



Cognitive Schemas in Placebo and Nocebo Responding: Role of Autobiographical Memories and Expectations

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ABSTRACT

Purpose: Placebo effects are presumed to be based on one's expectations and previous experience with regard to a specific treatment. The purpose of this study was to investigate the role of the specificity and valence of memories and expectations with regard to itch in experimentally induced placebo and nocebo itch responses. It was expected that cognitive schemas with more general and more negative memories and expectations with regard to itch contribute to less placebo itch responding.

Methods: Validated memory tasks (ie, the Autobiographical Memory Test and the Self-referential Endorsement and Recall Task) and expectation tasks (ie, Future Event Task and the Self-referential Endorsement and Recall Task) were modified for physical symptoms, including itch. Specificity and valence of memories and expectations were assessed prior to a placebo experiment in which expectations regarding electrical itch stimuli were induced in healthy participants.

Findings: Participants who were more specific in their memories regarding itch and who had lesser negative itch-related expectations for the future were more likely to be placebo itch responders. There were no significant differences in effects between the nocebo responders and nonresponders.

Implications: The adapted tasks for assessing cognitive (memory and expectations) schemas on itch seem promising in explaining interindividual

differences in placebo itch responding. Future research should investigate whether similar mechanisms apply to patients with chronic itch. This knowledge can be used for identifying patients who will benefit most from the placebo component of a treatment. (*Clin Ther.* 2017;39:502–512) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: autobiographical memory, cognitive bias, future expectations, itch, placebo effect.

INTRODUCTION

Placebo and nocebo effects are known to contribute to overall treatment outcomes in various conditions and symptoms (eg, pain, itch).¹ Whereas it is known that specific learning mechanisms (eg, conditioning) in general can result in placebo and nocebo effects, placebo and nocebo responses vary tremendously among individuals.^{2,3} In both experimental and clinical studies, individuals' placebo or nocebo responses have been shown to range from no effect to profound changes in symptoms or disease outcomes.^{4,5} Several studies have

Accepted for publication February 13, 2017.

<http://dx.doi.org/10.1016/j.clinthera.2017.02.004>
0149-2918/\$ - see front matter

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tried to identify the “placebo responder”, but this remains a challenge.⁶ Although the respective literature is still limited and inconsistent,⁶ certain traits have been proposed to contribute to placebo and nocebo responding, such as psychological traits, including optimism, neuroticism, or catastrophizing^{7–9}; genetic predispositions¹⁰; and cognitive factors, including cognitive schemas (ie, mental structure in which thoughts, information, and their inter-relationships are categorized) of memory about the past and expectations about the future.¹¹

Assessments of cognitive schemas of memories and expectations have shown that dimensions of specificity and valence of memories and expectations are of particular importance. With regard to specificity of memories and expectations, *overgeneral autobiographical memory*, defined as difficulty in retrieving specific autobiographical memories, has been shown to be related to depression and trauma-related psychopathology¹² and difficulties with social problem solving¹³ but specificity of autobiographical memory has never been investigated with regard to placebo and nocebo responses. With regard to valence of memories and expectations, positive previous experiences and positive expectations regarding a particular treatment are related to greater placebo responding, and negative previous experiences and negative expectations are related to greater nocebo responding.^{14–16} Furthermore, prior stimulus history can have an influence on placebo response.^{17,18} For example, results from a study by Geers et al¹⁷ showed that previous experience with a pain stimulus (cold pressor task) in daily life (pain trough contact with cold water) reduced the effectiveness of placebo analgesic expectation.

In the current study we sought to determine whether specificity and valence of memories and expectations are associated with placebo and nocebo itch responses. To answer this question, specificity and valence of participants’ memories and expectations regarding itch were assessed prior to a placebo and nocebo itch experiment in which expectations were induced by conditioning and verbal-suggestion procedures (see Bartels et al¹⁶). Both specificity and valence of memories and expectations were assessed with validated tasks modified for itch by our research group. We expected that, in particular, participants with more specific and more positive memories and expectations would show greater placebo responses, while participants with less specific and more negative

memories and expectations would be more likely to show nocebo responses. Furthermore, it was explored whether specificity and valence of itch-related memories were related to specificity and valence of itch-related expectations, respectively.

PATIENTS AND METHODS

Data were obtained in a single study, from which outcomes on the induction of placebo and nocebo effects on itch by different expectation inductions have been reported previously.¹⁶ The present study focused on the influence of individual cognitive schemas on placebo and nocebo itch responses. The methods (and data) concerning the cognitive schemas have not been described in the previous study. The methods concerning the induction of placebo and nocebo effects, and general preparatory steps, have previously been described¹⁶ and are briefly summarized here.

Ethics Statement

The study protocol was approved by a regional medical ethics committee (CMO Arnhem-Nijmegen, Nijmegen, the Netherlands) and follows the principles stated in the Declaration of Helsinki. All participants provided written informed consent and were reimbursed for their participation.

Participants

Healthy volunteers aged ≥ 18 years were recruited via an online research participant system (Sona Systems, Tallinn, Estonia) and at the Radboud University Nijmegen (Nijmegen, the Netherlands). Inclusion criteria were age ≥ 18 years and fluency in the Dutch language. Exclusion criteria were severe morbidity (eg, skin disease, multiple sclerosis, diabetes mellitus), psychiatric disorders (eg, depression), color blindness, regular use of medication in the preceding 3 months, use of pacemaker, pregnancy, and current or a history of chronic itch or pain.

Study Design

The study comprised 2 sessions in the laboratory, separated by ≥ 1 week. During session 1, participants’ cognitive schemas (ie, specificity and valence of memories and expectations regarding itch-related, pain-related, and standard events) were assessed. Specificity of memories was assessed with the Autobiographical Memory Test (AMT); specificity of

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