

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.

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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 diseases⁴ and mental disorders,⁴⁰ and they substantially modulate pain perception.^{8,22}

Although placebo analgesia has received substantial scientific scrutiny in adults,^{6,27,37,43} 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.^{15,60,79} For example, clinical trials of local anesthetics^{1,2} and venipuncture³³ 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^{6,27,43,78}; in addition, the PFC undergoes considerable maturation during childhood.^{31,32} 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.⁶⁹

Placebo analgesia has been shown to be mediated by the release of interacting endogenous neuromodulators, such as opioids and reward-related dopamine.^{5,68} Dopaminergic activity has also been associated with personality traits such as reward susceptibility,⁶⁷ which partially predicts the magnitude of placebo analgesia.^{66,67} More recently, the personality dimension of magical thinking (MT), which is thought to be related to dopaminergic function,⁴⁴ has been implicated in modulating expectation-related lateralized placebo analgesia in healthy adults.⁴¹ 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.^{62,81} MT in healthy adults has been associated frequently with enhanced meaning attribution,⁴⁴ and it has been shown to facilitate associative processing, possibly mediated by the right hemisphere.^{13,30} Indeed, right hemisphere dominance has been suggested as being related to both MT⁵⁴ and pain processing—albeit with inconsistent findings.^{20,73}

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,⁴¹ 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 inventory⁵⁷ (cutoff laterality quotient $\geq .60$; 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 Scales³⁴ (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

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