Original Research

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No evidence for an acute placebo effect on emotional processing in healthy volunteers

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Abstract

Placebo-controlled trials are the gold standard measure of efficacy in the development of new treatments for depression. However, the large placebo effects associated with standard measures of subjective symptoms reduce the sensitivity of such trials to detect antidepressant effects. There is a need to develop novel efficacy markers that are resistant to placebo effects. Measures of emotional processing, known to be sensitive to antidepressant treatment, may be such a marker, although the effect of an acute placebo treatment on these measures remains unclear. We assessed the influence of placebo on a validated battery of emotional processing tasks, the Emotional Test Battery (ETB), in healthy participants. Participants were informed they might receive the antidepressant drug bupropion, placebo or no treatment, with placebo effect being estimated as the difference between the placebo and no treatment groups. We found no significant difference between these groups on measures of emotional processing. There was also no effect of subjective treatment expectancy on performance in the tasks. This suggests that the ETB might be a useful tool for Phase I trials assessing novel antidepressant agents against placebo.

Keywords

Placebo, placebo effect, placebo response, depression, emotional processing

Introduction

Placebo-controlled trials are necessary to develop new treatments for depression¹. However, the placebo effect accounts for approximately 68% of the benefit of an active antidepressant². Such a large effect inevitably reduces the power of trials to identify antidepressant effects in novel compounds. Therefore, there is a need to identify methods of testing novel agents that minimise placebo effects and allow the value of any antidepressant drug action to be captured.

Patients with depression are known to exhibit a bias toward negative emotional stimuli³. Antidepressants typically abolish these biases, even after a single dose. For example, a single dose of citalopram or reboxetine increases the detection of happy faces compared with placebo^{4,5}. Changes in bias toward positive emotional stimuli and reductions in threat-relevant processing are also seen in sub-chronic administration of antidepressants⁶. These changes in emotional processing occur before changes in subjective mood become apparent. However, placebo treatments can also affect emotional processing. In two previous studies, placebo anxiolysis was induced in participants either through a conditioning procedure or through verbal instruction^{7,8}. Meyer et al.⁷ found that repeated administration of a placebo nasal spray reduced vigilance and arousal to threat of shock in healthy participants who were informed that the spray was a powerful anxiolytic. Petrovic et al.⁸ used a conditioning procedure to induce placebo anxiolysis in healthy participants. A dose of midazolam given intravenously reduced the subjective unpleasantness of distressing pictures on day 1. On day 2, subjects were instead given saline but informed they were given midazolam. Nevertheless, as with day 1, the “treatment” reduced subjective unpleasantness of the distressing pictures. Whether a single dose of placebo, without prior conditioning or instruction, can affect emotional processing biases in the context of an antidepressant trial is unknown. This question has clear implications for the development and validation of this experimental medicine model for early characterisation of novel compounds.

In this study, we aimed to measure the effect of a single dose of placebo on emotional processing in the context of an antidepressant trial in healthy volunteers. We carried out a double-blind randomized controlled trial with three parallel arms: bupropion, placebo and no treatment. Here, we report the data from the placebo and no treatment groups as an estimate of the placebo effect in this study. Data from the bupropion arm will be published separately.⁹ Carrying out this study as part of another trial allowed the possibility for participants to be allocated to active drug, simulating the uncertainty of treatment allocation seen in randomized controlled trials. Unlike other studies that have explored mechanisms of placebo response, we did not condition participants to respond to placebo treatment. We were instead interested in measuring the potential for a placebo effect in treatment-naïve volunteers in this experimental paradigm. Our comparison of interest was difference between placebo and no treatment in performance in a validated battery of cognitive tasks (Oxford Emotional Test Battery, ETB; P1 vital, Oxford, UK).

Methods

The study was approved by the University of Oxford research ethics committee (MSD-IDREC-C3-2014-004) and was carried out in accordance with the protocol and provisions of the World Medical Association Declaration of Helsinki. All participants provided written, informed consent.

Information Given to Participants

Potential participants responded to adverts displayed in University departments and on the internet. They were then sent a copy of the participant information sheet, which stated that we aimed to study the effects of the antidepressant bupropion on emotional processing. Participants were not informed of our secondary aim to investigate the effects of a single dose of placebo until they were debriefed at the end of the study. The sheet also gave information about bupropion's action as a noradrenaline-dopamine reuptake inhibitor and potential side effects that a person might experience after a single 150mg dose. Finally, participants were informed they would be randomized to one of three arms in this trial, leading to a 1 in 3 chance of receiving active medication. If participants remained interested in the study they were invited for a screening assessment where we reiterated the above information as part of the informed consent process.

Participants

We recruited 60 participants who were subsequently randomised into three equal groups: bupropion, placebo and no treatment (Figure 1). In this paper, we present data from the placebo and no treatment arms of the trial (baseline characteristics are summarised in Table 1). Eligible participants were sufficiently fluent in English to complete the behavioural tasks, free of current or past history of Axis I disorder on the Structured Clinical Interview for DSM-IV (SCID)¹⁰ and assessed as physically fit to take bupropion by a medical doctor. Participants were excluded from the study if they were currently taking any psychoactive medication or medication contraindicated with bupropion, had previous experience of the behavioural tasks, had participated in a psychological or medical study involving the use of medication in the previous 3 months, had a current or past history of substance misuse, or were currently pregnant or breastfeeding. We carried out a urine drug and pregnancy screen to ensure participants were not currently misusing substances or were pregnant.

Study Procedures

Eligible participants were invited to attend a testing session 1-2 weeks following the screening assessment. Prior to treatment administration, participants completed the following questionnaires to assess their mood and personality characteristics: The Hamilton rating scale for depression 17-item version (HAM-D)¹¹, The Positive and Negative Affect Schedule (PANAS)¹², The Full Mood and Anxiety Symptom Questionnaire (MASQ)¹³, The Befindlichkeits Scale (BFS)¹⁴, The Snaith-Hamilton Pleasure Scale (SHAPS)¹⁵, and The Adult Eysenck Personality Questionnaire (EPQ)¹⁶. We also asked participants to complete a side-effects questionnaire comprised of the side-effects most common for bupropion: nausea, dizziness, dry mouth, headache, agitation, itching, and sweating. Finally, participants rated their expectation of drug treatment causing a change in their emotional processing on a visual analogue scale (VAS) ranging from 0 - 100.

Following completion of the questionnaires, participants were randomised to either placebo treatment or no treatment. Participants were assigned a group at random, matched by age and National Adult Reading Test (NART)¹⁷-derived IQ and stratified by gender, using a computer program created and operated by an independent researcher in Microsoft Excel. To maintain blinding, treatment was administered by an independent researcher while the investigator left the room. Those in the placebo group were given an encapsulated lactose tablet, while those in the no treatment group were told they would receive no medication. A 3 hour wait period followed treatment administration, which was required for bupropion to reach maximum plasma concentration in those who received it¹⁸. Participants then completed the Oxford Emotional Test Battery (ETB) to assess emotional processing (see below). Following the ETB, participants again completed the PANAS, BFS, SHAPS, and side-effects questionnaire to assess for a change in mood state brought about by testing and to assess for side-effects.

The Oxford Emotional Test Battery

The Oxford Emotional Test Battery (ETB) comprises five validated, computerised cognitive tasks designed to assess the processing of a variety of emotionally valenced stimuli. The ETB is sensitive to the negative biases in emotional processing observed in depression and to the early effects of antidepressants on emotional processing¹⁹. The ETB comprises the following tasks, administered in order:

Facial Expression Recognition Task (FERT)

The task stimuli consist of a series of facial expressions associated with six basic emotions: anger, disgust, fear, happiness, sadness, surprise taken from the Pictures of Affect Series²⁰. These images have been ‘morphed’ in 10% steps of the shape and texture differences between the 0% neutral face and the 100% expression face²¹. In each trial, a face was presented on a computer screen for 500 msec followed by a blank screen. Participants were asked to identify the facial expression as quickly and as accurately as possible, by pressing a labelled button. Four examples of each emotion at each intensity were presented in a random order (six emotions X ten intensities X four examples = 240 trials). The Pictures of Affect Series uses 10 actors, and each actor’s neutral face was also shown. Hence, a total of 250 faces were presented to each participant. Outcome measures were recognition accuracy, percentage of misclassifications and average reaction time for correct responses for each emotion. Signal detection theory was also used to provide estimates of target sensitivity (d') and response bias (β) for each emotion.

Emotional Categorisation Task (ECAT)

A series of 60 words, either positive or negative descriptors of personality, were randomly presented in the centre of a display screen, each for 500 msec. The personality descriptive words were matched for word length, frequency and meaningfulness. Participants were instructed to indicate whether they would like or dislike to be called each word by pressing a correspondingly labelled button. Outcome measures were categorisation accuracy and average reaction time for correct responses.

Facial Dot-Probe Task (FDOT)

The FDOT is based upon a previously described task²². Briefly, this task begins with a central fixation cross displayed on a computer screen followed by a pair of faces: one above and one below the central point. Each face might be positive, negative or neutral. A probe (two dots) is then shown, with equal frequency, in the location of one of the preceding faces. Participants were asked to indicate whether the two dots were aligned horizontally or vertically as quickly and accurately as possible by pressing a correspondingly labelled button. Their response terminated the display and began the next trial.

In this study, participants completed a total of 96 trials. Forty-eight trials paired a positive facial expression (happy) with a neutral face, and the other 48 trials paired a negative facial expression (fear) with a neutral face. The faces were either 'unmasked' and presented for 500 msec, or 'masked' and presented for 14 msec followed by a mask of special characters displayed in the same position. The dot-probe appeared in either the same position as the emotional face (congruent trials) or in the position opposite the emotional face (incongruent trials). Each type of trial was presented in a random order, divided across 4 blocks. Reaction time was used as an outcome measure to calculate attentional vigilance scores for each emotion.

Emotional Recall Task (EREC)

We gave participants a surprise free recall test in which they were asked to write down as many of the self-referent words that they could remember from the ECAT within a 2 minute time limit. The outcome measure was the number of positive and negative self-referent words correctly and falsely recalled.

Emotional Recognition Memory Task (EMEM)

A series of 120 words, comprising the positive and negative self-referent words included in the ECAT and previously unseen distractor words were randomly presented in the centre of a display screen, each for 500 msec. Participants were instructed to indicate whether they had previously seen the word during the ECAT. Outcome measures were percentage accuracy, percentage misclassification of familiar words as novel and vice versa, and average reaction time for correct responses for positive versus negative words.

Statistical Analysis

Prior to statistical analysis, we visually inspected the raw behavioural data for anomalous values through the use of scatter graphs. In addition, trials with reaction times 3 or more standard deviations from the mean or below 200 msec were excluded prior to calculating the overall mean. We excluded one participant in the placebo group from the FERT since they scored 0% accuracy for recognising fearful faces meaning the average reaction time for correct responses could not be calculated. We also excluded one participant in the no treatment group from the FDOT analysis as a large number of trials were removed during trimming (64 of 192).

Statistical analysis was performed using the SPSS (IBM SPSS Statistics for Windows version 24.0; IBM Corp., Armonk, NY) and JASP (JASP version 0.8.1.2; JASP Team

(2017)) statistical packages. We analysed baseline demographic and trait measures through independent t-tests. Where questionnaires were repeated, we analysed the change in score to assess for change in mood state and side-effects over the experiment. We carried out independent t-tests for questionnaires with 1 scale and for questionnaires with multiple scales we used a repeated measures ANOVA. We analysed outcome measures in the ETB through mixed model ANOVA with repeated measures. For all measures, group (placebo or no treatment) was defined as the between-subject factor. The within-subjects factors were emotion (FERT), word valence (ECAT, EREC, EMEM) and masking, emotion, and congruency (FDOT). We did not correct the significance level for the number of tests across the tasks, as we wanted to minimise the chance of a type II error. This was important given our aim of identifying any evidence for a placebo effect in these tasks. To ascertain how likely our data were under the null hypothesis that there was no difference in performance on the tasks between the groups, we carried out post-hoc Bayesian repeated measures ANOVAs. In these ANOVAs, each model was compared with the null model. We interpreted the Bayes Factors according to Kass and Raftery²³ (Table 2). To assess for an effect of expectancy in the ETB, we carried out repeated measures ANCOVAs with expectancy as a covariant in the placebo group. The within-subject measures were as above. Again, we conducted post-hoc Bayesian repeated measures ANCOVAs to assess the likelihood of the null hypothesis that there was no effect of expectancy. We interpreted the Bayes Factors as described above. Finally, we calculated observed power of statistical tests by extracting partial η^2 values from SPSS and inputting these into G*Power²⁴.

Results

Participant Demographics & Characterisation

There were no significant differences between groups in gender, age, verbal IQ, expectancy, and baseline scores on the HAM-D and self-report questionnaires (Table 1).

Change in Mood and Side-Effects

Both groups showed a reduction in positive mood over the time of the experiment (Table 3). Both groups showed a similar change in scores on the questionnaires, other than in the SHAPS where the placebo group showed a significantly greater decrease over time ($t_{(24)} = 2.33$, uncorrected $p = 0.028$).

There was no significant evidence for treatment-induced side-effects. The majority of participants reported that side-effects were absent pre- and post-treatment. On repeated measures ANOVA, there were no significant changes in side-effect ratings over time ($F_{(3,126)} = 0.76$, $p = 0.528$) and no significant interactions with group ($F_{(3,126)} = 0.89$, $p = 0.454$).

ETB – Placebo vs No Treatment

The results of the ETB are summarised in Table 4. Overall, both groups showed similar behavioural results on the ETB, with a main effect of emotion seen in all the tasks as

described below. Group effects were not significant, and there were no significant interactions with Group.

In the FERT, we found a significant effect of emotion in all outcome measures (all $p < 0.001$). This was driven by both groups identifying happy faces more accurately than other emotions, and both groups responding slowest to fearful faces. The Bayesian analysis showed further evidence against a group effect. In all outcome measures, there was decisive evidence for models with a main effect of emotion ($\log_{10}(\text{BF}_{10}) > 3.38$). There was substantial evidence against an emotion*group interaction in response bias and reaction time (BF ratio = 5.28 and 8.23, respectively), and decisive evidence against this interaction in percentage accuracy, d prime and misclassifications (BF ratio > 24.95).

In the emotional categorisation and memory tasks, there was a significant effect of emotion in the ECAT, with reaction times being slower for negative words in both groups ($p = 0.002$). Bayesian analysis of these data showed strong evidence for an effect of word valence ($\log_{10}(\text{BF}_{10}) = 1.30$). However, the evidence for an interaction between word valence and group was inconclusive (BF ratio = 3.09). In the EREC, more positive words were recalled correctly than negative words ($p = 0.031$) and both groups made more positive than negative commission errors ($p = 0.004$). The Bayesian analysis also suggested both groups behaved similarly. There was strong evidence against an interaction between word valence and group in number of commission errors (BF ratio = 11.79). In number of words correctly recalled, there was inconclusive evidence for a word valence*group interaction ($\log_{10}(\text{BF}_{10}) = 0.11$) in the opposite direction to a placebo effect (i.e. worse recall of positive vs negative items after placebo compared to no treatment). Finally, in the EMEM, there was an emotion*misclassification type interaction in the frequentist analysis, with both groups misclassifying more positive words as familiar and more negative words as novel ($p < 0.001$). Bayesian analysis showed strong evidence against an interaction between group and misclassifications (BF ratio = 82.08). The evidence was inconclusive for an effect of group on reaction time ($\log_{10}(\text{BF}_{10}) = 0.09$). However, the data were unlikely under models including an emotion*group interaction for % accuracy and reaction time ($\log_{10}(\text{BF}_{10}) = -1.43$ and -1.16 , respectively).

In the FDOT, both groups demonstrated reduced reaction times in congruent fearful trials ($p = 0.044$) and increased vigilance to unmasked fearful faces and masked happy faces ($p = 0.007$). On Bayesian analysis of reaction times, unlike in the frequentist ANOVA, there was evidence against a main effect of emotion ($\log_{10}(\text{BF}_{10}) = 0.01$). In terms of vigilance, the evidence for an emotion*masking interaction was inconclusive ($\log_{10}(\text{BF}_{10}) = -0.15$). Nevertheless, in both outcome measures, the data were unlikely under models including an interaction with group ($\log_{10}(\text{BF}_{10}) < -0.66$).

ETB – Placebo group with expectancy as a covariant

Although there appeared to be no difference between the placebo and no treatment groups in the ETB, we wanted to ascertain whether expectation of a drug effect exerted an influence on emotional processing. Therefore, we carried out a repeated measures ANCOVA in the placebo group only with expectation as a covariant. We asked

participants to rate their expectation of a drug effect on a visual analogue scale (VAS) ranging from 0 to 100 prior to randomisation and treatment administration. Mean expectation was 31.1 (SD ± 23.1), with a median of 23.5. We found no significant effects of, or interactions with, expectancy in any of the tasks (Table 5). The results of Bayesian repeated measures ANCOVAs showed decisive evidence for an effect of emotion in the FERT ($\log_{10}(\text{BF}_{10}) > 2.65$). The evidence for an effect of expectancy alone was inconclusive to unlikely in all tasks ($\log_{10}(\text{BF}_{10}) < 0.04$, BF ratio > 17.89). The evidence for models including an effect of expectancy and emotion was inconclusive (BF ratio 1.92-2.72). For brevity the results of this analysis are summarised in the supplementary Table S1.

Effect size of placebo treatment

We next wished to determine the effect size of placebo treatment in the ETB. We first examined the effect size of medication to understand the power of this paradigm to detect a meaningful drug effect. When comparing bupropion with placebo in our study, we found that there was a significant emotion intensity*treatment interaction in recognition accuracy for happy faces in the FERT ($p < 0.01$)⁹. In a previous study by this group, in which a single dose of citalopram was compared with placebo in a similar sample of healthy volunteers, the effect size of citalopram on accuracy for identifying happy faces in the FERT was found to be large (means calculated were absolute accuracy: drug mean 25.8 ± 1.44 ; placebo mean 24.0 ± 2.88 ; Cohen's $d = 0.79$)²⁵. The effect size of bupropion in our study was $d = 0.74$ (means calculated were % accuracy: drug mean 80.0 ± 5.85 ; placebo mean 74.3 ± 9.36). Although the effect size of bupropion was smaller than the drug in the above study, the observed power of the repeated measures ANOVA to detect a within-between interaction was calculated to be 0.98.

We next carried out a post-hoc power analysis of the repeated measures ANOVA to detect a within-between interaction in the placebo and no treatment groups in this study. On each outcome measure, the effect sizes of placebo were small (Cohen's f ranged from 0.1 to 0.24) leading to a post-hoc power ranging from 0.12 to 0.64 (Table 6). This suggests that we would need a sample size of 27 participants per group to have an 80% chance of detecting a significant difference between placebo and no treatment in one outcome measure in the FERT. By contrast, 13 participants per group would be adequate to have an 80% chance of detecting the effect we saw in the FERT for bupropion compared with placebo.

Discussion

In this study, we aimed to measure the effect of a single dose of placebo treatment on emotional processing in antidepressant-naïve healthy volunteers. Compared with no treatment, we found that a single dose of placebo does not significantly alter measures of emotional processing in the ETB. There was also no effect of expectancy on performance in the tasks. On Bayesian analysis, the evidence was inconclusive or against models containing either group or expectancy effects. Finally, the effects of a placebo treatment appeared to be in the opposite direction to those generally seen for medication.

We did not find a significant difference between the placebo and no treatment groups in outcome measures of the ETB. This was not due to the tasks lacking sensitivity, as we found a significant main effect of emotion in all tasks. Additionally, we found significant differences between bupropion and placebo in this study.⁹ Our findings were supported by the Bayesian analysis. There was strong evidence for a main effect of emotion in all tasks except the FDOT, but the data were generally unlikely under a significant placebo effect. This evidence was stronger in some tasks (e.g. FERT and EMEM) and less conclusive in other tasks (e.g. ECAT). It is noteworthy that the tasks with the best evidence against a placebo response involved a stimulus duration of 500 msec or less. There are data to suggest that tasks in which stimuli are presented for less than 500 msec test affective attentional biases more consistently in high anxious participants than those with durations more than 500 msec.²⁶ It is possible that the tasks in the ETB test emotional biases that are not easily altered by acute placebo treatment.

Previous studies have shown that placebo treatment can affect the processing of emotional stimuli in healthy volunteers^{7,8}. Both of these studies involved either a 'conditioning' phase or giving participants verbal information to induce an expectation of reduced anxiety during the experiment. In the present study, we mimicked a clinical trial by giving participants only the information required to give informed consent, i.e.: the purpose of the study, our hypotheses, potential side effects of the drug, but also that we did not know how bupropion would affect emotional processing. We therefore did not attempt to alter the natural expectations of the participants through a conditioning paradigm or other manipulation. We found that, in this context, an acute placebo treatment did not differ from no treatment.

The placebo effect is thought to result from an interplay between learning and prior expectations³⁰. Hence, we attempted to determine whether expectancy influenced emotional processing by including it as a covariant in our analysis. We found that participants' subjective expectancy of drug effect did not influence performance on the tasks in the ETB. The Bayesian analysis also generally showed evidence against an effect of expectancy in the tasks. These results suggest the ETB could be a useful experimental medicine model for measuring potential antidepressant effects while minimising expectancy effects. The participants in this study had no previous experience of antidepressant treatment. They were therefore unlikely to have an expectation that the drug would alter their emotional processing based on prior experience. This is supported by the generally low expectation we saw in the placebo group. Nevertheless, placebo responses have been demonstrated in participants even when there is no conscious expectation of a benefit. Rutchick and Slepian³¹ found that asking participants merely to handle ibuprofen increased their pain tolerance during a subsequent cold pressor test. It is possible that previous experience of a treatment could define a person's expectation of the outcomes of future treatments^{32, 33}. Therefore, in the Rutchick and Slepian study³¹, it might be that the participants' previous experience of ibuprofen led to an unconscious expectation of impending pain relief. It would be interesting to explore whether our study would show similar results if we repeated it with participants who have previously been treated with antidepressants.

An interesting result was the significant reduction in SHAPS score seen over the experiment in the placebo group, although this was significant at an uncorrected p of <0.05 . A lower SHAPS score suggests increased hedonic capacity¹⁵. Reduced activity in the ventral striatum has also been implicated in the experience of anhedonia²⁷. Placebo treatment has been shown to cause dopamine release from the ventral striatum, most notably in Parkinson's disease^{28, 29}. It is theoretically possible that the placebo treatment increased activity in this area, explaining the apparent improved hedonic capacity. However, there was no difference between the groups on other measures of mood and no difference was seen in terms of emotional processing on the ETB. Therefore, the cause and significance of this result remain unclear.

The effect size of a placebo treatment in this study was small. Previous studies by this group have shown significant differences between a single dose of medication and placebo in the ETB with smaller sample sizes^{5, 25, 34}. Additionally, in the present study, we found significant effects of bupropion treatment compared with placebo but did not find any significant effects of placebo compared with no treatment⁹. The effect size of active medication was larger than placebo in outcome measures for the ETB at a sample size of 20 per group. This is important as randomised controlled trials are expensive and time consuming, often due to the large sample sizes required³⁵. The ETB potentially offers a method in which significant effects of medication can be seen with small sample sizes. As such, the ETB could be a reliable experimental medicine model for Phase I trials, which necessarily have small sample sizes. However, our power calculation suggested that it might be possible to detect a placebo effect in these tasks in larger samples. We therefore need to replicate our findings in a larger sample to determine whether placebo effects remain minimal.

The main strengths of this study are the randomised double-blind design, which mimicked an antidepressant trial, and the objective emotional processing measures that minimise the possibility of a subjective, or observer-rated, placebo response. This is also the first study to attempt to measure the effect of a single dose of antidepressant placebo on emotional processing. A further strength is the Bayesian analysis that showed inconclusive or evidence against the hypothesis that there was a placebo effect in this study. However, there are some limitations. First, it could be argued that the sample size in this study was too small to be adequately powered to demonstrate equivalence. However, we would argue that our results suggest that at sample sizes adequate to detect a significant drug effect⁹, placebo treatment appears to be equivalent to no treatment. Second, it would have been beneficial to assess expectancy again after treatment assignment, and possibly at the end of the study. This would have accounted for expectations being altered through participants receiving a tablet or experiencing side effects. However, this is not routinely done in a randomized controlled trial, and we did not want to potentially influence the results through repetitively asking this question.

Conclusion

We have shown that an acute placebo treatment does not differ from no treatment in antidepressant-naïve healthy volunteers completing the ETB. This suggests that the ETB might be a useful experimental medicine model for Phase I trials assessing novel antidepressant agents against placebo. Future studies should determine whether the ETB is also resistant to placebo effects in those who have had antidepressant treatment previously and in clinical populations.

Funding and Conflicts of Interest

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References

1. Baldwin DS, Broich K, Fritze J, Kasper S, Westenberg H and Moller HJ. Placebo-controlled studies in depression: necessary, ethical and feasible. *Eur Arch Psychiatry Clin Neurosci.* 2003; 253: 22-8.
2. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ and Hofmann SG. Meta-analysis of the placebo response in antidepressant trials. *Journal of affective disorders.* 2009; 118: 1-8.
3. Roiser JP, Elliott R and Sahakian BJ. Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2012; 37: 117-36.
4. Harmer CJ, Bhagwagar Z, Perrett DI, Völlm BA, Cowen PJ and Goodwin GM. Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2003; 28: 148-52.
5. Harmer CJ, Hill SA, Taylor MJ, Cowen PJ and Goodwin GM. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *The American journal of psychiatry.* 2003; 160: 990-2.
6. Harmer CJ, Shelley NC, Cowen PJ and Goodwin GM. Increased positive versus negative affective perception and memory in healthy volunteers following selective

- serotonin and norepinephrine reuptake inhibition. *The American journal of psychiatry*. 2004; 161: 1256-63.
7. Meyer B, Yuen KS, Ertl M, et al. Neural mechanisms of placebo anxiolysis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2015; 35: 7365-73.
 8. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K and Ingvar M. Placebo in emotional processing--induced expectations of anxiety relief activate a generalized modulatory network. *Neuron*. 2005; 46: 957-69.
 9. Walsh AEL, Huneke NTM, Brown R, Browning M, Cowen PJ and Harmer CJ. A dissociation of the acute effects of bupropion on positive emotional processing and reward processing in healthy volunteers. Submitted.
 10. First MB, Spitzer RL, Gibbon M and Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. 2002.
 11. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23: 56-62.
 12. Watson D. Intraindividual and interindividual analyses of positive and negative affect: their relation to health complaints, perceived stress, and daily activities. *J Pers Soc Psychol*. 1988; 54: 1020-30.
 13. Clark LA and Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J Abnorm Psychol*. 1991; 100: 316-36.
 14. Von Zerssen D, Strian F and Schwarz D. Psychological Measurements in Psychopharmacology. 1974.
 15. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D and Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry*. 1995; 167: 99-103.
 16. Eysenck SB, Eysenck HJ and Barrett P. A revised version of the psychoticism scale. *Personality and individual differences*. 1985; 6: 21-9.
 17. Nelson HE. *National Adult Reading Test (NART): For the assessment of premorbid intelligence in patients with dementia: Test manual*. NFER-Nelson, 1982.
 18. Jefferson JW, Pradko JF and Muir KT. Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. *Clinical therapeutics*. 2005; 27: 1685-95.
 19. Harmer CJ, Goodwin GM and Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *The British journal of psychiatry : the journal of mental science*. 2009; 195: 102-8.
 20. Ekman P and Friesen WV. Pictures of Facial Affect. 1976.
 21. Young AW, Rowland D, Calder AJ, Etcoff NL, Seth A and Perrett DI. Facial expression megamix: tests of dimensional and category accounts of emotion recognition. *Cognition*. 1997; 63: 271-313.
 22. Cooper RM and Langton SR. Attentional bias to angry faces using the dot-probe task? It depends when you look for it. *Behav Res Ther*. 2006; 44: 1321-9.
 23. Kass RE and Raftery AE. Bayes factors. *Journal of the american statistical association*. 1995; 90: 773-95.

24. Faul F, Erdfelder E, Buchner A and Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods*. 2009; 41: 1149-60.
25. Murphy SE, Norbury R, O'Sullivan U, Cowen PJ and Harmer CJ. Effect of a single dose of citalopram on amygdala response to emotional faces. *The British journal of psychiatry : the journal of mental science*. 2009; 194: 535-40.
26. Frewen PA, Dozois DJ, Joannis MF and Neufeld RW. Selective attention to threat versus reward: Meta-analysis and neural-network modeling of the dot-probe task. *Clinical psychology review*. 2008; 28: 307-37.
27. Keedwell PA, Andrew C, Williams SCR, Brammer MJ and Phillips ML. The neural correlates of anhedonia in major depressive disorder. *Biological psychiatry*. 2005; 58: 843-53.
28. Lidstone SC, Schulzer M, Dinelle K, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. *Archives of general psychiatry*. 2010; 67: 857-65.
29. de la Fuente-fernández R and Stoessl AJ. The biochemical bases for reward: Implications for the placebo effect. *Evaluation & the Health Professions*. 2002; 25: 387-98.
30. Benedetti F, Carlino E and Pollo A. How placebos change the patient's brain. *Neuropsychopharmacology*. 2011; 36: 339-54.
31. Rutchick AM and Slepian ML. Handling Ibuprofen increases pain tolerance and decreases perceived pain intensity in a cold pressor test. *PloS one*. 2013; 8: e56175.
32. Huneke NT and Baldwin DS. Does previous experience of antidepressants form the expectations necessary for a placebo response? *Br J Psychiatry*. 2015; 207: 561.
33. Kessner S, Forkmann K, Ritter C, Wiech K, Ploner M and Bingel U. The effect of treatment history on therapeutic outcome: psychological and neurobiological underpinnings. *PloS one*. 2014; 9: e109014.
34. Browning M, Reid C, Cowen PJ, Goodwin GM and Harmer CJ. A single dose of citalopram increases fear recognition in healthy subjects. *Journal of psychopharmacology (Oxford, England)*. 2007; 21: 684-90.
35. Sibbald B and Roland M. Understanding controlled trials: Why are randomised controlled trials important? *BMJ*. 1998; 316: 201.