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

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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 predispositions[10]; 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 psychopathology[12] and difficulties with social problem solving[13] 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 al[17] 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 al[16]). 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 described[16] 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 $\geq$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 $\geq$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 $\geq$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

future expectations, with the Future Event Task (FET); valence of memories and future expectations, with the Self-referential Endorsement and Recall Task (SER).

During session 2, placebo and nocebo effects of electrically induced itch were assessed. Participants were randomized to 1 of 4 groups in which they received either: (1) verbal suggestion; (2) conditioning; (3) a combination of verbal suggestion and conditioning to induce expectations for low, medium, and high itch intensity (intervention groups); or (4) a control procedure (control group) (see Bartels et al[16]).

General Procedures

Recruitment was conducted by an online research-participant system (Sona Systems, Tallinn, Estonia) and through flyers posted at Radboud University. Eligibility of potential participants was determined by means of online self-report screening questionnaires, assessed by Sona Systems (Tallinn, Estonia).

Session 1

At the first laboratory visit (session 1), written informed consent was obtained, and baseline itch, pain, and fatigue were assessed using numeric rating scales (NRSs) ranging from 0.0 (no itch/pain/fatigue at all) to 10.0 (worst itch/pain/fatigue ever experienced). Subsequently, the adapted AMT, FET, and SER were administered in a randomized order. Also their subtasks (itch, pain, and traditional (with emotional cue words)) were administered in a randomized order.

Tasks Assessing Cognitive Schemas

Autobiographical Memory Test

The AMT was used for assessing the specificity of memories of participants regarding specific cue words. Three different versions of the AMT were administered in this study: the traditional version (AMT-t)[19]; a version for itch developed by our research group (AMT-i); and one for pain developed by our research group (AMT-p). The AMT-i was the focus of this study.

In all versions of the AMT, the cue words were consecutively, but in randomized order, presented verbally, and participants were asked to recall and write down a memory in response to each cue word.[20] Participants were instructed to write down an autobiographical memory, that is, a personally experienced event, that happened any time in the past, but not on the day of or the day before the administration of the instrument. The event could be important or not. Participants were asked not to write down the same event twice. In accordance with the Minimal Instructions version of the AMT,[21] which is more sensitive for detecting reduced specificity of autobiographical memory in nonclinical individuals than is the standard version, participants were not explicitly asked to come up with a specific memory but were merely asked "Can you write down an event that the word *X* reminds you of?". No examples of correct or incorrect responses were given and no practice items were provided. Participants were given 60 seconds per cue word to write down a memory.

The AMT-t consisted of 6 positive and 6 negative emotional cue words (eg, *happy* or *sad*)[19] (see **Supplemental Appendix 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.004). The AMT-i consisted of 9 itch-related cue words (**Table I**). The instructions were identical to those of the traditional AMT, but the participants were explicitly asked to write down a memory concerning itch. The AMT-p consisted of 9 pain-related cue words (see **Supplemental Appendix 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.004) and the participants were explicitly asked to write down a memory concerning pain.

The cue words used for the AMT-i and AMT-p (also the FET-i and FET-p; see subsequent text) had been collected from the itch and pain questionnaires, online patient panels, and input from a group of volunteers with chronic itch and/or pain symptoms. Subsequently, this large pool of words was scored by 5 independent raters on: (1) applicability to itch/pain (applicable to itch, pain, or neither); (2) familiarity, ranging from 0 (completely unfamiliar) to 5 (completely familiar); and (3) conceivability, ranging from 0 (completely not conceivable) to 5 (completely conceivable). The 18 words that scored the highest on the 3 scales for itch were used in the AMT-i and FET-i, and the 18 words that scored the highest on the 3 scales for pain were used in the AMT-p and FET-p.

Future Event Task

The FET was used for assessing the specificity of future expectations of participants regarding specific cue words. Three different versions of the FET were administered in this study: the traditional version

Table I. Cue words of the itch versions of the adapted Autobiographical Memory Task (AMT-i) and the adapted Future Event Task (FET-i).*

Task	Cue Words
AMT-i	Itch remedy (*middel tegen jeuk*)
	Sunburn peeling (*vervellen*)
	Rubbing (*wrijven*)
	Mosquito bite (*muggenbult*)
	Itchy spot (*plek die jeukt*)
	Scratching (*krabben*)
	Wool (*wol*)
	Eczema (*eczeem*)
	Rash (*huiduitslag*)
FET-i	Dry skin (*droge huid*)
	Scratch open (*openkrabben*)
	Itchy (*jeukend*)
	Nettle (*brandnetel*)
	Bumps (*bultjes*)
	Tickling (*kriebelen*)
	Allergy (*allergie*)
	Skin (*huid*)
	Itch (*Jeuk*)

*Original cue words in Dutch are shown in parentheses.

(FET-t)[22]; a version for itch developed by our research group (FET-i); and one for pain developed by our research group (FET-p). The FET-i was the focus of this study.

In the 3 versions of the FET, the cue words were consecutively, but in randomized order, presented verbally, and participants were asked to write down an expectation in response to each cue word. Participants were instructed to write down an autobiographical expectation, that is, an expectation of an event that can be personally experienced, which can happen at any time in the future, but not on the day of or the day after the administration of the instrument. This expectation could be important or not important. Participants were instructed not to write down the same event twice. Also in the 3 FET variations, "minimal instructions" were used, that is, participants were not explicitly asked to come up with a specific expectation but were merely asked "Can you write down an expectation that the word *X* makes you think of?" No examples of correct or incorrect responses were given, and no practice items were provided. Participants were given 60 seconds per cue word to write down an expectation.

The FET-t consisted of 6 positive and 6 negative emotional cue words (eg, *happy* or *sad*)[22] (see **Supplemental Appendix 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.004). FET-i and FET-p each included 9 cue words (see **Table I** for FET-i and see **Supplemental Appendix 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.004 for FET-p). The instructions were identical to those of the general FET, but the participants were explicitly asked to write down expectations concerning itch and pain.

Coding of AMT and FET

Once a participant completed a version of the AMT or FET (itch, pain, traditional), they were instructed, in line with the procedure used by Debeer et al,[21] to assign a code to each response according to the following categories: 1 (specific memory/expectation), M (memory of an event that occurred more than once/expectation that will occur more than once), or > (memory/expectation of an event lasting for >1 day), or to leave the answer blank (no memory/expectation was written down by the participant).

Afterward, the participants' responses to the AMT and FET were coded by a trained researcher using a method corresponding to that of Debeer et al.[21] Memories/expectations were coded as *specific* (see "1" in preceding paragraph) when they referred to a particular event that occurred/will occur within the course of 1 day, at a particular time and place (eg, "When I went to the museum last month I wore a wool sweater which was very itchy"). Nonspecific memories/expectations were qualified as either *extended* (a memory/expectation of a period lasting for >1 day, eg, "Last week I wore a wool sweater for a couple of days"; see ">" in preceding paragraph), *categoric* (a memory/expectation that summarizes a number or category of events, eg, "Every time I wore a wool sweater when I was a kid it felt so itchy"; see "M" in preceding paragraph), or *semantic associates* (verbal association with the cue, eg, "Wool sweaters usually itch"). Failure to provide a memory/expectation was classified as an *omission*. Finally, a category of *nonresponses* included all incomplete responses and all responses on which the instructions had not been followed (ie, events

Table II. Itch cue words for the Self-referential Endorsement and Recall task adapted for itch and pain.*

Adjective Type	Past	Future
Itch-positive	Acceptable (*acceptabel*)	Brief (*kortdurend*)
	Reduced (*verminderd*)	Cooled (*verkoeld*)
	Manageable (*handelbaar*)	Improved (*verbeterd*)
	Tolerable (*verdraagbaar*)	Relieved (*verlost*)
	Governable (*beheersbaar*)	Calmed (*gekalmeerd*)
	Overcome (*overwonnen*)	Acceptable (*aanvaardbaar*)
Itch-negative	Annoying (*irritant*)	Uncontrollable (*oncontroleerbaar*)
	Dominating (*allesbeheersend*)	Untameable (*onbedwingbaar*)
	Constraining (*dwingend*)	Unbearable (*ondraaglijk*)
	Maddening (*gekmakend*)	Intense (*intens*)
	Provoking (*treiterend*)	Persistent (*hardnekkig*)
	Tormenting (*kwellend*)	Impelling (*opjagend*)

*Original cue words in Dutch are shown in parentheses.

mentioned more than once, unrelated to itch/pain, or that occurred on the day of, before, or after the administration of the instrument).

In cases in which a response was not clear to the researcher, the participant's assigned code was used as a guide, unless the researcher considered the answer to be a *semantic associate* or *nonresponse* (which the participant was not able to assign), in which case the researcher decided between *semantic associate* or *nonresponse*. If *specific, categoric,* or *extended* was the most likely code according to the researcher and this code matched the participant's assigned code, this code was used as the final code. If a participant's assigned code was not one of the researcher's possibilities, another trained researcher performed the coding, and the 2 codes were compared. If there was disagreement between the 2 researchers, a third trained researcher was consulted and a final code was decided on using majority voting. For analysis of the AMT and FET data, the proportion of specific memories/expectations relative to the total number of memories/expectations was calculated for each participant (eg, AMT-i = [No. of specific responses]/9 – [No. of omissions + No. of nonresponses]).[21]

Self-referential Endorsement and Recall Task Adapted for Itch and Pain

The SER[23] was used for assessing valence of memories and expectations of participants. The SER was adapted by our research group for itch and pain (SER-ip) and included 48 cue words (adjectives) presented on a laptop computer. The task included 12 positive and 12 negative adjectives concerning itch, 12 positive and 12 negative adjectives concerning pain, and 8 filler items, administered in randomized order. The cue words used in the SER-ip were collected from itch and pain questionnaires, online patient panels, and input from a group of volunteers with chronic itch and/or pain complaints and several researchers. Four researchers did the final selection of the words. The itch-related cue words were the focus of this study (**Table II**); the pain-related cue words can be found in **Supplemental Appendix 2** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.004. Participants were asked to indicate for each word separately, by clicking "yes" or "no" on the computer screen, whether the word described their experience of itch in the past, experience of pain in the past, expectation of itch in the future, or expectation of pain in the future. A practice trial with general words that were not directly related to itch or pain preceded the actual task to ensure that participants understood the instructions.

Session 2

The procedures of the second laboratory visit (session 2) have previously been described[18] and are summarized here.

Placebo and nocebo effects regarding itch stimuli were induced by verbal suggestion, conditioning, or a combination of both procedures, and compared with those from a control group without expectation induction. Itch was induced with an electrical stimulator (Isolated Bipolar Constant Current Stimulator DS5; Digitimer, Welwyn Garden City, United Kingdom) at a 50-Hz frequency with a pulse duration of 100 μs and at continuously increasing current intensity (0.05 mA/s) to a maximum of 5 mA. The intensity of the stimulation for the low-, medium-, and high-intensity stimuli used in the conditioning design was individually determined.

In the learning phase, 18 itch stimuli were applied, of which the intensities depended on the manipulation from the experimental group. Each itch stimulus was preceded by a colored cue (in total, 6 green, 6 yellow, and 6 red cues) presented on a computer screen. In the learning phase of the *verbal suggestion group* (n = 23), participants were told that different colored cues indicated that the stimulus intensity would be altered: "A green cue will signal a decrease in itch intensity; a red cue, an increase; and a yellow cue, no change in itch intensity." Regardless of the color of the cue displayed, all itch stimuli were applied at a medium intensity. In the *conditioning group* (n = 24), the green, yellow, and red cues were repeatedly paired with low, medium, and high itch stimulus intensities, respectively. In the *conditioning with verbal suggestion group* (n = 23), the conditioning procedure and the verbal suggestion procedure were combined. In the *control group* (n = 25), no expectations regarding the itch stimuli were induced, and the cues were shown with itch stimuli randomly applied at low, medium, or high intensity. Subsequently, in the testing phase, 15 stimuli of medium intensity were applied in all groups (preceded by, in total, 5 green, 5 yellow, and 5 red cues), together with the verbal suggestion that corresponded with the verbal suggestion—if any—given in the learning phase (see Bartels et al[16]). For the purpose of the study, that is, to identify possible placebo responders, only the results from the 3 placebo and nocebo induction groups (and not the control group) were used for the analyses.

Statistical Analysis

All analyses were performed using SPSS version 22.0 (SPSS Inc. Chicago, Illinois). AMT-i and FET-i data were available from 78 of 95 participants. Data from 17 participants were unavailable because we started the experiment using the standard AMT and FET instructions[19] but noticed almost no variation in participants' responses (ie, almost all responses were specific). Therefore, we switched to the Minimal Instructions version, which for the AMT-t has been shown to be more sensitive in detecting reduced autobiographical memory specificity in nonclinical individuals than the standard version.[21] SER-ip data from 1 participant were unavailable due to equipment failure.

The proportion of specific answers on the AMT-i and FET-i were calculated. Mean SER-ip scores on endorsement of itch-related words from the 4 categories (positive/negative, past/future) were separately calculated. Assumptions (eg, of normality) regarding the FET-i and SER-ip statistical test results were violated. Nonparametric tests were used because transforming of data did not result in normal distribution.

For placebo and nocebo responding, the means of the NRS itch scores were calculated for the placebo and nocebo effects in the testing phases of the different groups in session 2. The nocebo effect was calculated as the difference between the mean itch NRS scores associated with the 5 red cues and the 5 yellow cues in the testing phase, and the placebo effect was calculated as the difference between the mean itch NRS scores associated with the 5 green cues and the 5 yellow cues in the testing phase (see Bartels et al[16]). Subsequently, the median placebo and nocebo effect values from the 3 experimental groups (verbal suggestion, conditioning, and verbal suggestion with conditioning) combined were calculated, and placebo and nocebo responders were classified as being at or above median, while the nonresponders fell into the category of below median. This classification system, used separately for the placebo and nocebo effects, created the *median-split factor* for use in the analyses.

To exploratively investigate the association between memories and expectations with regard to specificity and valence, correlation between the specificity of memories (AMT-i) and the specificity of expectation (FET-i) was determined in all participants, using the Spearman correlation coefficient. Likewise, correlation between the valence (positive/negative) of memories and valence of expectations regarding itch (SER-ip) was

Table III. Proportions* of specific memories and expectations for the placebo and nocebo effect, as measured using the adapted Autobiographical Memory Test for itch (AMT-i) and the adapted Future Event Task for itch (FET-i). Data are given as mean (SD).

	Placebo†		Nocebo†		
Task	Responders (n = 31)	Nonresponders (n = 26)	Responders (n = 31)	Nonresponders (n = 26)	All Participants‡
AMT-i	0.33 (0.15)	0.24 (0.15)	0.30 (0.15)	0.27 (0.17)	0.29 (0.17)
FET-i	0.10 (0.15)	0.12 (0.17)	0.12 (0.16)	0.10 (0.16)	0.10 (0.15)

*Theoretical range, 0−1. n Values are based on median split.
†Includes participants in the different placebo and nocebo inductions/conditions (ie, the verbal suggestion, conditioning, and conditioning with verbal suggestion groups; the control group was excluded from data analysis).
‡AMT-i, n = 78; FET-i, n = 77; includes the control group.

determined in all participants, using the Spearman correlation coefficient.

To test the hypothesis that placebo responders (based on median-split analysis) had more specific memories and expectations regarding itch, while nocebo responders (based on median-split analysis) had less specific memories and expectations regarding itch, 2 independent *t* tests (regarding the AMT-i) and 2 Mann-Whitney *U* tests (regarding the FET-i) were performed. To test the hypotheses that placebo responders had endorsed more positive memories and expectations regarding itch and that nocebo responders had endorsed more negative memories and expectations regarding itch, 8 Mann-Whitney *U* tests were performed. For all analyses, the level of significance was set at $P < 0.05$.

RESULTS

Participants

All 95 participants were of Dutch nationality (a mean [SD] age, 22.7 [3.2] years; 77% women). For analysis of AMT and FET, data from 78 participants were available (see Statistical Analysis section). This population was not significantly different from the main sample with regard to age and sex.

Correlations Between Memory and Expectations for Itch

No significant correlations between the proportion of specific memories (AMT-i) and the proportion of specific expectations (FET-i) for itch were found.

Significant correlations were found between the valence of memories and expectations for itch; the positive and negative memories for itch were both significantly correlated with positive ($r_s = 0.422$; $P < 0.001$) and negative ($r_s = 0.483$; $P < 0.001$) expectations, respectively, for itch. This finding suggests that participants who endorsed more positive memories also endorsed more positive expectations, while those endorsing more negative memories also endorsed more negative expectations.

Specificity of Itch Memories and Expectations in Relation to the Placebo and Nocebo Effects

The mean (SD) proportions of specific memories (AMT-i) and expectations (FET-i) for the placebo and nocebo effects are shown in Table III. An independent samples *t* test showed that the mean (SD) proportion of specific memories generated in response to itch-related cue words was significantly greater in the placebo responders than in the placebo nonresponders (0.33 [0.15] vs 0.24 [0.15]; $t[55] = 2.32$; $P = 0.024$), indicating that participants with more specific itch memories responded more strongly to the placebo itch induction. The difference between the nocebo responders and nonresponders was not significant ($t\,[55] = 0.91$; $P = 0.365$). Mann-Whitney *U* test did not show a significant difference in FET-i specificity between the placebo responders and nonresponders ($U = 372{,}500$, $z = -.534$, $p = .593$) or between the nocebo responders and nonresponders ($U = 351{,}000$, $z = -.910$, $p = .363$).

Table IV. Valence of memories and expectations for the placebo and nocebo effects on the itch as measured with the adapted Self-referential Endorsement and Recall task. Data are given as mean (SD) number.

	Placebo[†]		Nocebo[‡]		All
Type/Subtask	Responders (n = 37)	Nonresponders (n = 33)	Responders (n = 35)	Nonresponders (n = 35)	Participants[§] (n = 94)
Positive					
Memories	4.54 (1.79)	4.76 (1.35)	4.54 (1.52)	4.74 (1.67)	4.61 (1.53)
Expectations	3.46 (1.73)	3.30 (1.31)	3.54 (1.69)	3.23 (1.37)	3.23 (1.53)
Negative					
Memories	2.84 (1.59)	2.73 (1.42)	2.82 (1.56)	2.74 (1.46)	2.73 (1.58)
Expectations	0.97 (1.48)	1.33 (1.11)	0.94 (1.14)	1.34 (1.47)	1.13 (1.33)

[†]Placebo responders and nonresponders, n = 37 and 33, respectively, based on median split. Includes participants in the different placebo and nocebo inductions/conditions (ie, the verbal suggestion, conditioning, and conditioning with verbal suggestion groups; the control group was excluded from data analysis).
[‡]Nocebo responders and nonresponders, n = 35 and 35, respectively, based on median split. Includes participants in the different placebo and nocebo inductions/conditions (ie, the verbal suggestion, conditioning, and conditioning with verbal suggestion groups; the control group was excluded from data analysis).
[§]Includes the control group.

Valence of Itch Memories and Expectations in Relation to the Placebo and Nocebo Effects

The mean (SD) values of the valence of memories and expectations regarding itch, as measured with the SER-ip, related to the placebo and nocebo effects are shown in Table IV. A Mann-Whitney U test showed significantly fewer negative itch-related expected events in the future in the placebo responders than in the placebo nonresponders (0.97 [1.48] vs 1.33 [1.11]; $U = 450.50$; $z = -1.992$; $P = 0.046$), indicating that participants with less negative itch expectations responded more strongly to the placebo itch induction. No significant differences were found between placebo responders and nonresponders with regard to itch-related negative memories ($U = 583.00$; $z = -0.330$; $P = 0.742$), positive memories ($U = 603.00$; $z = -0.092$; $P = 0.927$), or positive expectations ($U = 588.00$; $z = -0.270$; $P = 0.788$). In nocebo responders and nonresponders, no significant differences were found with regard to itch-related negative memories ($U = 581.50$; $z = -0.371$; $P = 0.711$), negative expectations ($U = 527.00$; $z = -1.063$; $P = 0.288$), positive memories ($U = 537.00$; $z = -0.926$; $P = 0.355$), or positive expectations ($U = 544.50$; $z = -0.813$; $P = 0.416$).

DISCUSSION

The findings from the present study suggest that healthy participants' cognitive schemas regarding specificity and valence of memories and expectations for itch are related to placebo responding on itch. More specifically, when investigating the cognitive schemas prior to the induction of placebo and nocebo effects, the placebo responders displayed more specific memories of itch-related events and endorsed fewer negative itch-related expectations for the future than did the placebo nonresponders. In nocebo responders, no significant results were found with regard to specificity and valence of cognitive schemas. Specificity of memories did not seem to be associated with the specificity of expectations, but the valence of memories and expectations were significantly correlated for both negative and positive valenced cognitive schemas. Overall, the findings from the present study suggest for the first time that cognitive memory and expectations tasks may be explored as possible relevant predictors of placebo responses.

The finding concerning specificity of memories and expectations, that is, that placebo responders had previously generated more specific itch-related memories than did nonresponders, is in line with findings

from studies on autobiographical memories in relation to psychopathology that indicated that a generalized autobiographic memory, that is, reduced specificity of memories, is related to negative outcomes such as depression and trauma-related psychopathology[12] and difficulties with problem solving.[13] The tendency to be more specific in memory consolidation might be beneficial for the integration of new information, such as learning placebo expectations in the present study. It has also been proposed that reduced autobiographical memory can result from preliminary stopping of the search for a specific memory prior to the retrieval of the specific memory, due to mechanisms such as rumination, avoidance, or reduced executive control.[12] The imagination of future events is sought to occur through the same hierarchical memory system.[24] Moreover, more specific memories have been shown to be related to a better ability to imagine the future[22,25] and thus possibly also imagining expectations regarding a certain treatment. This finding was however not supported by the associations between specificity of memories on itch and specificity of expectations on itch, which were not significantly associated in our study. In contrast to retrieving itch-related specific memories, participants in our study experienced difficulties in coming up with (specific) expectations for itch, as reflected by the relatively low FET-i scores, which might also explain the lack of the association between itch-related memories and expectations. Finally, no significant differences in specificity of memories or expectations for itch were found between nocebo responders and nonresponders. This finding could be explained by the fact that nocebo effects are easier to induce than are placebo effects, for instance by only 1 verbal suggestion,[26] and may therefore be less sensitive to previous experiences and resulting expectations regarding itch.

The finding concerning valence of memories and expectations, that is, that placebo responders had endorsed fewer negative (but not more positive) itch-related events in the future than did nonresponders, is in line with those from the large body of research that shows that expectations mediate placebo responses.[1] It is also consistent with findings from related studies showing that, compared with healthy controls, patients with chronic pain and depressed patients endorse more negative illness-related words.[23,27] Moreover, it extends this knowledge by showing that not only particular expectations regarding the (placebo) treatment, but also itch-related expectations irrespective of a treatment, may affect placebo itch responding. The link between these generic itch memories and expectations is underlined by the present findings of significant associations between endorsement of more positive and negative memories and expectations, respectively. However, we did not find significant differences in the endorsement of itch-related events in the past between the placebo responders and nonresponders. This finding is in contrast to those from previous studies showing that previous experiences with a certain treatment[14–16] or previous experience with a stimulus[17] can alter placebo responding. An explanation for this could be that the current tasks were conducted in healthy participants whereby we had purposely excluded people with any past (or current) experiences with chronic itch. Furthermore, no significant differences were found between nocebo responders and nonresponders with regard to valence of memories and expectations for itch, which may also be related to nocebo effects being less sensitive to previous experiences and resulting in expectations.

The present study had some limitations. First, participants had difficulties to come up with future expectations regarding itch on the FET. This difficulty may have limited the variability in scores and could explain the lack of findings with regard to this task. Second, minimal instructions were used for the AMT and FET to achieve more variability in the answers of healthy participants. Although previous studies in healthy participants have shown greater variability in specific and general answers and a relationship to depressive symptomatology,[21,28] one cannot exclude that participants came up with more general responses because they did not understand the task due to the limited instructions rather than due to participants' generalized retrieval style. Finally, as the present study was conducted in a nonclinical homogeneous sample, the conclusions cannot be generalized to the general population or to clinical samples, which should be assessed in future research. Moreover, several studies regarding memory specificity have shown that the mechanisms underlying the retrieval of specific memories might differ between patients and healthy participants.[29,30] Therefore it is not yet clear whether and how specificity and valence of memories and expectations regarding itch affect learning of placebo and nocebo itch responding in clinical groups, and patients with chronic itch in particular, which could be addressed in future studies.

This research suggests a relationship between cognitive schemas for memories and expectations regarding itch and placebo responding on itch. It suggests that investigating specificity and valence of memories and expectations seems useful for obtaining insight into the individual differences in placebo responses to further identify possible placebo responders. In the long term, these findings could be useful for identifying patients who will benefit most from the placebo components of a treatment.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

SUPPLEMENTARY MATERIAL

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REFERENCES

1. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases. *Annu Rev Pharmacol*. 2008;48:33–60.
2. Flaten MA, Aslaksen PM, Finset A, et al. Cognitive and emotional factors in placebo analgesia. *J Psychosom Res*. 2006;61:81–89.
3. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. *Annu Rev Psychol*. 2008;59:565–590.
4. Wager TD, Atlas LY, Leotti LA, Rilling JK. Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. *J Neurosci*. 2011;31:439–452.
5. Stein N, Sprenger C, Scholz J, et al. White matter integrity of the descending pain modulatory system is associated with interindividual differences in placebo analgesia. *Pain*. 2012;153:2210–2217.
6. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: Psychological and neurobiological mechanisms. *Pain*. 2013;154:511–514.
7. Geers AL, Helfer SG, Kosbab K, et al. Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. *J Psychosom Res*. 2005;58:121–127.
8. Geers AL, Kosbab K, Helfer SG, et al. Further evidence for individual differences in placebo responding: an interactionist perspective. *J Psychosom Res*. 2007;62:563–570.
9. Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. *Health Psychol*. 2016;35:1334–1355.
10. Hall KT, Lembo AJ, Kirsch I, et al. Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. *PLoS One*. 2012;7:e48135.
11. Bartels DJ, van Laarhoven AI, van de Kerkhof PC, Evers AW. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur J Pain*. 2016;20:8–13.
12. Williams JM, Barnhofer T, Crane C, et al. Autobiographical memory specificity and emotional disorder. *Psychol Bull*. 2007;133:122–148.
13. Goddard L, Dritschel B, Burton A. Role of autobiographical memory in social problem solving and depression. *J Abnormal Psychol*. 1996;105:609–616.
14. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain*. 2006;124:126–133.
15. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. *Pain*. 2008;136:211–218.
16. Bartels DJ, van Laarhoven AI, Haverkamp EA, et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One*. 2014;9:e91727.
17. Geers AL, Fowler SL, Wellman JA, et al. Prior experience with a pain stimulus as a predictor of placebo analgesia. *J Behav Med*. 2015;38:136–142.
18. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *Bmj*. 2008;336:999–1003.
19. Williams JM, Broadbent K. Autobiographical memory in suicide attempters. *J Abnormal Psychol*. 1986;95:144–149.
20. Raes F, Hermans D, de Decker A, et al. Autobiographical memory specificity and affect regulation: an experimental approach. *Emotion*. 2003;3:201–206.
21. Debeer E, Hermans D, Raes F. Associations between components of rumination and autobiographical memory specificity as measured by a Minimal Instructions Autobiographical Memory Test. *Memory*. 2009;17:892–903.
22. Williams JM, Ellis NC, Tyers C, et al. The specificity of autobiographical memory and imageability of the future. *Mem Cognit*. 1996;24:116–125.

23. Pincus T, Pearce S, McClelland A, Isenberg D. Endorsement and memory bias of self-referential pain stimuli in depressed pain patients. *Br J Clin Psychol*. 1995;34:267–277.
24. Anderson RJ, Dewhurst SA. Remembering the past and imagining the future: differences in event specificity of spontaneously generated thought. *Memory*. 2009;17:367–373.
25. Jing HG, Madore KP, Schacter DL. Worrying about the future: An episodic specificity induction impacts problem solving, reappraisal, and well-being. *J Exp Psychol Gen*. 2016; 145:402–418.
26. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain*. 2011;152:1486–1494.
27. Denton FJ, Sharpe L, Schrieber L. Cognitive bias in systemic lupus erythematosus. *Eur J Pain*. 2005;9:5–14.
28. Raes F, Hermans D, Williams JM, Eelen P. A sentence completion procedure as an alternative to the Autobiographical Memory Test for assessing overgeneral memory in non-clinical populations. *Memory*. 2007;15:495–507.
29. Watkins ER, Ramponi C, Barnard PJ. Reducing specificity of autobiographical memory in nonclinical participants: The role of rumination and schematic models. *Cogn Emot*. 2006;20:328–350.
30. Raes F, Watkins ER, Williams JM, Hermans D. Non-ruminative processing reduces overgeneral autobiographical memory retrieval in students. *Behav Res Ther*. 2008;46: 748–756.

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SUPPLEMENTARY MATERIAL

See Appendix 1 and Appendix 2.

Appendix 1. Cue words for the traditional version of the AMT and FET.

AMT	FET
Happy *(gelukkig)*	Laughing *(lachen)*
Interest *(belangstellend)*	Gift *(cadeau)*
Successful *(succesvol)*	Relaxed *(ontspannen)*
Safe *(veilig)*	Compliment *(compliment)*
Surprised *(verrast)*	Enthusiastic *(enthousiast)*
Proud *(trots)*	Helpful *(behulpzaam)*
Sad *(verdrietig)*	Crying *(huilen)*
Angry *(boos)*	(Being) late *(Laat (zijn))*
Clumsy *(onhandig)*	Fight *(ruzie)*
Hurt *(gekwetst)*	Failing *(fallen)*
Lonely *(eenzaam)*	Nervous *(zenuwachtig)*
Guilty *(schuldig)*	Disappointed *(teleurgesteld)*

Cue words of the traditional version of the Autobiographical Memory Task (AMT-t) and the Future Event Task (FET-t). The cue words translated to English and the original cue words used in Dutch are displayed.

Appendix 2. Pain cue words for the SER.

	Past	Future
Pain Positive adjectives	Tolerable *(tolerabel)*	Bearable *(draaglijk)*
	Decreased *(afgenomen)*	Controllable *(controleerbaar)*
	Manageable *(hanteerbaar)*	Maintainable *(houdbaar)*
	Temporary *(voorbijgaand)*	Eased *(verzacht)*
	Cured *(genezen)*	Tamed *(bedwongen)*
	Healed *(geheeld)*	Eased *(verlicht)*
Pain Negative adjectives	Overwhelming *(overweldigend)*	Burdening *(belastend)*
	Penetrating *(doordringend)*	Merciless *(genadeloos)*
	Untenable *(onhoudbaar)*	Debilitating *(slopend)*
	Nagging *(zeurend)*	Heavy *(hevig)*
	Ungovernable *(onbeheersbaar)*	Continuous *(aanhoudend)*
	Exhausting *(afmattend)*	Disturbing *(verontrustend)*

Pain cue words of the Self-referential Endorsement and Recall task (SER) adapted for itch and pain. The cue words translated to English and the original cue words used in Dutch are displayed.