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The Fascinating Mechanisms and Implications of the Placebo Effect

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It is becoming clear that any treatment is significantly modulated by placebo effects in clinical settings. Placebo effects are positive outcomes that are attributable to the psychosocial context and individual treatment expectations rather than the action of the medication or intervention (Colloca & Benedetti, 2005). Placebo effects also occur when placebos are given following the administration of active and effective medications (e.g., painkillers) creating drug-like effects (e.g., dose-extending placebos) (Colloca, Enck, & DeGrazia, 2016). Pharmacological studies indicate that placebos mimic the action of active treatments and promote the endogenous release of opioids and nonopioids in both humans and animals. Expectations of benefit facilitate the activation of pain and nonpain control systems leading to release of endogenous substances crucially involved in placebo-induced benefits. Indeed, neurobiological studies have identified dopaminergic, opioidergic, vasopressinergic, and endocannabinoidergic pathways as promising systems contributing to the modulation of pain experience and other symptoms. This book presents recent behavioral and neurobiological advances on placebo effects and expands on well-established proposed conceptual frame-works and theories. Since placebo effects act as “boosters” of treatment expectancy and clinical outcomes, gaining deeper understanding of the top-down mechanisms of symptoms modulation and well-being has enormous implications for personalizing and optimizing pain management and other symptoms.

One area that reserves further investigation to understand the mechanisms of placebo effects is research in animals that would allow the creation of much needed molecular models to determine the underlying brain and peripheral mechanisms. Despite the opportunities and excitement of animal research, there are aspects that need to be addressed in order to advance placebo research. Gaps and controversies have been acknowledged in pain placebo research (Keller, Akintola, & Colloca, 2018), but solid models and findings are provided for placebo effects in the immune system. Well-established learning paradigms have been developed in the context of the immune system in both animals and humans (Hadamitzky, Sondermann, Benson, & Schedlowski, 2018), where a novel taste is used as conditioned stimulus (CS) along with the administration of immunosuppressive drugs (e.g., cyclosporine A) that act as the unconditioned stimulus (US). Subsequently, the presentation of the CS

alone elicits, after a certain number of associations, the conditioned response (CR) including hormonal and body responses (Ader & Cohen, 1975; Tekampe et al., 2018).

Importantly, when a person expects and experiences a placebo analgesic effect, cognitive and emotional circuitries are activated with experience of pain reduction and improvements in other symptoms. Molecular neuroimaging studies using positron emission tomography and the selective μ -opioid receptor tracer [^{11}C]carfentanil have greatly contributed to current understanding of the neurobiology of the placebo effect. The self-healing capacity to activate endogenous opioid and nonopioid networks associated with the administration of a placebo (Pecina & Zubieta, 2018), or other surgical and pharmacological interventions, points to a sort of inner pharmacy with survival and evolutionary meanings. Partially determined by genetic factors (Colagiuri, Schenk, Kessler, Dorsey, & Colloca, 2015), maintained through learning mechanisms, and sustained by the cognitive dynamic integration of expectations surrounding the therapeutic environment, patient–clinician relationship, and the act of administering an intervention, placebo effects promote symptomatic improvements.

The delineation of these mechanistic advances has been guided by theories, models, and frameworks posited to understand components of the placebo effect (e.g., motivation) as well as grab its complexity in real-world settings. For example, basic tenets of the response expectancy theory, and its distinction between response expectancies and stimulus expectancies, help uncover the individual experience of placebo-induced benefits (Kirsch, 2018). On the other hand, conditioning and learning principles are relevant for placebo research because they clarify the change occurring at the behavioral and brain levels when someone is taking a pill that can contain either an active pharmacological substance or merely a drop of saline solution (De Houwer, 2018).

Placebo effects and positive outcomes resulting from expectations about a treatment outcome should be considered as powerful components of modern medicine. Persuasion that involves changes in beliefs or attitudes as a result of providing critical information can be embedded in daily clinical communication. Therefore, it is clear that the practitioner's attitudes, his confidence and competence, can at least in part favor the formation and magnitude of placebo effects (Geers et al., 2018). Similarly, mindsets may represent a critical mental construct that illustrates the role of the treatment contexts in shaping placebo effects (Zion & Crum, 2018). Moreover, the patient–provider therapeutic alliance contributes to placebo effects and health outcomes. Overall, the patient's *perception* of the clinician, his psychosocial orientation (e.g., loneliness, poor patient–clinician relationship), and perceptions of their interpersonal relationships may broadly influence placebo effects (Necka & Atlas, 2018).

Recently, compelling research is attempting to unravel how placebo effects are elicited in critical contexts with an understanding of what is minimally required to observe placebo effects from intellectual disability, to high altitudes to open-label placebos that challenge the common sense that placebo effects rely on deceptively administering placebos to patients. However, the effect of the placebo effect does not reside in the sham treatment itself; rather, it relies on expectancies that surround the patient and the intervention. Therefore, recent data suggest that patients with impaired cognitive functions may respond to placebos by virtue of

implicit cognitive processes that go beyond desire, suggestions, or verbal communication (e.g., conditioning). There are minimum requirements for eliciting placebo effects, both from the view of conscious awareness and from the perspective of brain functionality (Jensen, 2018).

When the brain preserves the primary ability of integrating incoming sensory information with the inner world that reflects the individual's prior experiences, placebo effects are generated primarily to promote adaptation to old and new environments and minimize trials and errors. Placebo effects reflect the ability to merge prior experience and ideas about treatment outcomes with sensory perception reconciling mismatches between *what is expected* and *what is experienced*. Expectations and sensory inputs are both finely modulated to provide the variety of nuances used in the interpretation of facts and experiences.

With this in mind, it is not surprising that critical life functions, like ventilation, oxygenation, circulation, and perfusion, can be shaped by placebo effects also in extreme contexts such as at an altitude as high as 3500, 4500, and 5500m, where oxygen pressures are 64%, 57%, and 50%, respectively, compared to the sea level. Oxygen-related body responses can be conditioned at high altitudes (Benedetti, Barbiani, & Camerone, 2018).

Placebo effects can also occur when patients know they have been given placebos. Open-label placebos can be interpleading in paradigms with therapeutic treatments so that learning and nondeceptive approaches are harnessed to minimize drug intake while reducing side effects and costs. Although there are distinct differences between open-label and dose-extending placebos, use of such placebos can be preauthorized (e.g., patients agree to receive, at some point, placebos along with medication) in accordance with professional norms governing disclosure and informed consent, and be used in combination with a standard use of treatment (Colloca & Howick, 2018).

Without invoking the use of any placebos, expectations can be shaped to make a treatment and/or an outcome most effective via psychotherapy. Indeed, there is a compelling notion that the placebo effect and psychotherapy represent two psychological interventions that share much more than their first letter (Gaab, Locher, & Blease, 2018). Through psychotherapy, communication, and framing styles, expectations can be positively manipulated as indicated by a recent randomized-controlled trial (RCT). A presurgery expectation optimization program, applied to patients scheduled for coronary artery bypass grafting, resulted in lower disability scores at 6-month post-surgery follow-ups (Rief et al., 2017). Expectations can be changed by a series of procedures with the scope to optimize outcome in medical settings (Doering, Glombiew, & Rief, 2018).

However, expectancy, patient–clinician relationships, and prior therapeutic histories can be negative, thus compromising clinical outcomes. The negative counterpart of the placebo effect is named “nocebo” effect (Colloca, 2017a, 2017b; Klinger, Blasini, Schmitz, & Colloca, 2017), and despite its relevance for modulation of mechanisms and clinical implications, the nocebo phenomenon has received less attention over the past decades than the placebo effect. However, laboratory and translational research is unraveling some of the

behavioral and biological mechanisms as well as the clinical implications. Nocebo effects have been investigated in the field of pain (e.g., experimental acute and visceral pain) (Elsenbruch & Labrenz, 2018; Kleine-Borgmann & Bingel, 2018), nausea (Quinn & Colagiuri, 2018), and other symptoms. Particular emphasis has been given to visceral pain, a model used for behavioral and neuroimaging studies that has helped foster the understanding of nocebo as compared to placebo mechanisms. The recent findings facilitate the transition of experimental research from bench to bedside and ways in which the environment can be manipulated to prevent, reduce, or eradicate nocebo effects (Elsenbruch & Labrenz, 2018). Preexposure to placebo stimulation (latent inhibition) prevents nocebo effects in experimental conditioned nausea (Quinn & Colagiuri, 2018).

Learning strategies, including overshadowing, latent inhibition, extinction, and contingency degradation, represent future research avenues that, if transitioned from bench to bedside, might promote strategies to reduce unintended nocebo effects to be used by clinicians and researchers while designing trials to test new interventions (Quinn & Colagiuri, 2018). Indeed, randomized controlled trials have shown an increased trend to fail, which may be due to both nocebo and especially placebo responses. The neurobiology of placebo effects highlights that patients' expectations interfere with the response to medications and therefore, new clinical trial approaches should be used to improve drug development (Vase & Carlino, 2018).

This series of 18 articles found their inspiration during the first meeting in 2017 of the Society for Interdisciplinary Placebo Studies (SIPS, <https://www.placebosociety.org/>) that is a newly created international association of scholars who share the goal of understanding the placebo effect in medical treatment, psychotherapy, and complementary and integrative medicine by promoting communication and cooperation between research centers and scholars. By using multidisciplinary approaches including neuroscience, psychology, anthropology, and philosophy, it may be possible to expand knowledge on the neurobiological mechanisms and brain functions as well as fully appreciate the implications of this research to develop ethically acceptable ways to harness placebo effects with the scope to optimize clinical trial designs, treatment outcomes, and therapeutic strategies.

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