and Beecher (1954), Shapiro (1960, 1964), and many others. These efforts have contributed to our understanding of the placebo effect and stimulated the development of the field. Parts of this work still continue to influence biobehavioral research (Olshansky, 2007). A placebo (as opposed to placebo effect) refers to "any treatment – including drugs, surgery, psychotherapy and quack therapy – used for its ameliorative effect

on a symptom or disease but that is actually ineffective or not specifically effective for the condition being treated"(Shapiro & Shapiro, 1997). Some have suggested that the psychophysiological responses that placebos elicit reflect a mind/body interaction guided by subjective factors like expectations, beliefs, meaning, hope for improvement, and relational parameters (Shapiro & Shapiro, 1997).

The placebo effect is the prototype response expectancy effect but it is not the only effect of this type (Kirsch, 1997). Response expectancies are anticipations of automatic subjective and behavioral responses to particular situational cues. Their effects can be viewed as a form of self-fulfilling prophecy (Kirsch, 1985; Kirsch & Lynn, 1999). Numerous studies in health sciences (Kirsch, 1999; Kirsch & Lynn, 1999; Stewart-Williams & Podd, 2004) suggest that expectations have a mediating role in placebo effects. Essentially, when a person receives a supposedly active substance or treatment, his beliefs about the substance or treatment activate response expectancies anticipating the subjective and/or behavioral consequences of using that substance or receiving medical treatment in general. These response expectancies, along with contextual factors unrelated to the substance or treatment, lead to subjective and behavioral outcomes, or placebo effects (Shiv et al., 2005).

When discussing placebo, one must consider not only the traditional, positive *placebo* effect, but also the *nocebo* effect. The traditional *placebo* effect involves positive feelings about a therapy that contribute to improving the outcomes of that therapy. The *nocebo* effect, however, refers to the case in which a person's expectations that a therapy has certain side effects increase the likelihood that the person will subsequently develop those side effects (Malani, 2008). According to Beecher (1959), placebo effects account for 30–40% of the effect of a psychological or medical intervention (though the methodology behind that finding has been much criticized). In contrast, healthy individuals have adverse side effects to a blinded sham intervention 15–27% of the time (Liccardi et al., 2004; Olshansky, 2007).

The placebo effect can be highly domain specific, and the nature of this specificity depends on the information available to the recipient (Beauregard, 2007). Placebo effects have been studied intensely in several domains, such as pain reduction (also known as placebo analgesia) (Zubieta et al., 2005; Wager et al., 2004; Baker & Kirsch, 1991; Petrovic, Kalso, Petersson, & Ingvar, 2002), depression (Kirsch & Sapirstein, 1999; Sneed et al., 2008), sexual arousal (Palace, 1999), hypnosis (Kirsch & Lynn, 1995; Perugini et al., 1998), treatment of ulcers (Malani, 2006), hypercholesterolemia

(Malani, 2006), cardiovascular health (Olshansky, 2007), and Parkinson's disease (Benedetti et al., 2004; de la Fuente-Fernandez et al., 2001).

Nonetheless, some scholars have challenged whether placebo effects actually exist. For instance, Kienle and Kienle (1997) argue that placebo effects could be explained by the natural history of a disease, regression to the mean, concomitant treatment, observer bias, and patient bias. These authors suggest that placebo effects are grossly overrated, illusory, and the product of sloppy methodological thinking. Subsequent investigations comparing placebo to no-treatment conditions further support the view that placebo might have a negligible impact and overestimated effect (Hrobjartsson & Gotzsche, 2001, 2004, 2006). The fact that some data indicate a real response to placebo and other data do not may be explained in part by the lack of consensus regarding what actually constitutes the placebo effect (Link, Haggard, Kelly, & Forrer, 2006).

2.2. Psychological Mechanisms of Placebo Effects

One prominent hypothesis is that placebo effects result from classical conditioning (Ader, 1988; Turkkan, 1989). According to this view, active medications are unconditioned stimuli and the vehicles that deliver them (e.g., pills, capsules, syringes) are conditioned stimuli. Thus, through repeated pairings between conditioned and unconditioned stimuli, vehicles per se could come to elicit the effects of active medications as conditioned responses. From this perspective, expectations are epiphenomena rather than causes or mediators of placebo effects. A study by Montgomery (1995) seemed to contradict this view by suggesting that a conditioning's effect on responses to placebo is fully mediated by expectancy. Therefore, conditioning might be only one of the mechanisms by which stimulus and response expectancies are acquired. In turn, these expectancies might mediate placebo effects (Kirsch, 1997; Pollo et al., 2001).

Another possible mechanism for the placebo effect is based on expectancies in relation to the construction of experience. According to the work of cognitive psychologist Jerome Bruner (1957, 1986), perception is influenced not only by what actually happens, but also by expectations about what should occur. These so-called self-confirming effects of expectancies may have evolved due to their impact on the speed of action: stimulus expectancies can speed perceptual processing, although sometimes at the expense of accuracy. As most studies have suggested, placebo effects are mediated by expectancies, a fact that will be detailed later in this chapter.

Essentially, expectancies may elicit subjective and objective changes in how people respond to an intervention. It is worth noting that the explanatory mechanisms of response expectancies and conditioning may not be mutually exclusive (Price, 2000).

2.3. Behavioral versus Physiological Pathways for Placebo Effects

Malani (2006) captures one of the most important criticisms of placebo studies – that they do not control for possible effects of contingent behavior that may nonetheless be independent of the intervention. For instance, more optimistic patients who have positive expectancies related to their treatment may modify their behavior in a manner that complements their therapy. More concretely, patients with non-gastric ulcers who believe in the effects of their treatment might also change their behavior by reducing their ingestion of spicy foods. This may in turn ameliorate their ulcer. If an investigator does not control for these behavioral changes, the favorable outcomes displayed by more optimistic patients could be wrongly interpreted as indicating placebo effects.

Recent studies argue that placebo might have a physiological as well as behavioral component. That is, individual expectations about therapy might alter the outcome of that therapy not only by modifying behavior, but also by triggering physiological changes in the brain and body (Zubieta et al., 2005; Wager et al., 2004). A recent review of neuroimaging studies on placebo indicated that beliefs and expectations can substantially modulate neuropsychological and neurochemical activity in brain regions involved in perception, movement, pain, and various aspects of emotion processing (Beauregard, 2007).

Among health issues, placebo analgesia has been most extensively studied. Wager et al. (2004) carried out two experiments using functional magnetic resonance imaging to investigate the neural mechanisms underlying the effects of expectations on placebo analgesia. The results indicated that the placebo treatment significantly decreased reported pain in over 70% of volunteers. Most importantly, placebo reduced the physiological responses in some of the brain regions known to be involved in the subjective experience of pain. These regions include the right anterior cingulate cortex, the anterior insula, and parts of the thalamus (Craig, Chen, Bandy, & Reiman, 2000).

In addition, during pain, placebo-induced increases in the dorsolateral prefrontal cortex, a brain region thought to be involved in the

representation and maintenance of information needed for cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000), were correlated with placebo-induced reductions in the contralateral thalamus, the insula, and the right anterior cingulate cortex. Another neuroimaging study on placebo analgesia found significant placebo-induced activation of mu-opioid receptor-mediated neurotransmission in certain brain regions, including the pregenual and subgenual anterior cingulate, the dorsolateral prefrontal cortex, the insular cortex, and the nucleus accumbens (Zubieta et al., 2005). Regional activations were paralleled by lower ratings in pain intensity, coupled with reductions in its sensory and affective qualities, and reductions in the negative emotional state of the volunteers. These data strongly suggest that cognitive factors are capable of modulating physical and emotional states through the site-specific activation of mu-opioid receptor signaling in the human brain (Zubieta et al., 2005).

While these data are compelling evidence of physiological effects, they nevertheless rely on subjective evaluations and responses, leaving open the question of whether one is measuring an effect or the reporting of an effect. Our study, described in detail later, contributes to this literature by providing data on objective physiological placebo effects. In particular, we assess how exogenously manipulated caffeine expectancies impact objectively measurable physiological outcome variables – in our case, blood pressure.

3. EXPERIMENT DESIGN AND PROCEDURES

Participants were moderate caffeine users who were instructed not to drink coffee for 24 h prior to the experiment. We employed a crossover design in which participants were sequentially exposed to four possible treatments: blinded and unblinded administration of caffeine (200 mg) pill, and blinded and unblinded administration of inert pill. More precisely, each participant arrived to the clinic on four separate days. On each of the first two days (blinded visits) the participant was randomized by means of a coin flip to either a caffeine pill (200 mg, the caffeine equivalent of two cups of coffee) or an identical-looking inert pill. The participant knew the probability (0.5) that he or she would receive the caffeine pill but did not know whether he or she actually received that pill.[2] On the third day (non-blinded visit) the participant was given either a caffeine pill in a vial labeled caffeine or an inert pill in a vial labeled inert. Participants were honestly told the content of the pill they were asked to ingest. The fourth day (non-blinded visit) mirrored the third, except that if the participant received caffeine during his or her third visit, he or she received inert pill on the fourth.

On each visit, a nurse would measure the participant's diastolic and systolic blood pressure 5 min before the participant was given treatment and 30, 60, and 90 min after the participants ingested his or her pill.[3] These measurements were made by means of an automated device. Importantly, the study participant was required to remain seated and permitted only to read airline magazines during the duration of his or her visit.[4] This ensured that the behavior of participants was held constant so that any observed placebo effects were generated by physiological rather than behavioral changes over the course of the different treatments. We chose airline magazines because they are designed not to induce anxiety in readers while they are passengers on an air flight.

Our hypotheses are as follows: (i) blood pressure would be highest when subjects were given the unblinded caffeine pill, since they would experience both the pharmacological effects of caffeine and the full expectation that they were receiving caffeine; (ii) in the blinded caffeine condition participants would have the second highest blood pressure, due to the full pharmacological effects of caffeine and chance (probability 0.5) expectation of receiving a caffeine pill; (iii) the third highest level of blood pressure would be observed in participants in the blinded placebo treatment, reflecting the only the chance (0.5 probability) expectation of receiving a caffeine pill; and, finally (iv) the lowest level of blood pressure would be observed in the unblinded placebo treatment where there was no expectation of receiving caffeine.

All experiments were conducted at the National Institute Health-funded General Clinical Research Center at the University of Virginia, and all physiological measurements were obtained by their associated staff of qualified health professionals.

4. RESULTS

4.1. Descriptive Statistics

A total of 50 people participated in our experiment. Table 1 provides descriptive statistics for our overall sample (final rows), as well as by agent received on each of their first two visits. Specifically, C denotes caffeine and P placebo so that, for example, the C/P category gives statistics for the set of people who, during their first two visits, randomly received caffeine once

Table 1. Total Sample Characteristics.

Treatment	Male	Age	Smoker	White	BPs Baseline	BPs 90 min	BPd Baseline	BPd 90 min
C/P	0.25	25.91	0.36	0.78	114.67	116.03	67.72	69.47
$N = 20$	(0.44)	(9.62)	(0.49)	(0.41)	(13.27)	(12.76)	(7.09)	(7.98)
	20	20	19	19	20	20	20	20
C/C	0.46	28.12	0.15	0.75	114.02	116.93	68.84	72.12
$N = 13$	(0.51)	(13.42)	(0.37)	(0.45)	(10.43)	(13.01)	(6.3)	(8.48)
	13	13	13	12	13	13	13	13
P/P	0.23	24.36	0.18	0.68	111.08	109.33	65.46	65.75
$N = 17$	(0.43)	(6.54)	(0.40)	(0.47)	(8.71)	(6.99)	(5.95)	(6.99)
	17	17	16	16	17	17	17	17
Total	0.31	26.13	0.23	0.73	113.28	113.99	67.24	68.9
$N = 50$	(0.46)	(9.86)	(0.42)	(0.44)	(11.06)	(11.49)	(6.53)	(8.04)
	50	50	48	47	50	50	50	50

and randomly received placebo once (in either order), while C/C reports statistics for the group who randomly received caffeine on each of their first two visits, and P/P reports statistics for the group who randomly received placebo on both visits.

As seen in Table 1, our overall sample included about 1/3 males, with a mean age of 26. About a fourth smoked and that same fraction was non-white. The final four columns in the table detail information about blood pressure. Changes in blood pressure will be discussed later. For now, it suffices to notice that baseline mean blood pressure readings (both systolic and diastolic, denoted by BPs and BPd, respectively) are normal. With respect to the treatment conditions, the key thing to note is that none of the condition-specific means departs very much from the others, or from the overall average.

The analysis we report below focuses on the 32 participants (64% of the sample) who displayed any positive blood pressure response in the condition where caffeine was known to have been ingested; that is, blood pressure was higher in the non-blinded caffeine state than in the non-blinded placebo state, a result we shall call a positive non-blinded treatment effect (NTE). The reason is that the non-responsive third of the sample evidently shows no reaction or a negative to caffeine that can mask placebo effects. Moreover, focusing on those with a positive NTE does not in any way imply that physiological responses among the four treatments will satisfy our naturally ordered hypothesis.

Table 2. Positive Unblinded Caffeine Effect.

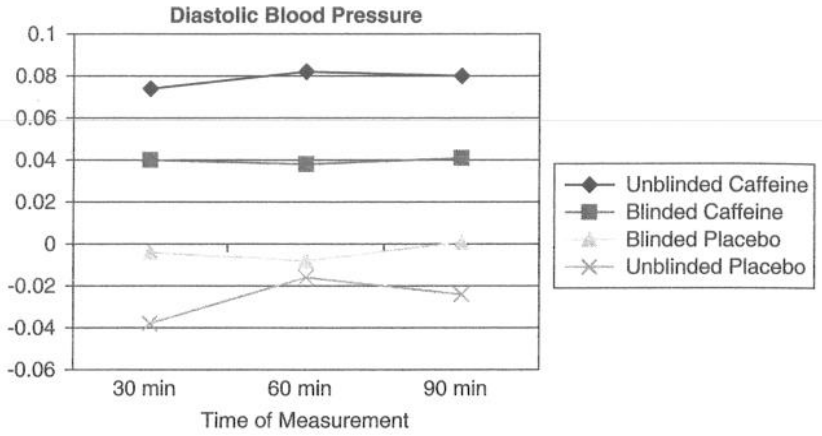
Treatment	Male	Age	Smoker	White	BPs Baseline	BPs 90 min	BPd Baseline	BPd 90 min
C/P	0.33	27.56	0.25	0.66	115.18	116.79	69.93	71.46
$N = 12$	(0.49)	(11.84)	(0.45)	(0.49)	(12.5)	(11.86)	(5.88)	(6.88)
	12	12	12	12	12	12	12	12
C/C	0.5	24.38	0.12	0.75	115.45	118.27	69.7	72.58
$N = 8$	(0.53)	(7.99)	(0.35)	(0.46)	(10.73)	(12.35)	(6.66)	(8.98)
	8	8	8	8	8	8	8	8
P/P	0.25	25.36	0.25	0.63	111.68	110.01	65.88	66.27
$N = 12$	(0.45)	(7.61)	(0.45)	(0.5)	(9.64)	(7.81)	(6.31)	(7.61)
	12	12	12	11	12	12	12	12
Total	0.34	25.94	0.21	0.67	113.93	114.62	68.35	69.79
$N = 32$	(0.48)	(9.3)	(0.42)	(0.47)	(11.81)	(10.93)	(6.34)	(7.96)
	32	32	32	31	32	32	32	32

Table 2 provides descriptive statistics for the 32 subjects analyzed below. A key point is that the non-responsive group was distributed roughly equally among treatments. In addition, the means for the retained sample do not in any case depart greatly from the means reported in Table 1. In particular, one cannot predict who will experience a positive NTE based on the sample characteristics we collected.

4.2. Blood Pressure Response to Expectations and Caffeine

Fig. 1, panels (a) and (b), details time-related mean changes in diastolic and systolic blood pressure in each of the arms of our experiment. The vertical axis is percent change in blood pressure from baseline (obtained each visit, 5 min prior to administration of a pill). The horizontal axis indicates the time at which measurements were taken. The numbers of subjects included in each mean can be inferred from Table 2, and is 32 for each of the non-blinded arms, 20 for blinded caffeine, and 24 for blinded placebo arms.

Both panels provide compelling visual evidence in favor of the ordered hypothesis advanced above. In particular, at each time point the greatest mean change in blood pressure occurs with non-blinded caffeine, the least affect occurs with non-blinded placebo. The two blinded treatments fall somewhere between, with blinded caffeine showing a greater blood pressure effect than blinded placebo.



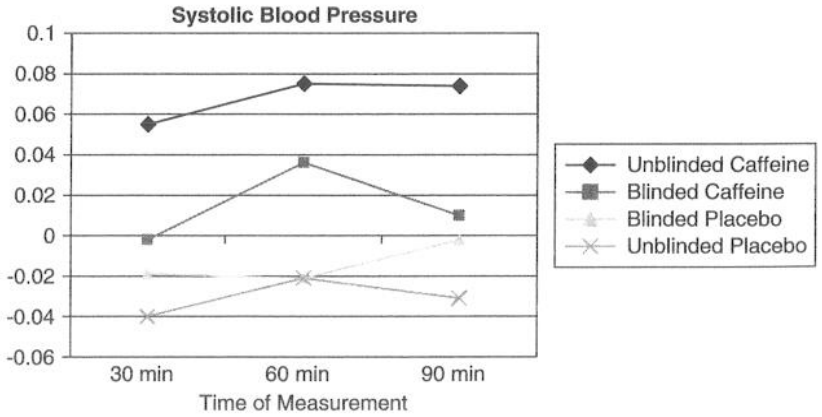


Fig. 1. Change in Diastolic and Systolic Blood Pressure in Each Arm of the Experiment.

It is worthwhile to note that, while non-monotonic, the blood pressure effects do not seem to systematically dissipate over the duration of the experiment. Indeed, in all cases mean change from baseline is roughly the same at both 30 and 90 min following ingestion of the pill. The effects at 90 min provide evidence against an anxiety-based explanation for our results: we would expect little residual anxiety following 90 min of relaxed reading of airline magazines.

To assess formally the validity of our hypothesis we conducted Jonckheere tests for ordered alternatives (Jonckheere, 1954). When $k = 2$, this test is equivalent to the well-known Wilcoxon–Mann–Whitney two-sample test for equality of medians. In our case, we test the null-hypothesis that the medians of the treatment effect distributions are the same against the alternative that the medians are ordered specifically as hypothesized above (non-blinded caffeine $\geq$ blinded caffeine $\geq$ blinded placebo $\geq$ non-blinded placebo), with at least one of the inequalities strict.[5]

We ran this test at the 90-min point for both systolic and diastolic blood pressure. We chose this point because, as noted above, it provides a control for possible anxiety effects on blood pressure outcomes. We find that the test overwhelmingly rejects the null-hypothesis in favor of our hypothesized ordering in both cases ($p<0.001$ for both systolic and diastolic blood pressure). This result is robust to alternative measurement times. Evidence in favor of our hypothesized ordering is found for both systolic and diastolic blood pressure at the 30, 60, and 90-min measurement points ($p<0.001$ in all cases).

5. CONCLUDING DISCUSSION

We reported data from novel clinical experiments with caffeine in order to provide evidence on the role of expectations in mediating placebo effects. In our experiment participants visited the clinic on multiple occasions. On each visit they ingested either a placebo or caffeine pill. Subjects knew only the probability with which the pill included caffeine. We obtained blood pressure measurements prior to ingestion, and provided only airline magazines to read to pass the time. Our design provides particularly clean inference because it (i) eliminates the possibility of behavioral confounds; (ii) provides for measurements at the individual level; (iii) manipulates beliefs without deception; and (iv) uses salient mechanisms to alter expectations (a coin flip). Our evidence supports the existence of physiological placebo effects, and provides compelling evidence that these effects are mediated by expectations.

Our experiment cannot identify the neural mechanisms ultimately responsible for these effects. However, our data are consistent with the possibility that the prefrontal cortex provides external, top–down control that modulates physiological outcomes (Wager et al., 2004). In addition, the proximate cause of the physiological effect (presumably hormones) is not informed by our study. In the case of blood pressure, it might be particularly challenging to document hormone levels, as the interventions (urinalysis or

blood testing) to measure those levels would themselves affect blood pressure response. Nevertheless, the biological underpinnings of the responses we identify remain important areas for future research. For example, when a placebo is ingested but the probability of receiving caffeine is high, it would be very interesting to know whether the biological mechanism simulates the true pharmacological effect of caffeine or, alternatively, the effect a person believes caffeine should have.[6]

Finally, although by now something of a straw-man, our evidence raises additional questions regarding the role of expected utility analysis in understanding and predicting human behavior. It raises the possibility that expectations might not only multiply but also change the shape of the underlying utility function. Thus, our results are convergent evidence that beliefs play a complex role in economic decisions, and further the case for the importance of research geared toward developing appropriate and tractable frameworks that accommodate non-linear relationships between expectations and preferences.

NOTES

1. That treatment may or may not be an inert substance. It is possible for a pharmacologically active treatment to have placebo effects on top of what we shall call the pharmacological effects of that treatment.
2. The research pharmacy, in an off-site location, randomized the pills into bottles labeled H for heads or T for tails. The nurses administering the medication did not know this assignment. Subjects were told that either the H or the T vial contained a caffeine pill and the other contained an inert pill. A coin flip determined which vial and thus pill the subjects received. The nurse reported the H or T allocation back to the research pharmacy.
3. These timing choices were based on the half-life of caffeine, as well as its rate of absorption into the body. The rate at which a person metabolizes caffeine depends on age as well as a variety of health factors. In the case of healthy adults caffeine's half-life is around 4 h. Caffeine is typically fully absorbed into the body through the stomach and small intestine within 45 min of ingestion.
4. Bathroom breaks were regulated such that they did not occur within 5 min prior to a blood pressure measurement.
5. The Jonckheere test assumes independence among treatments, an assumption that might be violated by our data because the same subjects are observed in multiple treatments. A test that takes account of repeat measures among subjects is suggested by Page (1963). However, this test requires that all subjects participate in all treatments, which is not the case for our data (because of our randomization procedure).
6. We thank Monica Capra for this interesting suggestion.

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