



PLACEBO AND NOCEBO

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- Historical and pioneering studies on the placebo effect
 - Many researchers have proposed that the history of prescientific medicine is in fact the history of the placebo effect
 - One of the first documented uses of placebo in a clinical trial was in France in 1784 to test the Franz Mesmer's claim
 - It was not until mid-1900's that interest in the placebo effect as an interesting phenomenon in its own right emerged

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- Placebo effect for active treatments
 - Evidence that placebo effects modulate active treatment outcomes in:
 - Postoperative pain
 - Anxiety
 - Parkinson's disease
 - Cardiovascular function
 - Surgery
 - Internal mammary artery ligation
 - Knee osteoarthritis

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- Placebo effect for active treatments
 - Placebo without deception
 - One of the most intriguing recent discoveries is that placebo effects may exist even when there is no deception
 - An open-label placebo study significantly improved irritable bowel syndrome symptoms
 - An important implication of placebo effects without deception is that might circumvent many of the potential ethical issue to do with using the placebo effect in the clinic

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- The nocebo effect
 - Another critical finding was that in addition to beneficial effects, placebo can also produce aversive outcome, referred to as the nocebo effect
 - Various studies have since confirmed nocebo effect for:
 - Pain
 - Nausea
 - Headaches
 - Fatigue
 - Skin irritation
 - Bronchoconstriction

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- Placebo
 - A change in the body-mind unit that occurs as a result of the symbolic significance that one attributes to an event or an object in the healing environment
- Nocebo
 - The opposite effect of placebo. It involves the pathogenic consequences of placebo administration within a negative psychosocial context

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- How the placebo effect works
 - Many attempts have been made to conceptualize the placebo effect
 - Expectancy theory
 - An individual will behave or act in a certain way because he/she is motivated to select a specific behaviour over other behaviours due to what they expect the result of that selected behaviour will be
 - Classical conditioning
 - It is a learning technique (also known as Pavlovian or respondent conditioning) associated with the relation between a stimulus and its response
 - Context effects
 - States that the context (environmental factors) that surrounds an event effects how an event is perceived and remembered
 - Meaning response
 - The meaning response is defined as the physiological or psychological effects of meaning in the treatment of illness
 - Recently it has been proposed a new strategy based on Integrative Framework Theory

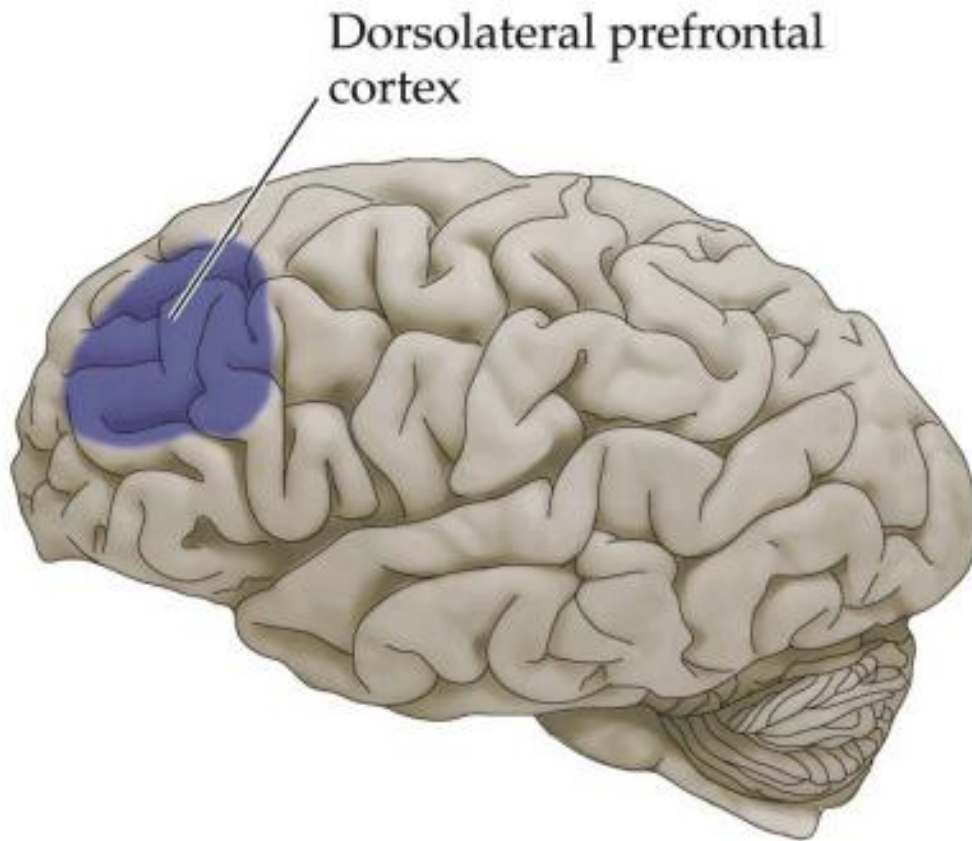
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- Learning mechanism
 - Conditioning
 - It is the learning mechanism most frequently invoked to explain the placebo effect
 - This mechanism operates via the specific biological system activated by the pharmacological agent
 - Morphine-conditioned placebo analgesia involves the opioid system
 - As predicted by this mechanism, the longer the training period the larger the placebo and nocebo effect
 - According to this mechanism placebo and nocebo effects can be established even when there is some variability in treatment effectiveness
 - Verbal suggestion
 - Social learning
 - Placebo effects can also be established via social learning

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- Integrative Framework Theory
 - This theory propose that the placebo effect is a learned response, whereby various types of cues (verbal, conditioned, and social) trigger expectancies that generate placebo effects via the central nervous system

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- Neurobiology of the placebo effect
 - Analgesia is accompanied by reduced activation in pain responsive regions
 - The dorsolateral prefrontal cortex (DLPFC) is crucial in the processing of placebo and nocebo effects
 - It has been proposed that DLPFC is involved in maintaining and updating the expectancies that drive the placebo effect

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- Drug and placebo additivity
 - In the field of pain, both additive effects and interaction have been found
- Endogenous opioid and nonopioid activations underlying placebo analgesic effects
 - Placebo analgesic effects are related to the activation of endogenous brain modulatory systems and the release of endogenous opioid and non opioid neurotransmitters
 - Placebo analgesic effects are not merely modulated by the opioid system and its receptor. Other system such as dopamine, cannabinoid and cholecystokinin systems are involved in the enhancement and reduction of placebo analgesia in humans

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- Genetic influences on the placebo effect
 - The analysis of the genetic variants involved in the placebo effect, has centred around four systems:
 - Dopamine system
 - Opioid system
 - Serotonin system
 - Endocannabinoid system

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- Dopaminergic pathways
 - One of the gene variants with the most support for being involved in the placebo effect in patient populations is an exonic SNP in COMT gene, rs46880
 - In the context of the placebo effect, this SNP has been associated with better outcomes in patients with IBS and placebo in healthy subjects
- Opioidergic pathway
 - In terms of genetic influences, the functional rs1799971 polymorphism in the μ -opioid receptor gene (OPEMI) has been found to associate with placebo-mediated activation of dopamine neurotransmission in the nucleus accumbens during placebo analgesia