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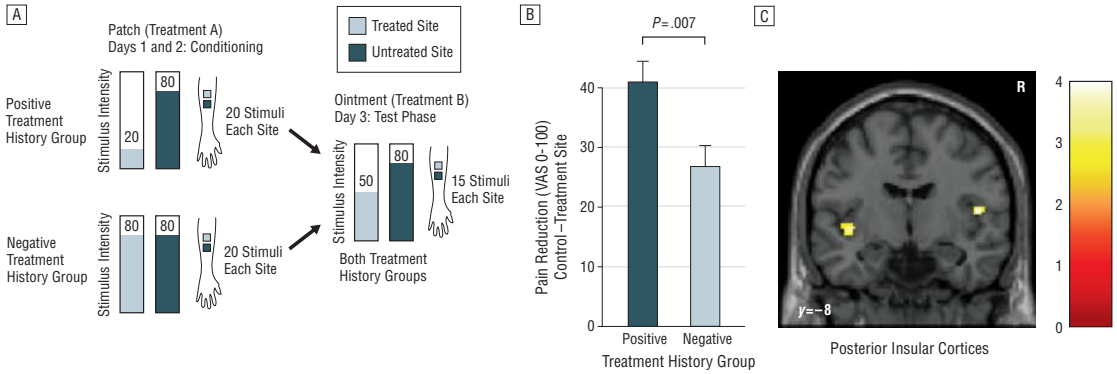
## The Effect of Treatment History on Therapeutic Outcome: An Experimental Approach

Therapeutic context can critically determine treatment outcome.[1] Prior experience with a treatment is an important contextual factor that has been shown to modulate treatment efficacy.[2,3] To date, this influence of prior treatment experience has been studied only within the same treatment approach. However, in clinical practice, treatments are often changed, particularly in case of failure. The aim of this study was therefore to investigate whether the effects of treatment history carry over from one treatment approach to another.

**Methods** | In this combined behavioral and neuroimaging study, we experimentally investigated the influence of treatment history with one analgesic treatment on the efficacy of *another*, *unrelated* analgesic treatment approach. To allow for the assessment of treatment history effects irrespective of pharmacological peculiarities, an experimental manipulation was used to mimic analgesic treatments. A total of 39 healthy volunteers (aged 22-36 years; 20 male) were investigated on 3 consecutive days after written informed consent had been obtained (**Figure**, A). Painful heat stimuli were applied to 2 sites at the left forearm (treatment site and untreated [control] site). First, stimulus intensities were calibrated to individual pain levels of 20, 50, and 80 on a visual analogue scale (VAS, 0-100). After randomization into 2 groups, either a positive or negative treatment experience with an inert patch treatment, introduced as analgesic, was induced by a stimulus intensity manipulation.[4] In the positive treatment history group (n = 19), a low stimulation intensity (VAS 20) was applied to the patch treatment site to mimic analgesia while an intensity of VAS 80 was applied to the untreated site. This manipulation was performed unbeknownst to the participants. In the negative treatment history group, the same stimulation intensity of VAS 80 was applied to the untreated site and the patch treatment site. The procedure consisted of a series of heat stimuli applied to the patch treatment site and the untreated site. Each series consisted of 20 heat stimuli (duration 20 seconds with an interstimulus interval of 40 seconds) and was performed on 2 consecutive days. Groups did not differ with respect to age, sex, and scores on anxiety and depression scales.

On day 3, we compared responses to a second, unrelated analgesic treatment between groups. Both groups were instructed that another analgesic with a different pharmacological profile would be administered, and an inert white ointment was applied. In all participants, a stimulus intensity of VAS 50 was applied at the ointment treatment site and of VAS 80 at the untreated site (15 stimuli each). The analgesic effect

Figure. Experimental Design and Behavioral and Neuroimaging Results




A, The experiment took place on 3 consecutive days. On days 1 and 2, either a positive or negative treatment experience was induced by combining an inert patch treatment with a conditioning procedure. On day 3, the analgesic response to a second analgesic treatment, applied as an ointment, was assessed. Bars indicate the stimulation intensities of applied heat pain stimuli on a scale of 0 to 100, with 0 indicating no pain and 100 indicating unbearable pain. B, The therapeutic effect of the ointment treatment, defined as the pain reduction on the treated compared with the untreated site, was significantly lower in the negative than in the positive treatment history group. Bars (error bars) show the mean (standard error of the mean) difference in VAS pain ratings between the treated and untreated sites for the positive and negative treatment history groups; $P$ = .007. C, Functional magnetic resonance imaging responses as a physiological marker of analgesia showed a weaker reduction of pain-related activity in the posterior insula in the negative compared with the positive treatment history group. Interaction contrast [(Control Site − Treatment Site$_{\text{Positive Group}}$) − (Control Site − Treatment Site$_{\text{Negative Group}}$)] thresholded at $P$ < .005 for visualization purposes is overlaid on a T1-weighted structural brain image. Peak voxel, 48, −8, 10 in Montreal Neurological Institute coordinates; $t$ = 4.0; $P$ = .04 corrected using small volume correction (20-mm sphere). R indicates right; color bar indicates $t$-value.

of this second treatment, defined as the difference in pain ratings on the ointment-treated site and the untreated site, was compared between the positive and the negative treatment history groups. In addition, functional magnetic resonance imaging (fMRI) was performed to assess pain-related brain activity as a physiological measure of analgesia. Specifically, we tested whether the difference in pain-related responses between the treated and untreated sites differed depending on treatment history (interaction effects). The fMRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The study was approved by the local ethics committee.

**Results** | The therapeutic effect of the ointment treatment was significantly lower in the negative than in the positive treatment history group (negative group: mean ΔVAS = 27, from a mean [standard error of the mean] of 81 [3] to 54 [3]; positive group: mean ΔVAS = 41, from 81 [2] to 40 [4]; unpaired *t* test, $P = .007$; Figure, B). In the brain, this adverse effect of a negative treatment history on analgesia was paralleled by more activation in the bilateral posterior insular cortices ($t = 4.0$), known to reflect afferent nociceptive processing[5] (Figure, C), and reduced engagement of the right dorsolateral prefrontal cortex, implicated in pain inhibition.[5]

**Discussion** | To our knowledge, we provide the first behavioral and neurobiological evidence that the influence of treatment history transfers over time and over therapeutic approach. Our results therefore emphasize that therapeutic outcome is not solely determined by the genuine (eg, pharmacological) properties of a treatment but is substantially modulated by contextual factors, including treatment history. Such carryover effects might be particularly relevant in chronic diseases in which treatments often fail repeatedly and negative treatment experiences accumulate along the course of the disease. Moreover, our data suggest that prior treatment experience should also be assessed in clinical trials because it might explain part of the response to the treatment under investigation. Although these experimental findings require replication in larger clinical populations, we believe that awareness of this effect is important for every physician and that concerted effort is required to avoid or overcome the negative effects of prior experience on treatment outcome. These findings may even challenge the use of common step care approaches in which treatment failure must precede the prescription of next-in-line interventions.[6]

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## Somatic Symptoms in Patients With Coronary Heart Disease: Prevalence, Risk Factors, and Quality of Life

A broad spectrum of somatic symptoms is common in primary care, and more than half of medical visits are due to nonspecific symptoms (eg, nausea, headache, dizziness).[1] Patients with frequent somatic symptoms show increased health care use, functional impairment, and a decreased quality of life.[2] Although patients with coronary heart disease (CHD) might present with more than only cardiac symptoms (such as angina pectoris), research on the prevalence of somatic symptoms and their burden on health is rare and historic.[3,4] Numerous studies showing that the somatic-affective component of depression predicts worse cardiac outcomes underpin the importance of examining somatic symptom severity in CHD.[5]

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To our knowledge, this is the first study in patients with CHD that investigates the prevalence and the spectrum of perceived somatic symptoms and tests their associations with quality of life and cardiac and psychological risk factors.