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The magnitude of placebo analgesia effects depends on how they are conceptualized

Karen Lund [a], Gitte L. Petersen [b], Mogens Erlandsen [c], Vilfredo De Pascalis [d], Lene Vase [b], Troels S. Jensen [a,e], Nanna B. Finnerup [a,*]

[a] Danish Pain Research Center, Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Psychology, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark
[c] Section of Biostatistics, Department of Public Health, Aarhus University, Aarhus, Denmark
[d] Department of Psychology, La Sapienza, University of Rome, Rome, Italy
[e] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

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ABSTRACT

Objective: Placebo effects are usually calculated as the difference between placebo treatments and no treatments. Recently, placebo-like effects have been investigated using open and hidden administrations of active treatments. The aim of the study was to directly compare the two types of placebo effects and examine how they are influenced by personality traits.

Methods: In a within-subject, randomized, blinded, balanced placebo trial design study with 48 healthy volunteers, we compared placebo and placebo-like effects and tested if expectancy, absorption and suggestibility correlated with these effects. Subjects completed the Tellegen Absorption Scale and the Sensory Suggestibility Scale, and pain was induced by injections of hypertonic saline into the masseter muscle. Participants received four injections of hypertonic saline with lidocaine or matching placebo in randomized order: open treatment, hidden treatment, placebo and control. The placebo effect was defined as the difference in pain between the placebo and the control condition and the placebo-like effect as the difference in pain between the open and hidden condition.

Results: Placebo effects were significant both in the traditional paradigm: mean placebo effect AUC 1626 mm^2 (95% CI 958–2293) and the open–hidden paradigm: mean placebo-like effect AUC 801 mm^2 (95% CI 134–1469), but there was a significant difference between the magnitude of the two effects ($p = 0.049$). Absorption and suggestibility did not predict the placebo or the placebo-like effect. Estimated expected pain relief correlated with placebo effects but not placebo-like effects.

Conclusion: The magnitude of placebo effects differs depending on how they are conceptualized and calculated.

Introduction

Placebo is an inert agent, and the placebo effect has traditionally been defined as the difference in response across a no-treatment and a placebo treatment group or condition [1–3]. So far, pain conditions have been the best studied field in placebo research [4]. Traditional placebo designs make it possible to estimate the effect of an inert agent controlled for the natural history of pain, such as spontaneous fluctuations in pain and regression towards the mean [1]. Placebo effects have also recently been investigated by using open and hidden administrations of active drugs, i.e., without administration of an inert placebo agent [3,5]. In the open condition, the subject is aware of the administration of the drug, whereas in the hidden condition, the drug is administered without the subject's knowledge. The difference in pain levels has been termed a placebo-like effect since only an active drug is administered [6]. Possible differences between the two methods of conceptualizing and calculating placebo effects have received little attention.

The balanced placebo trial design balances the open and hidden treatments with a placebo treatment and a control condition [7]. The balanced placebo trial design was designed to test the interaction between instruction/belief/verbal information and drug content. In the within-subject, balanced placebo trial design, the subjects receive an inert agent twice and an active drug twice, and the information given to the subjects (correct or false) is balanced with the administration of drugs (active or inactive). It therefore allows comparisons of control, placebo and hidden and open drug administrations in the same trial. In this study, we originally showed that the treatment effect was smaller than the sum of the drug effect and the placebo effect, supporting that

* Corresponding author at: Danish Pain Research Center, Department of Clinical Medicine, Aarhus University Hospital, Norrebrogade 44, building 1A, DK-8000 Aarhus C, Denmark. Tel.: +45 7846 4230; fax: +45 7846 3269.
E-mail address: finnerup@clin.au.dk (N.B. Finnerup).

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drug and placebo effects are subadditive [8]. The balanced placebo trial design also allows estimation of placebo and placebo-like effects in the same trial, which is the focus of the current part of the study.

Studies have shown that an individual's previous experiences and expectations of pain [2,9,10], classical conditioning [9] and relief of stress, fear and anxiety [11,12] all play an essential role for the placebo effects in pain studies. Little is known of the extent to which personality traits systematically influence the placebo effect [13–15]. Absorption is the tendency to become immersed in, e.g., movies, acting, nature, voices and past events [16]. The absorption trait is associated with hypnotizability [17], which in turn is related to levels of suggestibility [18]. Suggestibility is a person's susceptibility and responsiveness to suggestions, e.g. verbal information about the benefits of a treatment. One study conducted by De Pascalis and colleagues found that individual differences in suggestibility contributed significantly to the magnitude of placebo analgesia effects with the largest placebo effect observed in highly suggestible subjects who received verbal suggestions presumed to elicit high expectancy for drug efficacy [19].

The aim of this study was to compare placebo and placebo-like effects and to test if expected pain, absorption and suggestibility scores correlated positively with placebo and placebo-like effects. Parts of the results are reported elsewhere [8].

Methods

Participants

Healthy volunteers were recruited through advertisement at educational institutions, and all subjects were financially compensated for their participation with Danish Kroner 1200. The following exclusion criteria were applied: age younger than 18 years; chronic pain and pain on examination days; inability to cooperate; psychiatric, neurological, or other significant medical disorders; previous significant problems in teeth or jaw; diabetes; allergy to lidocaine; intake of pain medication during the past week; alcohol and drug abuse; and previous participation in trials using the same method (injection of hypertonic saline into the masseter muscle).

The study was carried out at the Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark, and at the Department of Psychology, School of Business and Social Sciences, Aarhus University, Denmark, from March 7 to November 21, 2012. The study was approved by the Ethical Committee of the Central Denmark Region (Number 1-10-72-114-12) and by the Danish Data Protection Agency (Number 1-16-02-19-12), and all participants gave informed written consent. Participants were informed that the aim of the study was to investigate the variability of pain intensity by means of an experimental pain model with and without concomitant analgesic treatment and to investigate the influence of psychological factors on pain variability.

Experimental protocol

All participants attended three sessions on 3 separate days:

Day 1: A baseline session where all participants received an injection of 0.2 ml 5% hypertonic saline. Half of the participants were randomized to a conditioning injection with a high dose of lidocaine in order to increase the inter-individual variability in placebo effect sizes [20,21]. Participants who were not conditioned received an injection of hypertonic saline (5% in 0.2 ml). Participants in the conditioning group received an additional injection of hypertonic saline (10% in 0.08 ml) mixed with lidocaine (1% in 0.12 ml) in front of the participant in order to give the participants a prior experience of pain relief in association with the injection [8]. Participants were placed in a hospital bed in a supine position, and all examinations were performed by the same investigator (K.L.).

Day 2: A psychological assessment session, where participants were tested with the *Tellegen Absorption Scale* (TAS) [16] and the *Sensory Suggestibility Scale* (SSS) [22]. The psychological assessments on Day 2 were performed by G.L.P., with participants divided into groups of 4–13 subjects.

Day 3: An experimental session that included a control condition, an open and a hidden administration of lidocaine and an inert placebo administration in a within-subject, balanced placebo trial design [23] as described earlier [8]. On this day, participants received four injections in randomized order using a computer-generated randomization list. Two of the injections of hypertonic saline included lidocaine (0.1 ml HS 10% mixed with 0.1 ml lidocaine 1%): one was open (D) and one was hidden (B) (Fig. 1). The two remaining (A and C) injections consisted of hypertonic saline and matching placebo (0.1 ml HS 10% mixed with 0.1 ml sterile water): one of which was mixed in full view of the participants (C) (Fig. 1). Prior to injections A and B, the participants were told that "You will receive an injection of saline that produces experimental muscle pain", and in C and D that "The saline will now be mixed with a potent pain killer". It was emphasized to the participants that injections of saline produce pain of various intensities depending on the precise site of the injection. The investigator (K.L.) was blinded to whether the injection (A/B) or the vial added to the hypertonic saline (C/D) was with or without lidocaine [8]. The two vials (C/D) and injections A and B were identical in appearance. The injections were given first in the left masseter. After the pain had subsided completely a next injection was given in the right masseter muscle and after a 2-hour break, the 3rd and 4th injections were given in the right and then in the left masseter muscle. Injection 4 was given after the pain from injection 3 had subsided completely [8]. Participants were placed in a hospital bed in a supine position and all examinations were performed by K.L.

Pain model

Pain was induced by injections of hypertonic saline (5% in 0.2 mL) into the masseter muscle which yields a stable and moderate pain lasting approximately 3 min as previously described [24]. Pain intensity was continuously rated on a 100-mm electronic visual analogue scale (eVAS), with 0 mm indicating 'no pain' and 100 mm 'worst pain imaginable', until pain had subsided completely. Pain intensities were sampled every second by the computer. Lidocaine (1%) was used as analgesic treatment.

Psychological measures

In a psychological assessment session, participants were tested with the *Tellegen Absorption Scale* (TAS) [16] and the *Sensory Suggestibility Scale* (SSS) [22]. Participants first filled in the TAS, consisting of 34 items that measures the capacity to become absorbed in mental imagery. Each item is a statement which should be answered with either "yes" or "no" (e.g. "I am easily touched by elegant or poetic speech"). The answers should be given without too much consideration. Subsequently, the participants were tested with the SSS. The SSS was similar to the one used in the study by De Pascalis and colleagues [19] and at a workshop in Rome, Vilfredo De Pascalis carefully trained us in the use of the test and he supervised the back and forth translation of the scale from English to Danish. The scale consists of 14 exercises, of which 10 are true and 4 are false; only the results from the 10 true exercises are included in the total score. In each exercise, the participants are exposed to verbal suggestions along with potential sensory stimuli. For example, participants are given suggestions to the effect that a flash

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