Direct verbal suggestibility as a predictor of placebo hypoalgesia responsiveness

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Abstract

Objective: Reliably identifying good placebo responders has pronounced implications for basic research on, and clinical applications of, the placebo response. Multiple studies point to direct verbal suggestibility as a potentially valuable predictor of individual differences in placebo responsiveness, but previous research has produced conflicting results on this association.

Methods: In two double-blind studies, we examined whether behavioural direct verbal suggestibility measures involving a correction for compliance would be associated with individual differences in responsiveness to conditioned and unconditioned placebo hypoalgesia using an established placebo analgesia paradigm. In Study 1 (N=57; M_{Age}=23.7, SD=8.1; 77% women), we used behavioural hypnotic suggestibility as a predictor of placebo hypoalgesia induced through conditioning and verbal suggestion whereas in Study 2 (N=78; M_{Age}=26.1, SD=7.4; 65% women), we measured non-hypnotic suggestibility and placebo hypoalgesia induced through verbal suggestion without conditioning.

Results: In Study 1, the placebo hypoalgesia procedure yielded a moderate placebo response (g=0.63 [95% CI: 0.32, 0.97]), but the response magnitude did not significantly correlate with hypnotic suggestibility (r_s=.11 [-.17, .37]). In Study 2, the placebo procedure did not yield a significant placebo response across the full sample (g=0.11 [-0.11, 0.33]), but the magnitude of individual placebo responsiveness significantly correlated with non-hypnotic suggestibility (r_s=.27 [.03, .48]).

Conclusion: These results suggest that the extent to which direct verbal suggestibility captures variability in placebo responsiveness depends on the use of conditioning and highlights the utility of suggestibility as a potential contributing factor to placebo responding when placebo hypoalgesia is induced through verbal suggestions.

Keywords: conditioning; expectancy; hypnosis; pain; suggestion; suggestibility

Abbreviations: MHGS = Modified Harvard Group Scale of Hypnotic Susceptibility, MHGS – CC = Modified Harvard Group Scale of Hypnotic Susceptibility – Compliance Corrected, VAS = Visual Analogue Scale, μs = Microseconds, ms = milliseconds, FPQ = Fear of Pain Questionnaire, PASS = Pain Anxiety Symptom Scale, BSS = Brief Suggestibility Scale

Introduction

The placebo response varies markedly across individuals (1). The reliable identification of individuals who are highly responsive to placebos has implications for research seeking to understand its mechanisms as well as its clinical applications. Identifying so-called good placebo responders has the potential to assist in minimizing the placebo response in drug studies to enhance internal validity, augmenting responsiveness to boost treatment outcome, and personalizing treatment based on an individual's neurocognitive profile (2). Nevertheless, the notion of a good placebo responder remains controversial as there is mixed evidence for uniform placebo responsiveness across contexts (3-5).

Verbal suggestions provide a valuable starting point from which to elucidate individual differences in placebo responsiveness because suggestions are widely recognized as a prominent component of placebos (6). Suggestions are communications for involuntary changes in behaviour and experience (e.g., "this pill will reduce your symptoms" (7)). Neurotypical adults vary in their responsiveness to direct verbal suggestions (suggestibility), which can be reliably assessed using behavioural scales involving the administration of multiple suggestions and corresponding assessment of one's magnitude of response (8-10). Direct verbal suggestibility is highly stable over time (11), across hypnotic and non-hypnotic contexts (12, 13) and associated with unique neurocognitive characteristics (11). High direct verbal suggestibility is characterized by a pronounced experience of involuntariness in response to suggestions (10, 14) and is distinct from other forms of suggestibility (e.g., interrogative suggestibility) that are closely related to compliance. These features provide good reason to hypothesize that suggestibility will account for some of the variability in placebo responsiveness. Suggestions are believed to produce their effects in part by building upon expectations that subsequently influence perceptual states (15). Highly suggestible individuals thus may have a unique capacity to form precise priors that bias perception in favour of suggestions administered as part of a placebo manipulation (16-18).

Despite these parallels, previous research has produced conflicting results on the relationship between placebo responsiveness and suggestibility. Multiple studies have observed a linear association between the two (19, 20), whereas others have failed to replicate this effect (21, 22). Some studies have hinted at

potential moderators of this association, including response expectancies (19), but the sources of inter-study heterogeneity remain unclear. Many studies did not use robust measures of placebo responsiveness and suggestibility and none, to our knowledge, have corrected for compliance during suggestibility assessment (23). It is possible that participants may comply with demand characteristics as they are able to infer the expected outcome of a placebo study. Moreover, it is unclear to what extent experimenters were aware of participants' suggestibility levels in some of these studies. Experimenter unmasking inflates effect sizes (24) and is likely to influence placebo responsiveness, particularly in highly suggestible individuals who may display elevated responsiveness to demand characteristics (15).

In two double-blind studies, we assessed the extent to which direct verbal suggestibility (henceforth, suggestibility) would account for variability in placebo responsiveness. We used an established placebo analgesia paradigm (25) and corrected suggestibility measures for compliance (13, 23). In Study 1, we evaluated hypnotic suggestibility as a predictor of placebo hypoalgesia, induced through conditioning and verbal suggestion, which when coupled are known to maximize responsiveness (25). In Study 2, we measured non-hypnotic suggestibility and placebo hypoalgesia induced through verbal suggestion without conditioning, in order to more specifically target individual differences in responsiveness to suggestion. We expected that suggestibility would account for a significant amount of the variance in placebo responsiveness and that this would be more pronounced when suggestion was the primary means of placebo induction.

Study 1

METHODS

Design

This study, which was conducted from April 2017 to April 2018, used a repeated-measures design in which all participants underwent screening for hypnotic suggestibility and, in an independent session, underwent an assessment of responsiveness to a conditioned hypoalgesia procedure (see **Figure 1**). The placebo experiment was undertaken by a different experimenter in a non-hypnotic context in which no

mention of hypnosis, including the previous hypnotic suggestibility screening, was made to the participants and no induction was administered. In addition, the experimenter was unaware of participants' hypnotic suggestibility, thereby ensuring a double-blind design. The study was approved by the Research Ethics Committee of the Department of Psychology at Goldsmiths, University of London.

The conditioned hypoalgesia paradigm consisted of three phrases (stimulation calibration, conditioned hypoalgesia, and experimental hypoalgesia assessment), that were completed in a single one-hour session. Self-reported pain in response to varying electrical stimulation applied to the left forearm was measured in the calibration phase for determining stimulation levels in subsequent phases. The conditioning phase aimed to produce an association between lower pain expectancies and perceived pain, with stimulation of a placebo-treated region relative to a control-treated region through the surreptitious administration of different stimulation levels to each region. In the experimental phase, participants underwent a similar procedure but with the same level of stimulation applied to both placebo and control regions of the forearm.

Participants

57 individuals were recruited from a research participant database and ranged in age from 18 to 62 (M_{Age}=23.68, *SD*=8.09). Participants were primarily female (44 females, 13 males). All participants were right-handed, psychology students with normal or corrected-to-normal vision and did not meet the following exclusion criteria: 1) history of chronic pain or cardiovascular, neurological or psychiatric diseases or any dermatological conditions, 2) contraindications for electrical stimulation, 3) consumption of any kind of sedative in the last 12 hours, 4) history of being on chronic medication or allergic reactions to topical anaesthetics, or 5) being (possibly) pregnant. Participants were informed that the study concerned the relationship between time perception and pain using an analgesic cream. No reference was made to the suggestibility screening, hypnosis, or placebo in the information sheet given to participants or in any verbal communication. All participants provided informed written consent and were compensated at a rate of £10/hour. After completing the experiment, participants were debriefed regarding the purpose

of the study and given the opportunity to withdraw their data, with none reporting any adverse opinions pertaining to the deception and none withdrawing their data. We determined sample size through an *a priori* power analysis (r=.40, two-tailed, α=.05, power=.90), with the effect size being an approximation derived from previous studies on the relation between placebo and suggestibility (rs=.35-.46; (26, 27)), resulting in a planned sample size of 61. We ceased data collection following recruitment of N=57 participants as the experimenters were no longer available for further testing; data were not inspected until collection was complete.

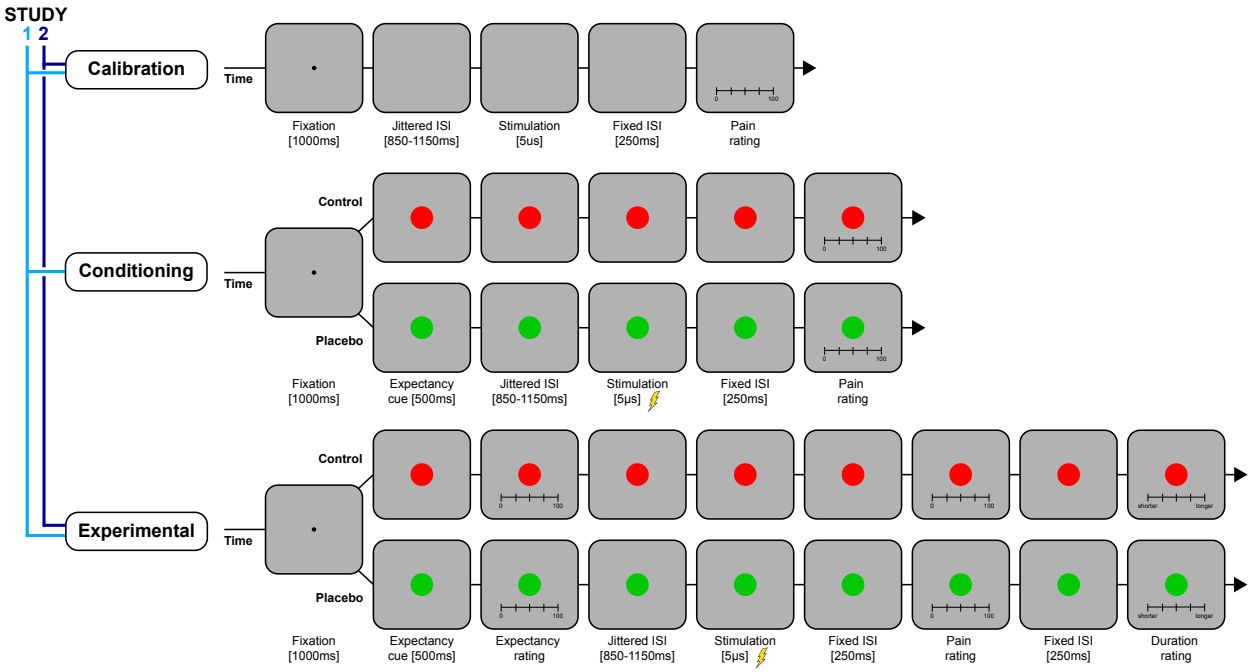

Figure 1. Diagram depicting different phases of Study 1 and Study 2. Stimulation magnitude in the calibration phase varied on a trial-by-trial basis. In the conditioning phase, stimulation magnitude was fixed at 80% (control) and 40% (placebo) of the visual analogue scale estimated from the calibration phase. In the experimental phase, stimulation magnitude as fixed at 60% (both conditions) of the visual analogue scale estimated from the calibration phase.

Procedure

Experimental preparation

During all phases, participants were seated approximately 60cm from a computer monitor with their left forearm positioned on a desk with the volar side facing up. Three stimulation areas (1x1 cm^2) separated by 1cm were drawn on the left forearm with the centre square corresponding to the midpoint between the wrist and elbow. A black square was drawn in the centre (calibration) and green (placebo) and red (control) squares were drawn on either side (position counterbalanced across participants) (28). Electrical stimulation always consisted of a single pulse (500microseconds [μs]; range: 0-100mA) delivered to one of the forearm locations using an isolated, constant current stimulator (Digitimer Ltd, model DS7A, Hertfordshire, England) via a square-wave pulse current through a concentric surface electrode (WASP Electrode, Specialty Developments UK). Stimulus presentation and Digitimer triggering was implemented using Psychtoolbox (v. 3 (29) in MATLAB (R2016b, MathWorks, Natick, MA). Participants were instructed to rate their pain intensity without using any pain suppression strategies in all phases.

Calibration phase

In order to calibrate the stimulation intensity to the individual level of sensitivity, each participant underwent a stimulus calibration procedure. The electrode was placed in the black (calibration) square. Each trial consisted of a black fixation circle (1000ms), a blank screen (jittered interval: 850, 950, 1050, or 1150ms) and then stimulation of varying amplitude. Participants subsequently used a mouse to click on a visual analogue scale (VAS) that included numerical and verbal anchors (0%="no pain at all" to 100%="unbearable pain") with no time limit. Stimulation amplitude was updated on a trial-by-trial basis after each rating. Participants were administered gradually increasing stepwise stimuli on each trial in a pseudorandom sequence controlled by the experimenter until a pain rating of 80% was reached, at which point the procedure was repeated with an aim to cover the spectrum of ratings between 0% and 80% (28). The initial stimulation amplitude was presented at ~5% on the VAS (~5mA) and increased in estimated

steps of approximately 10%, with minor adjustments of step sizes based on participants' shifts in VAS ratings between trials as well as the proximity to the upper (80%) boundary. VAS ratings were subsequently regressed on stimulation amplitudes using linear regression to estimate stimulation intensities corresponding to pain ratings of 40%, 60%, and 80%.

Conditioning phase

The conditioning phase followed an established placebo analgesia protocol which includes conditioning and verbal suggestions (28). This paradigm aims to instil strong expectations for lower pain in response to stimulation of a region treated with an inert placebo cream (identified as an anaesthetic), relative to a region treated with the same inert cream (identified as a control cream).

The experimenter first applied swabs of moisturizing cream (E45® moisturizing lotion, Reckitt Benckiser Group plc, Slough, UK) to control (red) and placebo (green) squares. These colours were used as they are known to influence the placebo response (26, 30). Concurrently, the experimenter gave participants verbal suggestions that the cream applied to the green square was a highly effective numbing agent, whereas the cream applied to the red square was a standard moisturiser that served as a sensory control and would have no effect on pain. Participants were given verbal cues and reinforcements of the effectiveness of the placebo cream throughout the duration of the experiment, particularly when the creams were applied ("this is a highly effective anaesthetic cream containing the local anaesthetic Lidocaine® which will numb your skin and minimize pain in response to the stimulation") and just prior to the conditioning procedure ("you should now be feeling less pain due to the powerful anaesthetic taking effect"). Both creams were kept in professionally labelled bottles that were visible to participants throughout the experiment in order to further reinforce the suggestions. Participants were next told that they would need to wait for 10 mins in order to allow the anaesthetic cream to take effect and sufficiently numb the area.

Participants subsequently completed 12 conditioning trials in which the experimenter surreptitiously lowered the stimulation level (VAS 40%, based on the calibration procedure, M=13.9mA, SD=12.3)

applied to the placebo (green) area relative to the level applied to the control (red) area (80%, *M*=39.6mA, *SD*=22.8). The block involved 6 placebo and 6 control trials in randomized order. Trials commenced with a black fixation circle (1000ms), followed by an expectancy prompt (red or green circle) denoting the area that would be stimulated, to which participants provided a VAS expected pain rating for the upcoming stimulus. The stimulation cue remained present (jittered interval as above) followed by stimulation applied to the control or placebo area. Participants were next prompted to provide a VAS pain rating followed by a fixed inter-trial interval (1000ms).

Experimental phase

In the test phase, stimulation amplitude remained uniform across all stimulation areas and trials (VAS 60%, *M*=26.3mA, *SD*=16.4). Participants completed 8 blocks (4 placebo, 4 control) of 8 experimental trials, which were randomized on a block-by-block basis. Trials consisted of the same sequence as in the conditioning phase, except after the pain rating participants also rated the perceived duration of the stimulation relative to the average of the preceding trials using a VAS (0%="shorter than average" to 100%="longer than average"). This was done in order to assess the relation between perceived pain and perceived stimulus duration; these data are not reported here. After the conclusion of the task, participants were queried regarding what they thought the purpose of the experiment was using a single sentence in a questionnaire (*n*=2 correctly identifying the placebo manipulation) and were subsequently debriefed.

Materials and Measurements

Hypnotic suggestibility

Participants were first invited to take part in a modified version of the *Harvard Group Scale of Hypnotic Susceptibility* (31) (henceforth MHGS), an index of hypnotic suggestibility (13). The scale was administered to participants in groups (>30 participants) in an auditorium by the senior author and consisted of a relaxation-based hypnotic induction followed by 10 suggestions for motor or perceptual alterations, which were assessed using brief behavioural tests. Responsiveness to the suggestions was

measured by having participants estimate the extent to which they responded to each suggestion using a four-point scale (0-3) using behavioural criteria. Modifications included the use of the scale, which enhances item sensitivity (32) and removal of 6 items with poor psychometric properties (23, 33), which were replaced with 4 items drawn from other scales (arm levitation; positive visual hallucination; auditory hallucination; negative visual hallucination; (34, 35). Subsequently, participants rated their experience of involuntariness for each suggestion using a 6-point scale (0-5) (36). Both measures exhibited strong internal consistency (Cronbach's α: MHGS: .80, involuntariness: .80). Suggestibility was corrected for compliance (23) by summing standardized (z) scores for the two measures, which penalizes voluntary responding (henceforth, MHGS-CC (13).

Statistical Analysis

Data are freely available here: osf.io/w52aq. Data were analysed using MATLAB (R2016b, MathWorks, Natick, MA). Dependent measures included mean pain intensity ratings, mean expectancy ratings, and compliance-corrected hypnotic suggestibility (MHGS-CC). Contrasts between control and placebo conditions were performed with paired-samples *t*-tests. Correlations between suggestibility and placebo response, operationalized as the condition difference (control – placebo), were computed using the Robust Correlation toolbox (37). Spearman correlations were used whenever data violated distribution normality or homoscedasticity. When multivariate outliers (minimum covariance determinant estimation and box-plot rule) were omitted in the computation of skipped correlations (37), the number of omitted outliers is reported. We report Bootstrap 95% confidence intervals (CIs; 10,000 samples) for effect size estimates (Hedges's *g* and correlation coefficients). The correlational analysis between hypnotic suggestibility and placebo response was supplemented with a Bayes factor (*BF*) in order to index the likelihood that the result favoured the null or alternative hypothesis (38). The *BF* was computed in MATLAB (39, 40) using an expected correlation drawn from a previous study with a similar methodology showing a positive association between suggestibility and placebo response (26). The *BF* was computed using a half-normal distribution with a specific *SD* ($BF_{0,SD}$) (38), where the *SD* corresponds to the magnitude of the expected

effect. Correlation coefficients were *z*-transformed prior to computing the *BF*. As per convention, we interpreted *BF*s less than 0.33 and greater than 3.0 as providing substantial evidence in favour of the null and alternative hypotheses, respectively, and in-between values as reflecting insensitive evidence (40, 41).

Results

Conditioning and expectancy

During the conditioning procedure, participants reported (*M*±*SD*) significantly greater pain for the control area, 0.64±0.15, than the placebo area, 0.41±0.20, $t(56)=8.11$, $p<.001$, $g=1.24$ [0.93, 1.63], thereby confirming that the conditioning procedure was effective in convincing participants regarding the efficacy of the sham analgesic cream. This was further corroborated by expectancy ratings in the test phase when the control and placebo conditions included the same level of stimulation. As can be seen in **Figure 2**, pain expectancy ratings were greater in the control condition, 0.65±0.13, than in the placebo condition, 0.48±0.19, $t(56)=5.80$, $p<.001$, $g=1.00$ [0.68, 1.37], indicating higher expectations for the hypoalgesic effects of the placebo.

Placebo response and hypnotic suggestibility

In the test phase, pain ratings were significantly greater for control stimulation, 0.62±0.16, than placebo stimulation, 0.51±0.20, $t(56)=3.88$, $p<.001$, $g=0.63$ [0.32, 0.97], reflecting a robust placebo response (**Figure 2**). We operationalized the magnitude of the placebo response and placebo expectancy as the difference in mean pain ratings between conditions (control – placebo) for perceived pain (range: -0.40 to 0.78, 0.12±0.23) and expected pain (range: -0.36 to 0.80, 0.17±0.22), respectively. Placebo expectancy significantly correlated with placebo response, $r_s=.96$, $p<.001$ [.92, .98] (4 outliers). Behavioural MHGS scores ($M=9.96$, $SD=6.21$) were comparable to the larger sample from which participants were drawn ($N=695$, $M=10.18$, $SD=5.76$), reflecting a relatively normal level of hypnotic suggestibility. Although there was a weak, albeit non-significant, tendency for compliance-corrected hypnotic suggestibility (MHGS-CC) to positively correlate with placebo expectancy, $r_s=.25$, $p=.066$ [-.04, .49] (1 outlier),

placebo response did not significantly correlate with MHGS-CC scores, r_s=.11, p=.44 [-.17, .37]. However, using an expected effect size from a previous study reporting an association between suggestibility and placebo responding (26), the Bayes factor was insensitive in adjudicating between the null and alternative hypotheses, $BF_{0,.37}$=.71, rendering this non-significant result ambiguous.

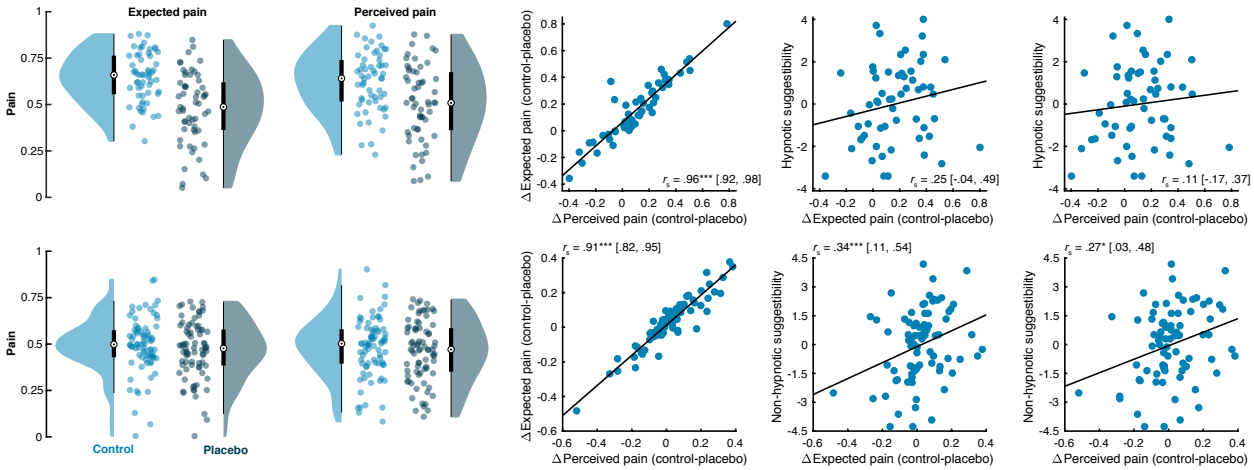

Figure 2. Placebo hypoalgesia effects. Expected and perceived pain shown in control and placebo conditions in Study 1 (top) and Study 2 (bottom). Correlations between measures indicated on right of figure.

* p<.05 ** p<.01 *** p<.001

Discussion

These results indicate that the conditioning and suggestion procedure effected a significant placebo response that correlated with the difference in expected pain between control and placebo conditions. There was a weak, albeit non-significant, association between hypnotic suggestibility and the reduction in pain expectancy in the placebo condition, but not with the placebo response. One possible explanation for the latter was the inclusion of conditioning in the placebo protocol, as a previous study similarly found

that hypnotic suggestibility did not significantly correlate with conditioned placebo hypoalgesia (22). It remains unclear whether suggestion and conditioning operate through overlapping or distinct mechanisms. Preliminary evidence suggests that hypnotic suggestibility is not associated with responsiveness to conditioning (e.g., (42)) although this question has not been systematically studied to our knowledge. Accordingly, the use of conditioning and suggestion in the same protocol may mask individual differences in placebo responsiveness that are driven by suggestion. This warrants attention to the role of suggestibility in placebo responses that are driven solely by suggestions.

Study 2

This study, which was conducted from March 2018 to July 2018, sought to evaluate the hypothesis that suggestibility relates to placebo responsiveness when suggestion is the primary agent in the placebo protocol. Toward this end, we omitted the conditioning procedure from the placebo protocol in order to better capture individual differences in suggestion-mediated placebo responsiveness. We further modified the procedure by using a measure of direct verbal non-hypnotic suggestibility (13), which reliably correlates with hypnotic suggestibility (12, 13). Non-hypnotic suggestibility has greater relevance to placebo hypoalgesia, which is typically assessed in a non-hypnotic context. Additionally, we examined whether the placebo-suggestibility association is independent of fear of pain and pain-related anxiety (26). We predicted that suggestibility would be positively associated with hypoalgesia and that this effect would be independent of these variables but mediated by placebo expectancy.

METHODS

Design

The design of this study was similar to that of Study 1 and involved a repeated-measures design in which all participants were screened for direct verbal non-hypnotic suggestibility and subsequently underwent an assessment of responsiveness to a suggested hypoalgesia procedure in a single session in counterbalanced order. As in Study 1, no mention of hypnosis was made to participants and no induction

procedure was administered. The experimenter was unaware of participants' suggestibility, thereby ensuring a double-blind design. The study was approved by the Research Ethics Committee of the Department of Psychology at Goldsmiths, University of London.

Participants

80 individuals took part in this study. Two withdrew after completing the pain calibration procedure resulting in a final sample of 78 participants (age range: 18-61; M_{Age}=26.1, *SD*=7.35; 51 females, 27 males). Participants met the same inclusion/exclusion criteria as in Study 1. Participants provided informed written consent in accordance with approval from the Research Ethics Committee in the Department of Psychology, Goldsmiths, University of London and were compensated at a rate of £10/hour. Participants were informed that the purpose of the study was to examine the relationship between pain and time perception. On the basis of a previous study (26), we determined our sample size through an *a priori* power analysis (*r*=.35, two-tailed, α=.05, power=.90), resulting in a planned sample size of 81. We ceased data collection prior to this due to the unavailability of the experimenter; data were not inspected until collection was complete.

Procedure

The experimental preparation, calibration and experimental phases, including the verbal suggestions administered to participants, were the same as in Study 1, with the exception that the conditioning phase was omitted. The stimulation amplitude (VAS 60%, based on the calibration procedure) was *M*=19.4mA, *SD*=16.9. In addition, participants completed two psychometric measures (see below) during the phase when they were informed that the analgesic cream was taking effect. The experiment lasted approximately seventy minutes.

Materials and Measurements

Direct verbal suggestibility

Participants completed the *Brief Suggestibility Scale* (BSS (13)), a behavioural measure of non-hypnotic suggestibility. The scale consists of an audio recording of a female voice actor administering six suggestions for alterations in motor control (e.g., paralysis) and perception (e.g., auditory hallucination). Each item involved a suggestion for a specific response followed by the cancellation of the suggestion. Participants completed a measure of responsiveness to each suggestion on a scale from 0 to 1 that included behavioural anchor criteria and a measure of involuntariness for each suggestion on a 6-point scale (0="did not experience at all", 1= "voluntary response" to 5="involuntary response") (36). Each participant completed the scale alone in a laboratory via headphones. The two scales had acceptable internal consistency (α = .65 and .63, respectively). As in Study 1, we corrected suggestibility for compliance by summing z-transformed scores of the two measures (BSS-CC).

Fear of Pain and Pain Anxiety

Participants completed the 9-item *Fear of Pain Questionnaire* short form (FPQ-9 (43), which measures the extent to which people fear certain types of pain. The questionnaire uses a 5-point scale with higher scores indicating more fear with scores ranging from 9 to 45. Participants also completed the 20-item *Pain Anxiety Symptom Scale* short form (PASS-20 (44), which measures fear and anxiety associated with pain using a 5-point scale with scores ranging from 0 to 100.

Statistical Analysis

Data were analyzed in the same manner as in Study 1, other than the addition of partial Spearman correlations (r_{ps}) in which different covariates were included (pain anxiety, fear of pain, age, and sex), a mediation analysis to evaluate placebo expectancy as a mediator of the association between suggestibility and placebo response, and comparison of correlation coefficients using Bootstrap resampling (45); the magnitude of different correlation coefficients were compared by iteratively sampling with replacement from each data set, standardizing the coefficients, and computing the correlation difference (10,000 samples). 95% CIs of this distribution were then used to infer statistical significance. *BF*s were computed

as in Study 1 (39, 40) with expected effect sizes drawn from Study 1 for analyses of the magnitude of placebo expectancy and response and the correlations among variables; from a previous study on the association between suggestibility and placebo responsiveness (26); and from the association between suggestibility and placebo responsiveness in Study 2. In each case, we specify the source of the respective expected effect size.

Results

Expectancy

Participants reported higher pain expectancy ratings in the control condition, .50±.15, than in the placebo condition, .47±.16, although this did not achieve statistical significance, $t(77)=1.62$, $p=.11$, $g=0.18$ [-0.03, 0.40]. Using the magnitude of placebo expectancy from Study 1 as an expected effect size, this result was inconclusive in distinguishing the null (no difference between studies) and alternative (difference between studies) hypotheses, $BF_{0,.17}=0.67$. These data suggest that the placebo manipulation, in the absence of conditioning, was not sufficiently powerful to significantly modulate participants' expectancies.

Placebo response and suggestibility

Similar to expectancy ratings, average pain ratings across participants were lower in the control condition, .48±.16, than in the placebo condition, .46±.16, but this difference was non-significant, $t(77)=0.96$, $p=.34$, $g=0.11$ [-.11, 0.33]. Using the magnitude of the placebo response of Study 1 as the expected effect size, these data yielded insufficient evidence to distinguish between the null and alternative hypotheses, $BF_{0,.12}=0.38$.

We next examined whether different measures would still account for variability in the magnitude of the placebo response between participants, operationalized as the condition difference (control – placebo; range: -0.52 to 0.38, 0.02±0.16). Placebo response did not significantly correlate with pain anxiety (PASS), $r_s=.16$, $p=.17$ [-.08, .38], or fear of pain (FOP), $r_s=-.03$, $p=.77$ [-.28, .21] (1 outlier). BSS behavioural scores, 0.38±0.19, were comparable to a previous sample, $N=205$, 0.36±0.20 (13), indicating

average suggestibility. Placebo response was significantly positively correlated with compliance-corrected suggestibility (BSS-CC), r_s=.27, p=.017 [.03, .48]. The magnitude of this effect was consistent with both a previous association (26), $BF_{0,.37}$=7.15, and the non-significant result of Study 1, $BF_{0,.11}$=4.82, and remained stable when adjusting for pain anxiety, r_{ps}=.26, p=.021 [.02, .48], fear of pain, r_{ps}=.27, p=.018 [.04, .49], age, r_{ps}=.28, p=.015 [.05, .49], and sex, r_{ps}=.24, p=.035 [-.00, .46]. A final multiple regression examined whether the magnitude of this association was independent of potential task order (BSS vs. placebo). Placebo response was regressed on three predictors: BSS-CC, task order, and their interaction (to assess moderation) and yielded a significant model, $F(3,74)$=4.02, p=.011, adjusted R^2=.11. BSS-CC remained a significant positive predictor, b=.26, t=2.34, p=.022, and order was a borderline non-significant negative predictor, b=-.21, t=1.98, p=.052, but, critically, their interaction did not significantly predict placebo response, b=.09, t=0.86, p=.39. This indicates that the association between suggestibility and placebo response was independent of psychometric, age, sex, and task order and was not significantly moderated by task order.

We next contrasted these effects against the corresponding results in Study 1. The correlation between placebo response and suggestibility in Study 2 did not differ from that in Study 1, r_s *Mdn* difference=.16 [-.18, .51]. The same held for the correlation between suggestibility and placebo expectancy, r_s *Mdn* difference=.07 [-.29, .42].

Placebo pain expectancy as a mediator of the suggestibility-placebo association

Our final analyses considered whether the suggestibility-placebo association was mediated by placebo expectancy (control – placebo; range: -.48 to .40, 0.03±0.15). Placebo response strongly positively correlated with placebo expectancy, r_s=.91, p<.001 [.82, .95] (3 outliers), yielding robust evidence in replication of the corresponding effect in Study 1, $BF_{0,1.95}$=1.80x10^{34}. BSS-CC was also significantly positively correlated with placebo expectancy, r_s=.34, p=.002 [.11, .54], similar to in Study 1, $BF_{0,.26}$=27.83. A mediation analysis corroborated the hypothesis that placebo expectancy fully mediated the association between suggestibility (BSS-CC) and placebo response. In particular, once placebo

expectancy was included in the model, BSS-CC scores no longer predicted placebo response, direct effect: b=0.001 [-0.01, 0.01], z=-0.19, p=.85, whereas the indirect effect (suggestibility-placebo expectancy x placebo expectancy-placebo) was highly significant, b=0.025 [0.01, 0.04], z=3.07, p=.002. The suggestibility-placebo association (when adjusting for placebo expectancy), r_{ps}=-.11, p=.33 [-.35, .12], was also significantly lower than the original correlation, r_s *Mdn* difference=.29 [.03, .53]. The correlation (-.11) yielded evidence in favor of the null hypothesis (no association between suggestibility and placebo responsiveness) using the original correlation as an expected effect size, $BF_{0,.28}$=.23, but ambiguous evidence for or against the null hypothesis (similarly-sized coefficients in Studies 1 and 2) relative to this association in Study 1, $BF_{0,.11}$=.48.

Discussion

In two double-blind studies, we investigated whether individual differences in suggestibility account for variability in placebo hypoalgesia responsiveness with and without conditioning (25, 28). Suggestibility did not significantly correlate with placebo responsiveness when the placebo manipulation included both conditioning and suggestion (Study 1), but significantly correlated with responsiveness when the manipulation only included suggestion (Study 2). These results suggest that suggestibility confers predisposition to placebo hypoalgesia, but that this effect is only present, or most pronounced, in the absence of conditioning and/or with non-hypnotic suggestibility. These findings have implications for the current understanding of variability in responsiveness to suggestion within the context of placebos and warrant greater attention to the study of inter-individual differences in placebo responding.

There is disagreement regarding the association between responsiveness to suggestion and placebo due to mixed findings in the literature (5). It seems plausible that this variability is attributable to methodological differences, including variability in the strengthening of response expectancies (19), placebo paradigms, and suggestibility measures (8). Here we used two different, albeit correlated (12), measures of hypnotic and non-hypnotic direct verbal suggestibility, corrected scores for compliance, and augmented response expectancies through either conditioning and/or repeated direct suggestions. In Study

1, we replicated previous results showing that conditioning coupled with suggestion effects a strong placebo response (25, 28). By contrast, after omitting conditioning in Study 2, the placebo response became weak and non-significant, as in previous studies that only included suggestion (e.g. (46)). Despite the larger effect in Study 1, we did not observe a significant correlation between suggestibility and placebo responsiveness, similar to a previous study (22), although Bayesian analyses suggested the results were insensitive in discriminating the null and alternative hypotheses. However, in Study 2, suggestibility significantly predicted placebo responsiveness, with this effect remaining stable when adjusting for potential confounding variables, thereby replicating and expanding upon research using self-report suggestibility measures (26). Although the magnitude of the placebo-suggestibility effect was larger in Study 2, Bayesian analyses suggested that it was consistent with that observed in Study 1. The association between conditioning and suggestion is poorly understood, but there is preliminary evidence that they operate through distinct mechanisms (47). In turn, coupling the two procedures within a single protocol may serve to inter-mix the capacities to respond to each, thereby attenuating the potential to capture variability in responsiveness to suggestion (but see (19)). This has implications for clinical placebo experiments which usually involve classical conditioning paradigms (48). Suggestibility is likely to be a valuable predictor of responsiveness to treatments in which suggestion is the primary agent, such as hypnosis (49).

Despite this divergence in the magnitude of the placebo response and its relation to suggestibility, placebo responsiveness was strongly related to placebo expectancy in both studies, thereby reaffirming the close coupling of expected and perceived pain (6, 18, 50). Of note, suggestibility was either suggestively or significantly related to placebo expectancy in both studies, which indicates that highly suggestible individuals appear to have an increased capacity for developing strong hypoalgesia expectations. Critically, the association between suggestibility and placebo responsiveness in Study 2 was fully mediated by placebo expectancy (see also (26). This result is consistent with Bayesian models of placebo hypoalgesia (16, 18), the association between response expectancies and suggestibility (15) and the moderating influence of expectancy on the association between suggestibility and placebo responding

(19). These effects further accord with the proposal that highly suggestible individuals are characterized by an enhanced propensity for forming precise priors that are subsequently over-weighted against sensory evidence (17).

These results have further implications for the stability of the placebo response and the notion of a good placebo responder (5). Quasi-stability of responding across contexts is implicit in this notion and thus necessary for identifying correlates of placebo responsiveness. Suggestibility is highly stable and heritable (11) and may underlie, or covary with, other factors related to placebo responding. For example, greater placebo responsiveness among children (51) and highly empathic individuals (52) may be influenced by elevated suggestibility in both of these populations (53, 54). Previous research showing that responsiveness to different placebos does not tend to correlate (3, 4) has been leveraged to argue against the stability of placebo responsiveness. However, in the former study, response expectancies remained a reliable predictor of responsiveness to different placebos and responsiveness to the same placebo correlated across testing sessions. Coupled with the present results, suggestibility plausibly represents an ability characterized by a propensity for forming strong hypoalgesia expectations that generalizes across suggestion protocols.

Despite the value of our results, they should be considered against some limitations. The most notable confound in comparing the results of our studies is that we used a hypnotic suggestibility scale in Study 1 and a non-hypnotic scale in Study 2. Although these two scales moderately correlate (13), it is possible that the differential correlations between suggestibility and placebo hypoalgesia in the two studies is driven by the use of different scales rather than the differential inclusion of the conditioning protocol. Indeed, previous studies reporting positive associations between suggestibility and placebo responsiveness used non-hypnotic suggestibility measures (19, 26). Accordingly, further research is required to more rigorously evaluate this association with and without conditioning with different types of scales. A related concern is whether the results are in any way shaped or moderated by a hypnotic context effect, whereby the presumed role of hypnosis augmented the placebo response. It seems unlikely that such a context effect played a role, as the magnitude of the placebo response in Study 1, which included a

measure of hypnotic suggestibility, was notably lower than that observed in a comparable study (Cohen's *d*=~2; (26) and no mention of hypnosis was made in either study. By contrast, insofar as direct verbal suggestibility and placebo hypoalgesia were measured in the same experiment in Study 2, an open question is whether the results will generalize to contexts in which these variables are measured in independent sessions. A further confound in these studies could be a response bias in which participants responded to the placebo manipulation in order to please the experimenter rather than because of a genuine response. This effect might have been further magnified by the use of a subjective VAS and participants' ability to infer the expected response (55). Such a bias cannot be ruled out, but neuroimaging studies demonstrate that subjective reports are accompanied by physiological changes (6). Moreover, by correcting for compliance, our suggestibility measure is unlikely to be related to such compliance effects. The results are also potentially confounded by a habituation effect of repeated stimulation of the same area of the arm (56). However, insofar as this effect would be similar for placebo and control conditions, it is unlikely to account for the observed effects. These limitations are not specific to this study but rather found in the majority of placebo hypoalgesia studies.

In summary, we found that suggestibility is associated with placebo hypoalgesia responsiveness only in the absence of conditioning. This work corroborates the extant literature suggesting the presence of at least two distinct cognitive mechanisms underlying placebo responsiveness: conditioning and suggestion. The present results indicate that suggestibility may only be relevant to variability in placebo responsiveness when suggestion is the primary agent of the placebo.

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