Expectancy-Induced Placebo Analgesia in Children and the Role of Magical Thinking

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Abstract: Expectations and beliefs shape the experience of pain. This is most evident in context-induced, placebo analgesia, which has recently been shown to interact with the trait of magical thinking (MT) in adults. In children, placebo analgesia and the possible roles that MT and gender might play as modulators of placebo analgesia have remained unexplored. Using a paradigm in which heat pain stimuli were applied to both forearms, we investigated whether MT and gender can influence the magnitude of placebo analgesia in children. Participants were 49 right-handed children (aged 6–9 years) who were randomly assigned—stratified for MT and gender—to either an analgesia-expectation or a control-expectation condition. For both conditions, the placebo was a blue-colored hand disinfectant that was applied to the children's forearms. Independent of MT, the placebo treatment significantly increased both heat pain threshold and tolerance. The threshold placebo effect was more pronounced for girls than boys. In addition, independent of the expectation treatment, low-MT boys showed a lower tolerance increase on the left compared to the right side. Finally, MT specifically modulated tolerance on the right forearm side: Low-MT boys showed an increase, whereas high-MT boys showed a decrease in heat pain tolerance. This study documented a substantial expectation-induced placebo analgesia response in children (girls > boys) and demonstrated MT and gender-dependent laterality effects in pain perception. The findings may help improve individualized pain management for children.

Perspective: The study documents the first experimental evidence for a substantial expectancy-induced placebo analgesia response in healthy children aged 6 to 9 years (girls > boys). Moreover, the effect was substantially higher than the placebo response typically found in adults. The findings may help improve individualized pain management for children.

Key words: Placebo analgesia, expectation, children, magical thinking, pain.

Placebo responses arise from complex and heterogeneous psychoneurobiological learning processes,23 involving contextual conditioning, expectation formation, and social learning mechanisms.22 They can be elicited by a variety of psychosocial and environmental cues that are associated with the patient-clinician relationship.5 Placebo responses account for a significant portion of clinical outcomes in many somatic diseases3 and mental disorders,40 and they substantially modulate pain perception.8,22
Although placebo analgesia has received substantial scientific scrutiny in adults, empirical investigations in children are rare. This is especially noteworthy because findings from the small number of pediatric clinical trials that have been conducted so far suggest that placebo responses might be more pronounced in children than in adults. For example, clinical trials of local anesthetics and venipuncture suggest that placebo responses in children are substantial. This is even more interesting from a neurobiological perspective, as the prefrontal cortex (PFC) has been consistently shown to be important in the top-down mediation of expectation-related placebo responses, in addition, the PFC undergoes considerable maturation during childhood. Surprisingly, to date there have been no experimental attempts to study placebo analgesia in healthy children. Moreover, very few clinical studies of pediatric placebo responses have differentiated between subgroups or examined potential moderator variables.

Placebo analgesia has been shown to be mediated by the release of interacting endogenous neuromodulators, such as opioids and reward-related dopamine. Dopaminergic activity has also been associated with personality traits such as reward susceptibility, which partially predicts the magnitude of placebo analgesia. More recently, the personality dimension of magical thinking (MT), which is thought to be related to dopaminergic function, has been implicated in modulating expectation-related lateralized placebo analgesia in healthy adults. MT—the belief that one can bring about a circumstance or event simply by thinking about it or wishing for it—is a fundamental dimension of a child’s thinking. MT in healthy adults has been associated frequently with enhanced meaning attribution, and it has been shown to facilitate associative processing, possibly mediated by the right hemisphere. Indeed, right hemisphere dominance has been suggested as being related to both MT and pain processing—albeit with inconsistent findings.

We used a lateralized heat pain paradigm to address 3 aims: 1) to determine the magnitude of expectation-related placebo analgesia in healthy children, 2) to examine whether MT and gender influence placebo analgesia and pain perception, and 3) to explore whether there is an asymmetry between the hemispheres in pain perception. In a between-subjects design, boys and girls with high and low MT underwent pain assessments on both forearms before and after assignment to either an analgesia-expectation or a control-expectation treatment condition.

We tested 3 main hypotheses. First, we predicted that a deceptive induction of analgesia expectation would produce placebo analgesia, as shown by an increase in heat pain threshold and tolerance. Second, we predicted that placebo analgesia would be moderated by MT. Specifically, we predicted greater placebo analgesia in high-MT children compared to low-MT children. Finally, on the basis of adult data, we hypothesized that pain perception would be asymmetric as a function of MT, with higher pain sensitivity for the left compared to the right forearm.

Methods

Subjects

Forty-nine healthy right-handed children (23 girls, 26 boys) aged 6 to 9 years (mean = 8.17; standard deviation [SD] = .84) were included in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of the Canton Basel, Switzerland.

Participants were screened using a health assessment questionnaire for parents. Exclusion criteria were acute or chronic disease, neurological disorder, mental illness, skin pathologies or sensory abnormalities, acute or chronic pain, or current regular use of any medication that would affect study measurements.

Right-handedness was determined using the standard Edinburgh self-report handedness inventory (cutoff laterality quotient ≥ .60; mean = .93; SD = .11; range = .60–1.00). Sufficient receptive German language skills were assessed and confirmed for all children with the Intelligence and Development Scales (cutoff score ≥ 3.5; mean = 7.63; SD = 1.89; range = 3.50–11.00). All children received a CHF 30 toy shop gift certificate and a medal for their participation.

Participants were recruited through mass mailing. Children of the targeted age group were randomly selected through the birth announcements of the Canton Basel-Stadt. Families who were still living in the canton or its surrounding area were contacted by letter. Of the 430 letters sent to parents, 47 families (11%) responded, resulting in 47 participating children. Additionally, 2 children of university staff members participated in the study, for a total of 49 participants. The letters that were sent to the parents introduced the study as an “Investigation to better understand children’s heat and pain perception.” All parents gave written informed consent and all children provided assent after being provided with information about the test procedure. They were informed that they could interrupt the study at any time without any relational disadvantages or personal consequences from the authorities, such as the experimenter (C.S.) or the parents. At the end of the experiment, children and parents were debriefed and fully informed about the true aims of the experiment (delayed informed consent).

Half of the children were randomly allocated—stratified for MT score and gender—to either the analgesia-expectation condition or to the control-expectation condition (Fig 1). The randomization code was generated using the built-in random number generator in Microsoft Excel for the Macintosh, version 11 (Microsoft Corp, Redmond, WA). The placebo was a blue-colored hand disinfectant lotion. In the analgesia-expectation condition, children were informed that the study was evaluating the effectiveness of a powerful lotion that helps children feel much less pain. In the control-expectation condition, children were told that the lotion...
was necessary in order to facilitate pain measurements but would have no effect on the pain experience itself. Participants in both treatment conditions were divided into high- and low-MT groups based on the median split on their Magical Thinking Questionnaire (MTQ) scores (Fig 1). The 4 groups were matched for a comparable girl-to-boy ratio ($\chi^2 = 1.90, P = .593$).

All participants were tested individually in a quiet room at constant temperature without their parents. The children could not see the investigator during pain assessments. Parents were asked to leave the room before the start of the experiment to avoid any psychological stimulation potentially influencing the child’s behavior. The study session lasted approximately 2 hours.

One child was frightened by the pain measurements and withdrew from participation. The last tolerance measurement of a second participant is missing because the child did not wish to complete it.

**Heat Pain Stimuli and Measurement**

Heat pain measurement procedures were performed twice for each participant, at baseline and after treatment, regardless of expectation condition. Heat stimuli were administered in a randomly counterbalanced order to the left and right volar forearm using a 30 x 30-mm Peltier device (TSA-II; Medoc, Ramat Yishai, Israel) placed at the midpoint between wrist and elbow and secured using a Velcro strap. To avoid physical injury, the heat pain measurements stopped automatically at 50°C ($122.00^\circ$F). Before the actual measurements, an elaborate training session was performed to familiarize the participants with the heat sensations and the controlling device as well as to ensure that the experimental procedure and instructions had been understood properly.

Individual *pain threshold* was measured using the self-control search method starting at 32°C (89.60°F), with a mouse-click-induced increase of 0.1°C (.18°F) per click. Participants were asked to adjust the magnitude of the heat stimulus till they felt it change from “hot” to “painful.” Thus, the child controlled the onset and increase of the thermal stimulation and stopped it when the heat became painful. They were further instructed to determine the transition point as precisely as possible. The experimenter (C.S.) demonstrated the procedure using equally long response intervals (ie, constant rate of mouse clicks per time unit) for augmenting temperature.

**Pain tolerance** was determined by the method of limits: individuals were asked to stop the heat stimulus the moment it became too uncomfortable or painful. Three measurements starting at 32°C (89.60°F), with a rise of 1.5°C/s (2.70°F/s), were averaged. After each tolerance measurement, the child first rated pain intensity using the Faces Pain Scale–Revised and then the affective dimension of pain using the Facial Affective Scale (FAS). Pain threshold was always measured before measuring pain tolerance in order to minimize interference between pain threshold and tolerance.

**Expectation Induction and Placebo Administration**

Robust placebo and nocebo responses are highly dependent on the expectations induced during the description of the experiment. We therefore developed an elaborate child-oriented narrative that used a metaphor to suggest that the experimental lotion had powerful analgesic properties.

Participants in the analgesia-expectation condition were told a story by the (female) experimenter (C.S.) about a child who wants to go treasure hunting in the

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**Figure 1.** Experimental design. Half of the children were randomly assigned—stratified for MT and gender—to either the analgesia-expectation (blue hand disinfectant as painkiller [upper panel]) or a control-expectation condition (blue hand disinfectant as measurement facilitator [lower panel]). Children’s heat pain tolerance and threshold as well as subjective pain judgments by means of Faces Pain Scale—Revised and FAS were measured on both volar forearms (counterbalanced and homologous site) at baseline and after the expectation induction procedure. Participants’ state anxiety was assessed before each of the 2 pain measurements. Trait anxiety was judged at the end of the experiment.
This study, we translated the questionnaire into German.

Participants were then told that the purpose of the experiment was to test how well this lotion protects a person from heat. The placebo, a cool blue–tinted hand disinfectant with no anesthetic properties, was then applied on both volar forearms.

The analgesia-expectation instruction was as follows: “This is a lotion that helps children by making you feel much less pain. We will measure how much warmer the temperature can get until it starts hurting and how much longer you can wait until you press the button.”

Participants in the control-expectation condition read a nonfiction animal book with the experimenter, thus ensuring the same amount of contact and attention but with no induction of analgesia expectations. The same hand disinfectant was also applied on both volar forearms with the explanation that the lotion was necessary to facilitate measurement and maximize accuracy. The control-expectation instruction was as follows: “We will measure how warm the temperature can get until it starts to hurt and how long you can wait until you press the button. The lotion is necessary to better measure the temperature of the device.”

The experimenter was trained to convey the instructions to both groups in a warm, truthful, encouraging, and caring manner because it has been shown that a good relationship between health provider and patient plays an important role in shaping the placebo response.38,39 Both instructions were conveyed in a standardized manner to ensure that the participant-experimenter relationship was comparable in terms of friendliness and attention across both treatment groups.

**Questionnaires**

**Magical Thinking**

Participants’ MT was assessed at the beginning of the experiment with the validated 30-item MTQ.8 The MTQ has 2 subscales, thought and action, each consisting of 10 questions. The thought subscale questions ask whether it is possible to make an event happen by just thinking about it (eg, “Is it possible to make something good happen to you or someone else just by thinking about it?”). The action subscale questions ask whether it is possible to perform an action to make an event happen even if the specified action is causally unrelated to the specified event (eg, “Is it possible that a friend could get the flu just because you argued with them?”). These 2 subscale scores are combined to form the MTQ total score. The remaining 10 questions assess bias for responding yes or no. Each question can be answered with yes, no, or maybe, which are scored as 2, 0, or 1 points, respectively. MT scores range from 0 to 40, with higher scores indicating more pronounced MT. The authors of the measure report a test-retest reliability of .90 (N = 17) for the MTQ total score in a sample of children and adolescents aged 5–17 years. For the purpose of this study, we translated the questionnaire into German.

**Subjective Pain Judgments**

Participants rated pain intensity and unpleasantness immediately after each pain tolerance measurement. Pain intensity was assessed with the Faces Pain Scale–Revised.36 The child was asked to point to the face that best reflected his or her experienced pain intensity from a series of 6 pictures of facial expressions, arranged in a horizontal sequence that depicts progressively increasing pain intensity from least to most pain. The reliability and validity of the Faces Pain Scale–Revised for the assessment of pain intensity in children aged 4 to 12 years has been repeatedly supported,74 and excellent interscale agreement has been demonstrated in children as young as 4 years of age.36

After the intensity rating, the child rated the affective dimension of pain using the FAS.51 The FAS is a self-report measure used to assess the unpleasantness of a child’s pain experience. It is composed of 9 face drawings presented in a randomized 3-by-3 matrix representing gradual increases in distress. The child was asked to choose the face that best fit his or her affective state from the set of faces. The specific instructions were as follows: “Now I am going to show you some faces and I want you to choose the face that looks like how you feel down inside. Choose the face that looks like how you feel down inside, not just the face you show on the outside.” The FAS is scored on a 0 to 1 scale, where the maximum negative affective value equals 1 and the maximum positive value equals 0. The endpoints were explained as “very happy” and “very sad.” The FAS has been validated in a sample of children aged 5 to 17 years.51

**Measurement of Participants’ Anxiety**

Participant anxiety was assessed with the State-Trait Anxiety Inventory for Children (STAIC).70 The STAIC consists of two 20-item self-report scales. Each item is rated on a 3-point intensity scale. The trait scale measures long-term trait anxiety, which addresses how the child generally feels, while the state scale measures short-term anxiety specific to a particular moment in time. The STAIC was originally designed and normed for use with fourth-, fifth-, and sixth-graders (aged 9–12 years), though the usefulness of the STAIC has also been demonstrated in younger children (6–9 years) with average or above average reading ability.35 Both the STAIC-State subscale (Cronbach’s alpha ranging from .71 to .76) and the STAIC-Trait subscale (Cronbach’s alpha ranging from .82 to .89) have demonstrated good reliability coefficients.79 State anxiety (STAIC-S) was assessed prior to each of the 2 pain measurements. Trait anxiety (STAIC-T) was measured at the end of the experiment.

**Subjective Treatment Efficacy**

In order to minimize social reporting biases, perceived treatment efficacy was assessed indirectly after all pain measurements had been taken using systemic relational circular open-ended questions. In particular, the child was asked how he or she would describe the function of the lotion to parents, siblings, or friends, and whether he or she would recommend the lotion to those persons.
Perception of the Experimenter

After subjective treatment efficacy was assessed, the likeability of the experimenter (C.S.) was measured indirectly by using a relational circular open-ended questionnaire assessing what the child would tell parents, siblings, or friends about the experimenter.

Statistical Analyses

Initially, 4 separate 3-way analyses of variance (ANOVAs) were conducted with strength of right-handedness, trait anxiety, baseline state anxiety, and age as dependent variables. The independent variables were treatment condition (analgesia vs control), MT group (high vs low), and gender (boys vs girls). To assess the effect of treatment condition on state anxiety, we computed a difference score by subtracting posttreatment state anxiety from pretreatment state anxiety.

To assess placebo responses, the principal outcome measures were within-subject difference scores between baseline and posttreatment for heat pain threshold and tolerance (in degrees Celsius). Negative values indicate lower threshold and tolerance compared to baseline. Positive values indicate placebo analgesia. For these 2 outcomes, group differences were analyzed using separate 4-way, repeated-measures analyses of covariance (ANCOVAs) with treatment condition (analgesia vs control), MT group (high vs low), and gender (girls vs boys) as the 3 between-subject factors, and the forearm side of pain application (right vs left) as the sole within-subject factor, and including age and trait anxiety as covariates. The selection of the 2 covariates was based on the results of the 4 initial 3-way ANOVAs.

In order to assess effects of repeated pain measurements (eg, altered sensitivity or fatigue), deviations from baseline were tested by means of 1-sample t-tests and were compared against a value of zero.

Subjective pain rating differences between treatment and baseline condition were analyzed using nonparametric tests, because an interval level of children’s pain intensity and unpleasantness ratings cannot be guaranteed. The difference scores between treatment and baseline were subjected to Mann-Whitney U tests for the treatment condition, MT, and gender factors, and to Wilcoxon signed rank test for related samples for the forearm-side factor.

Perceived Treatment Efficacy

The open-ended answers that the children provided regarding the efficacy of the lotion were categorized into 4 degrees of perceived treatment efficacy: 1) “no efficacy,” 2) “a little helpful” (eg, “it stopped the pain, but only a little”), 3) “helpful” (eg, it hurts less with the blue lotion), and 4) “very helpful” (eg, I could wait much longer until it started to hurt).

To assess experimenter likeability, children were asked about the experimenter. All gave a positive answer and used at least 1 of the following adjectives: nice, great, good, or funny. The answers were categorized into 3 groups: 1) only 1 of these adjectives, 2) more than 1 adjective or positive characteristics (eg, polite, you had good ideas, or I trusted you), and 3) 1 or more adjectives or characteristics reinforced with “very, very much” or a similar expression. Associations between perceived treatment efficacy or likeability and the different groups (treatment condition, MT, and gender group) were analyzed with chi-square tests.

Post hoc comparisons were performed using 2-tailed Student t-tests. Homogeneity of covariance matrices was checked by Box’s M tests (pain tolerance; F = 1.189, P = .249). Homogeneity of variances in the pain measure was assessed using Levene’s test (pain tolerance; F = 1.677, P = .143). Normal distribution of these 2 measures was assessed by the Kolmogorov-Smirnov test (Z ≤ .933, Ps ≥ .348). All P values are 2-tailed, and the level of significance was set to α ≤ .05. Sphericity was assessed, and when the assumption was violated, the Greenhouse-Geisser correction was applied.

All statistical analyses were computed using SPSS for Mac, version 21 (IBM Corp, Armonk, NY).

Results

Subject Characteristics

The 8 groups (treatment condition × MT group × gender) did not differ in strength of right-handedness (F[1, 40] ≤ 1.846, Ps ≥ .182) or baseline state anxiety (F[1, 40] ≤ 3.126, Ps ≥ .084). However, there were group differences in trait anxiety (F[1, 40] = 5.149, Ps ≥ .029) and age (F[1, 40] ≤ 7.399, Ps ≤ .010) (Table 1).

State Anxiety

The 3-way ANOVA for state anxiety difference scores revealed neither statistically significant main effects (F[1, 40] ≤ 1.657, Ps ≥ .205) nor interactions (F[1, 40] ≤ 2.351, Ps ≥ .133).

Pain Threshold

The ANOVA for pain threshold indicated a significant main effect for treatment condition (F[1, 38] = 59.950, P < .001, ƞp² = .612, Cohen’s d = 2.512; analgesia > control) and for the covariate trait anxiety (F[1, 38] = 5.384, ƞp² = .124, Cohen’s d = .753; low > high). Among the 2-way interactions, those between treatment condition and gender (F[1, 38] = 9.778, P = .003, ƞp² = .205) and MT group and gender (F[1, 38] = 5.221, P = .028, ƞp² = .121) were significant. For the first interaction (treatment condition × gender), post hoc comparisons revealed a higher pain threshold score in the analgesia-expectation than in the control-expectation condition for boys (P = .003) and girls (P < .001, Fig 2). Moreover, in the analgesia-expectation condition, the pain threshold score increase was comparable for the 2 gender groups (P = .083), but there was a lower threshold score in girls as compared to boys in the control-expectation group (P = .036) (Fig 2).

For the second interaction (MT group × gender), post hoc comparisons showed a marginally higher threshold score for the boys in the low-MT compared to the high-MT group (P = .078), but no such difference for the girls (P = .869) (Fig 3).
The ANOVA for heat pain tolerance indicated a significant main effect for treatment condition (F[1, 37] = 35.573, P < .001, η² = .490, Cohen's d = 1.960; analgesia > control) and for the covariate age (F[1, 37] = 7.821, P = .008, η² = .175, Cohen's d = .921; older > younger). Moreover, there was a significant interaction between treatment condition and forearm side (F[1, 37] = 6.838, P = .013, η² = .156) (Fig 4). Post hoc t-test comparisons revealed a higher tolerance increase for participants in the analgesia-expectation than in the control-expectation condition on both forearm sides (Ps < .001). Within both treatment conditions, tolerance scores between the right and left forearms were comparable (Ps > .085).

In addition, there was a significant interaction between MT group and forearm side (F[1, 37] = 7.461, P = .010, η² = .168) (Fig 5A). Post hoc t-test comparisons revealed a higher tolerance score for the right than the left forearm side in the low-MT group (P = .016), but no difference in the tolerance score between forearm sites in the high-MT group (P = .170). For both forearms, there were no MT group differences in the tolerance score (Ps > .169).

This interaction was also dependent on gender because there was a 3-way interaction between MT group, forearm side, and gender (F[1, 37] = 5.392, P = .026, η² = .127). As shown in Figs 5B and 5C, forearm side and MT group differences were evident in boys (Fig 5C) but absent in girls (Ps > .228) (Fig 5B):

### Table 1. Descriptive Data of the Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Low MT (n = 13)</th>
<th>High MT (n = 11)</th>
<th>Low MT (n = 12)</th>
<th>High MT (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys (n = 6)</strong></td>
<td><strong>Girls (n = 7)</strong></td>
<td><strong>Boys (n = 7)</strong></td>
<td><strong>Girls (n = 4)</strong></td>
<td><strong>Boys (n = 5)</strong></td>
</tr>
<tr>
<td>Age (y)</td>
<td>7.47±(.19)</td>
<td>8.33±(.81)</td>
<td>8.14±(.96)</td>
<td>8.21±(1.0)</td>
</tr>
<tr>
<td>Handedness</td>
<td>.90 (.11)</td>
<td>.94 (.10)</td>
<td>.97 (.08)</td>
<td>.95 (.10)</td>
</tr>
<tr>
<td>State anxiety</td>
<td>30.83 (4.02)</td>
<td>27.71 (3.45)</td>
<td>26.71 (3.68)</td>
<td>26.25 (5.68)</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>30.83 (6.52)</td>
<td>35.57±(5.77)</td>
<td>31.71 (3.30)</td>
<td>36.25±(10.15)</td>
</tr>
<tr>
<td>MT</td>
<td>3.33 (3.08)</td>
<td>2.57 (1.40)</td>
<td>15.86 (4.45)</td>
<td>12.50 (4.66)</td>
</tr>
<tr>
<td><strong>Note:</strong> Data (mean [SD]) correspond to the 2 treatment conditions (analgesia-expectation or control-expectation) and the 4 corresponding subgroups (low and high MT in boys and girls). Superscript letters (a, b, c) indicate significant between-group differences (*P &lt; .05)</td>
<td></td>
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</table>

Girls in the analgesia-expectation group showed higher trait anxiety scores compared to the control-expectation group.

**Pain Tolerance**

The ANOVA for heat pain tolerance indicated a significant main effect for treatment condition (F[1, 37] = 35.573, P < .001, η² = .490, Cohen’s d = 1.960; analgesia > control) and for the covariate age (F[1, 37] = 7.821, P = .008, η² = .175, Cohen’s d = .921; older > younger). Moreover, there was a significant interaction between treatment condition and forearm side (F[1, 37] = 6.838, P = .013, η² = .156) (Fig 4). Post hoc t-test comparisons revealed a higher tolerance increase for participants in the analgesia-expectation than in the control-expectation condition on both forearm sides (Ps < .001). Within both treatment conditions, tolerance scores between the right and left forearms were comparable (Ps > .085).

In addition, there was a significant interaction between MT group and forearm side (F[1, 37] = 7.461, P = .010, η² = .168) (Fig 5A). Post hoc t-test comparisons revealed a higher tolerance score for the right than the left forearm side in the low-MT group (P = .016), but no difference in the tolerance score between forearm sites in the high-MT group (P = .170). For both forearms, there were no MT group differences in the tolerance score (Ps > .169).

This interaction was also dependent on gender because there was a 3-way interaction between MT group, forearm side, and gender (F[1, 37] = 5.392, P = .026, η² = .127). As shown in Figs 5B and 5C, forearm side and MT group differences were evident in boys (Fig 5C) but absent in girls (Ps > .228) (Fig 5B):

![Figure 2](image1.png)

**Figure 2.** Difference score (°C; scale range: 29.84–37.76°F) (treatment condition – baseline condition) of heat pain threshold (mean ± standard error of the mean) for girls (white bars) and boys (gray bars) in both expectation conditions (control-expectation or analgesia-expectation). Baseline level = 0; placebo analgesia = positive values. Asterisks indicate significant post hoc and baseline comparisons (*P < .05; **P < .01; ***P < .001). Data are averaged over the MT group (low and high MT) and side of pain application (left and right forearms).

![Figure 3](image2.png)

**Figure 3.** Difference score (°C; scale range: 32.00–35.96°F) (treatment condition – baseline condition) of heat pain threshold (mean ± standard error of the mean) for both MT groups (low MT or high MT) in girls (white bars) and boys (gray bars). Baseline level = 0; placebo analgesia = positive values. Asterisks indicate significant post hoc and baseline comparisons (*P < .05; **P < .01; ***P < .001). Data are averaged over expectation condition (control-expectation and analgesia-expectation) and side of pain application (left and right forearms).
Post hoc t-test comparisons revealed a higher tolerance score for the right than the left forearm side in the low-MT group ($P = .031$). In addition, boys in the high-MT group showed a tolerance increase on the left but a decrease on the right side ($P = .021$). Moreover, MT group differences were absent for the left forearm ($P = .936$) but were significant for the right forearm ($P = .021$): Although low-MT children showed an increase, high-MT children demonstrated a decrease in heat pain tolerance.

### Subjective Reports

#### Perceived Treatment Efficacy

Chi-square analyses revealed that there was a significant association between the perceived treatment efficacy and treatment condition ($\chi^2[3] = 36.76$, $P < .01$), but no significant association between perceived treatment efficacy and MT group ($\chi^2[3] = .38$, $P = .94$) nor between perceived treatment efficacy and gender ($\chi^2[3] = 1.83$, $P = .61$).

#### Experimenter Likeability

Chi-square analyses revealed that there were no significant associations between likeability and the treatment condition ($\chi^2[2] = .07$, $P = .97$), between likeability and the MT group ($\chi^2[2] = 1.02$, $P = .60$), or between likeability and gender ($\chi^2[2] = 5.04$, $P = .08$).

### Discussion

This study reports the first experimental evidence for a substantial expectancy-induced placebo analgesia in healthy children aged 6 to 9 years. The effect was influenced by gender and was substantially higher than the placebo response typically found in adults. Contrary to our expectation, children's placebo response was not affected by MT. However, MT did influence their pain perception and was further modulated in complex ways by gender and laterality (ie, right vs left forearms).

Our results clearly indicate that heat pain perception in children is a complex psychological state that is mediated...
by context-induced, short-term expectancies of analgesia as well as long-term beliefs such as MT.

**Placebo Analgesia Responses**

In line with our first hypothesis, children exposed to the “analgesia-expectation” condition via a single verbal suggestion with a strong metaphorical character demonstrated a substantial placebo analgesia response, as shown by a significant increase in heat pain tolerance and threshold on both forearm sides. Moreover, the analgesia expectancy effect for heat pain threshold was greater for girls than for boys. All associated subjective pain ratings were uninfluenced by any of these factors.

It has been suggested that children and adolescents generally show larger placebo responses than adults. Our experimental approach strongly supports this age effect. The difference scores between baseline and posttreatment in the analgesia-expectation group were 5.6 times higher for heat pain tolerance and 3.6 times higher for heat pain threshold than those found in a healthy adult sample using a similar paradigm. Several psychological and neurodevelopmental reasons may account for the larger placebo responses in children. First, children may be predisposed to larger placebo responses because of their higher suggestibility. Suggestibility changes over the processes of neurodevelopment and has been shown to increase steadily from an early age, to peak between 9 and 12 years, and to decline thereafter. Moreover, conceptualizing placebo processes as learning phenomena, children may show higher placebo responses because of their possibly greater learning capacities, openness to new experiences, and learning motivation. Also, Parellada et al pointed out that children’s framing and belief system might not yet have been modulated by experience as it is in adults. Similarly, their prediction and prejudice system is not yet shaped by learning. Finally, the larger placebo responses may also relate to differences in placebo interventions. Indeed, hero role playing-induced modulation of self-perception has been demonstrated to increase heat pain tolerance in healthy adults.

There are several reasons why experimenter or “parent” bias are unlikely as explanations for the present findings: 1) All children were tested individually without their parents, 2) children were visually shielded from the experimenter during the pain assessment, and 3) experimenter and study likability—assessed via systemic indirect circular questions—were not judged differently across the treatment conditions.

Expectations of analgesia induced by verbal suggestions have been repeatedly demonstrated to be pivotal initiators and modulators of placebo responses. Several psychological mechanisms have been proposed to explain placebo analgesia, including such activation of reward processes, reframing, reduction in self-defeating thoughts, motivational gain, and anxiety reduction. However, anxiety reduction seems to be an unlikely explanation for our results. Although higher trait anxiety scores were associated with lower heat pain threshold scores, state anxiety difference scores were comparable in both treatment conditions.

Our behavioral data only allow for speculation about the neural underpinnings that might explain why children appear to exhibit a more robust placebo analgesia response as compared to adults. There are, of course, significant structural and functional differences between adults and children. The PFC and its connectivity with the rest of the brain has been repeatedly demonstrated as being critically important in the top-down, expectation-mediated model of adult placebo responses. The PFC does not reach maturity and full connectivity until at least adolescence, and possibly not even until early adulthood. Moreover, patterns of cortical activation during cognitive tasks such as word generation, response inhibition and selective attention have been reported to be more diffuse in children and to rely more on subcortical brain network activation. The changing balance between early-maturing subcortical and limbic systems and late-maturing, high-association frontal lobe cortical networks make comparisons between pediatric and adult populations difficult. Presumably, expectation-related placebo analgesia in children relies more on subcortical neural pathways and processing strategies relative to adults’ susceptibility to placebo treatment. As contrasted with a more cognitively mediated placebo analgesia in adults, we speculate that in children, reward-related motivational and emotional appraisal (eg, safety) and associated changes in intrasubcortical limbic-related circuitries as well as attachment may be critical mediators of placebo analgesia.

**Gender-Dependent Differences in Placebo Analgesia**

The placebo response for heat pain threshold was stronger for girls compared with boys. The literature regarding gender differences in placebo responding is sparse and equivocal, and studies of gender-specific placebo responses in the pediatric population have been especially neglected. Whereas one review failed to find differences, another reported a slight placebo susceptibility advantage for girls in a migraine headache. In the adult population, several factors have been proposed as explanations for gender differences in placebo responding, including differences in stress levels, cortical processing styles, type of placebo learning paradigm, hormonal influences, reporting biases, or the gender of the experimenter. Given that our participants were prepubertal, our results suggest mechanisms other than hormonal influences, such as a slightly higher suggestibility for girls (but see Bruck et al for an opposing view), which is not attributable to differences in receptive language skills.

**MT Modulates Pain Processing in Boys, but Not Placebo Analgesia**

The findings both contradict and support our original hypotheses. Contrary to our prediction, placebo analgesia was not influenced by MT. Previous findings in a
study by Klemenz et al in healthy adults suggested greater placebo susceptibility for high-MT participants. Several reasons may account for our failure to replicate this finding. First, pronounced MT is a healthy property of a child’s thinking and not an indicator of subclinical psychotic development. Therefore, quantitative and qualitative differences in youngsters’ versus adults’ MT may hamper direct comparison with previous studies. Likewise, suggestibility is extremely high at around 12 years of age, which may have blurred hypothesized MT-related suggestibility differences because of a ceiling effect. Lastly, these inconsistencies may have been produced by differences in the type of pain stimuli and the absence of a control group without a placebo intervention. Such inconsistencies may have been produced by differences in the type of pain stimuli and the absence of a control group without a placebo intervention in the study conducted by Klemenz et al.

In line with our hypothesis, pain perception was asymmetrically modulated by MT. In the group with low MT, pain tolerance was higher for the right than the left forearm. Surprisingly, however, no such difference was observed in the high-MT group. This modulation is an exact replication of the pattern that has recently been reported in a similar study with healthy men and may be a consequence of reduced functional hemispheric differences characteristic of declared MT in adults, on both the behavioral and electrophysiological levels. The present result suggests that the association between MT and a heightened right hemispheric activity, previously described in adults, can also be observed in children. A general bias toward right-hemisphere processing has long been described in infants and children. However, the complex interaction among gender, MT, and the laterality of pain perception must await further research.

Limitations, Implications, and Future Studies

Undoubtedly, our study findings require replication in larger samples. Moreover, the underlying neural mechanisms of expectation-induced placebo analgesia need to be unraveled, especially as they relate to the cognitive and emotional development of children. It would be interesting to compare children with adults to examine how progressively greater maturity in cognitive and motivational neurodevelopment affects placebo responses, focusing especially on the connections between subcortical areas and the prefrontal cortex.

Acknowledgments

We thank Marco Annoni for thoughtful advice regarding ethical issues and Ted Kaptchuk for helpful comments in the preparation phase of the manuscript.

References


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Regarding assessment tools, the German adaptation of the MTQ needs to be validated in a large sample. In addition, given that heat pain threshold was difficult to assess reliably in our study, more intuitive, real-time, and nonverbal measurement tools such as the recently proposed “pain mouse” or immediate analgesic rescue designs could be implemented in future pain assessment designs.

The generalizability and potential implications to clinical practice of our data are limited because our study was designed to investigate the role of experimentally induced placebo analgesia in acute, controllable thermal pain. Also, our present data do not allow us to disentangle the different components of the placebo intervention, such as the expectancy-inducing narrative; the color, smell, or other characteristics of the disinfectant; or the warm relationship with the experimenter. Future studies should compare different types of verbal versus nonverbal and conscious versus nonconscious suggestions, as well as investigate the use of other learning paradigms such as associative learning and learning by observation and imitation to induce placebo responses in children.

In conclusion, the present study provides the first experimental evidence for a substantial expectation-related placebo analgesia response on pain threshold and pain tolerance in healthy children. In addition, independent of analgesia expectations, MT modulated pain tolerance exclusively in male children. Overall, this research suggests that context-induced, short-term analgesia expectations and long-term MT beliefs independently modulate the experience of pain. These findings challenge the simple view of interpolating adult findings to the pediatric population. An improved understanding of the interaction among subjective belief and meaning systems, gender, and age-related neurodevelopmental phases in pain processing has the potential to enhance therapeutic outcomes in the individualized management of children’s pain.

We thank Marco Annoni for thoughtful advice regarding ethical issues and Ted Kaptchuk for helpful comments in the preparation phase of the manuscript.
negative to positive co-activates opioid and cannabinoid systems. Pain 154:361-367, 2013


