# Placebo, nocebo, and care effect

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ABBREVIATIONS

BDNF: Brain derived neurotropic factor

COMT: Cathecol-O-methyltransferase

DBH: Dopamine  beta hydroxylase

DRD3: Dopamine receptor 3

FAAH: fatty acid amine hydrolase

FDA: food and drug administration

fMRI: functional magnetic resonance imaging

MAO-A: Monoamine oxidase

Met: Methionine

NICE: National Institute for health and Care Excellence

OPRM1: opioid mu receptor 1

PET: Positron emission tomography

RCT: randomized controlled trial

RR: Relative risk

mRNA: messenger ribonucleic acid

NSAID: Non-steroidal anti-inflammatory drug

Ser: Serine

SNP: Single-nucleotide polymorphism

TPH: Tryptophan hydroxylase

Val: Valine

**Summary**

Placebo, nocebo and care effect by Mathilde Alice Krähenbühl. Placebo, nocebo and care responses are an interesting challenge of eastern medicine. From their definitions and the problems arising through them, to their usage in randomized controlled trials, they fascinate and confuse. However, when demystified and properly defined, they represent a very good model for the understanding of the role of context within treatment and can be used to the advantage of modern science. The placebo, nocebo and care effect have biological and neurophysiological consequences that are at the basis of our understanding of cures, diseases, and the art of medicine. Learning how to maximize the placebo and care effects as well as minimize the nocebo effect, understanding which major conditions are concerned and changing our perceptions concerning them are some of the possible applications of bettering our understanding of this mysterious-sounding subject.

The present article is based on a survey of literature, among which about a hundred key publications, enlighting different aspects related to the placebo question, are being reviewed. It starts with history and how the placebo concept gradually emerged as a well-founded and important component of the art of medicine (section IV). During the last century, a typology of the placebo effects gradually emerged, and different aspects were identified, such as the effects of deception, conditioning and suggestion (section V). Also, two distinct placebo mechanisms (bottom up and top down) were identified. In section VI, some of the major scientific contributions concerning the relation between placebo / nocebo and neurological changes are being reviewed. The responders to placebo are numerous. In section VII, main responders are mentioned. They include personality and genetics, for which present state of the art knowledge is presented. Trying to maximize the placebo effect is an important concern. In section VIII, various influence parameters are listed and commented in reference to corresponding research studies, including the care effect and doctor-patient interaction, as well as the influence of a multiplicity of factors such as medication labelling and pricing, frequency of administration, type of treatment (oral vs subcutaneous, physical vs oral), and belief of the subject concerning the treatment. Finally, to understand and quantify the placebo effects it is necessary to relate them to the notion of pain. The state of the art concerning that question is being presented in section IX, in which the efficacy of placebo for the treatment of depression and anxiety is being discussed on the basis of state of the art knowledge.

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**Placebo, Nocebo, Care effect**

## I. Why is it interesting?

Although the placebo effect has long been recognized and used by healers, particular attention had been directed to it following the generalization of randomized controlled trials in the mid-1900 and its popularization by Beecher in 1955 (Beecher HK, 1955) and Haas in 1959 (Haas H et al., 1959). Beecher had reviewed 15 articles, including all together 1052 patients and estimated the strength of the effect to be around thirty percent of the total effect of a drug or therapy. A few years later, Haas confirmed those results by a review of 96 articles encompassing 1400 cases. As a result, theories surrounding the placebo effect were interpreted in the form of an additive model, as the difference between the global effect observed and the pharmacological effect. Its definition was based on causality and seen simply as "the clinical effect produced by the administration of a placebo". The placebo is, in this context, "produced by" something, even though the relation observed is a simple correlation. In 1997, however, some authors (Kienle and Keine, 1997) started to question this definition. After analysing over 800 articles (considerably more than was previously done), they concluded that "false impressions of the placebo effect can be produced in various ways" including regression to the mean, additional treatment, scaling bias, answers of politeness and the list goes on. However difficult the definition, medical practitioners seem to believe in the efficacy of the placebo effect and use it rather widely. According to a study realized in Denmark, 86% of general practitioners admitted to the use of a placebo at least once, while 46% to the use of it at least ten times during the last year (Hrobjartsson A and Norup M, 2003). These results were supported by other studies in different countries. In the United States, it has been shown that among academic physicians, 45% had used a placebo in clinical practice. The same study also pointed out that 96% believed in its therapeutic effect.(Sherman R and Hickner J, 2007)

## II. History

The history of the placebo, nocebo and related care effect is intimately linked with the history of medicine itself. It can be considered that most treatments in medical past have been placebos as long as we consider a placebo an ineffective treatment for the symptoms or the diseases being treated. Indeed many treatments have been used without scientific rationale or assessment of efficacy, emerging from pure belief, sociological influence, ignorance and lack of other solutions. There are

countless examples of sham treatments used throughout history, such as purging, bleeding or blistering, to name a few.

It is realistic to expect that most of the remissions occurring after the use of such treatments can reasonably be considered dependent upon only believes or spontaneous remission of the patient, the belief being reinforced by the amelioration of the conditions of some patients after the treatment. It can be assumed that some patients were simply stressed and experienced remission after the care of the healer. It may also be noted that strange treatments without scientific testing are still widely used today, including homeopathy (Shang A et al, 2005), talismans and other treatments falling in the category of alternative medicine.

Defining the placebo and placebo effect has always been a challenge. The definitions are changing over time and the concept in itself is still questioned today.

Already in ancient Egypt, there was reference to placebos. Galen (139-201) stated the relationship to the doctor and treatment was more important than the treatment itself. But healing arts of the time did not make a clear distinction between physicians, priests and magicians and the definition of the effect changed when, progressively, it started to be introduced as a tool for clinical research.

During the mid-1700, in parallel with the development of knowledge in anatomy and physiology, scepticism grew concerning a number of conditions and the first blinded trials started to emerge (Kaptchuk TJ, 1998). Franz Anton Mesmer invented a theory which he called "mesmerism" in the second part or the 1700s. The theory was based on the idea of the existence of "animal magnetism", a healing intracorporal fluid. King Louis XVI appointed a comity lead by Benjamin Franklin to prove the existence of such a fluid. The experience has been lead in a manner that woman were blindfolded and asked where the mesmeric energy was applied. It showed that when blindfolded women would show areas of the body sometimes quite far from where the energy was supposedly applied, when not blindfolded they would, on the contrary, show the part of the body where the therapist would apply the energy. This experience also demonstrated that sham mesmerism worked as well as the "real" mesmerism, disproving the theory once and for all.

The word placebo is old, it comes from the latin "to please" and was first used to describe sham treatments given by the therapist to the patient with the intention to please the patient and reduce anxiety. The term evolved through time and with development of evidence based medicine to now point towards signifying a control group receiving a sham treatment. To give a sham treatment to a

patient means to give a patient a placebo. The effect that follows such treatment is then called the placebo effect. This creates, still today, a lot of confusion concerning the definition of a placebo, the improvement being only difficultly differentiated from a spontaneous remission or regression to the mean. It is important to point out the difference between a true placebo effect and an improvement in the placebo arm of a randomized controlled trial, separating the "true" from the "perceived" placebo effects (Ernst E and Resch KL, 1995). A true placebo is the psychobiological phenomenon occurring after the administration of a placebo treatment, in contrast, a perceived placebo is an improvement occurring after the placebo treatment but due to a multitude of factors that are not a placebo effect, such as spontaneous improvements, regression to the mean, psychosocial factors, biases and co-interventions.

The reason for such confusion is encored in the purpose of the Randomized Controlled Trial. The goal of a RCT is to prove superior efficacy of a drug as compared to a sham treatment, but it does not look at the placebo arm of the treatment to uncover the possible underlying biological mechanisms behind what is loosely called the placebo effect. It can therefore only difficultly be distinguished from other effects participating in the remission of the control group.

As awareness about the psychological influence of treatment on healing grew, the first double blinded clinical trials started to develop. Between 1911 and 1914, 937 patient were blindly assimilated to either a placebo (normal horse serum) or a treatment (diphtheria antitoxin) group for the treatment of diphtheria with the hope to not only uncover which part the imagination had in the treatment but mostly how treatment was making a difference compared to the natural course of the disease (Bingel A, 1918).

In today’s medical trials an "active placebo" is sometimes used. This one mimics the side effects of the non-sham treatment. This is useful in case the treatment can be easily recognized by its side effects, possibly unblinding the placebo arm of the trial. There is, however, ethical considerations when using such a strategy, as it involves, to a certain degree, doing purposeful harm to the patient.

Different trials today use the placebo in different manners (Enck P et al., 2013). In a cross-over trial, patients will switch from an active treatment to a placebo during the course of the trial, improving the power of the results. Problems, however, persist as the dropout rate is higher in such study designs due to their longer durations. It should as well be considered that the active treatment may have lasting metabolites "polluting" in this way the following placebo part of the treatment.

Placebos are being tested in other types of trials, such as placebo run-in, where the population is first given a placebo with the aim to exclude placebo responders and people with poor adherence before randomization to, this time, an active treatment arm and placebo arm. The question remains however, concerning the viability of such tests and how representative a population of poor placebo responders is of the general population.

The balanced placebo type of trial, on the other hand, has been specifically designed to understand the role of suggestion in the therapeutic outcome (Ross S et al., 1962). Studies featuring such a design show the effect of the therapeutic intervention in both the placebo arm and the treatment arm of the trial. A balanced placebo trial will have a placebo arm and a treatment arm, but will entail that in each arms one group will be told they receive the treatment and one the placebo, this can be seen as unethical because it cannot be done without deception.

## III. Definitions

### III.I Placebo

As we have started to explore, when trying to define the placebo and its effect, one is faced with problems. Firstly because a lot of definitions are based on the opposition between a placebo effect and the specific action of a drug. However, an active drug that has a mechanism of action not yet known is not either a placebo. While it is possible to compare only the effects without worrying about the physiology behind, this approach also poses problems, as a drug that is less effective than the standard drug is not either necessarily a placebo. Similarly, the therapeutic illusion, which is the process by which a treatment is thought to be useful based on positive results after its administration, does not imply that a placebo becomes an active drug because it improves the patients' health (Macedo A, Farré M, Baño J-E, 2003).

Body and mind interactions have a very strong importance when considering the placebo effect. The work of Brody (Brody H, 2000), contributed in pushing the definition of the placebo and its effect beyond the idea of a mere sham treatment and defined it as a "change in the body, or the body–mind unit, that occurs as a result of the symbolic significance which one attributes to an event or object in the healing environment". This definition outlines the importance of expectations in symbols and, by this mean, of the therapeutic relationship. The therapeutic context induces expectations, leading to an improvement in health by shaping behavior and experience. The placebo is generally considered as

an inert pill given to please the patient. However, this definition is flawed. The placebo cannot both be inert and have a measurable effect. Thus, it is important to take in account that the sham treatment has only a relative importance in comparison to the context in which the placebo response is induced, and cannot be taken out of this context. Indeed, a pharmacologically inert substance, like sugar, will never acquire therapeutic proprieties. The effect is due to the context of belief, rituals associated with the treatment and verbal suggestions of clinical benefits. The placebo effect cannot be separated from the context in which it has been given, it then would better be defined as the addition of not only the inert treatment but also the indication to the patient that a healing act is being performed.

Placebo= inert substance + belief in healing act

Concerning the effect in the context of a randomized controlled trial, it is composed of different elements. First there is measurements errors that were made during the course of a trial, such as regression to the mean, spontaneous remission, the Hawthorne effect, the Simpson paradox and the Will Rogers phenomenon. The Harwthorne effect happens when the subjects change their behaviour because of their participation in a study. The regression to the mean happens when subjects with extreme values (may they be high or low) are included in the study, making it seem like the statistical variations of subsequent measurements are in fact improvements due to the treatment. Simpson's paradox describes the influence of cofounder factors, in which a trend appears in groups of data analysed separately but disappears when those groups are analysed together. Finally, the Will Rogers phenomenon happens when the diagnostic method is improved and the prevalence of a disease, as well as the apparent prognosis of the patient, are artificially increased (Kleist P, 2006). If all those variables are subtracted, what remains is then termed "true" placebo effect (Ernst, 1995). For simplification sakes, in this work, we will refer to the placebo as if it were only and always the “true placebo” effect. However, it is useful to keep in mind the traps and pitfalls that emerge from the mere definition of such a complex subject.

### III.II Nocebo

The term nocebo, meaning "I shall harm" was introduced in the middle of the twentieth century

(Kennedy WP, 1961). The nocebo is a form of inverse placebo. It happens after the administration of an inert substance associated with a negative context, stimulating expectations of worsening of symptoms or health. Ethically the nocebo effect is difficult to investigate.

### III. III Care effect

According to our previous definition, an effect occurring without the administration of an inert substance cannot be defined as placebo effect. However, it is important to underline the fact that suggestions and context can in some circumstances lead to a placebo-like effect of their own. This will be here referred as "care effect". A research led by T.Katchpuk (Karchpuk T et al, 2008) at Harvard Medical School on patients with irritable bowel disease showed the importance of human relationships in the healing process. Patients were told they would be participating in a trial about the effects of acupuncture on their symptoms. Unknowingly to the patients, none of the groups were given actual acupuncture, as the needle did not pierce the skin. One group, however, received the sham treatment from a friendly and empathetic therapist, as the other received it from a rude one. The group being assigned to the caring researcher showed a tendency for better improvements in their symptoms.

We could define the care effect as the improvement in health following the opportunity of the patients to feel heard and cared for.

## IV. Does it exist after all?

### IV.I. Is the placebo Powerless?

As mentioned in the previous sections, the placebo effect is difficult to separate from regression to the mean or remissions due to the natural course of the disease. For this reason, randomized controlled trials are not the best setting for evaluating the placebo effect. Some authors have been sceptics concerning the quality of evidence of the placebo effect, questioning its mere existence. To investigate the subject, in 2001, A.Hrobjartsson and P.C. Gotzsche (Hrobjartsson A, Gotzsche PC, 2001) conducted a meta-analysis of 130 clinical trials, including 32 having a binary (e.g. proportion of alcohol abusers and non-alcohol abusers) outcome and 82 with a continuous (e.g. amount of alcohol consumed) outcome, comparing placebo and non-treatment groups. They separated the

placebo in three categories, physical (manipulation), pharmaceutical (pills) and psychological (conversations) and calculated the pooled relative risk and standardized mean difference as shown below:

$$\text{Pooled RR} = \frac{\text{(Number of patients with unwanted outcome / total number of patients) Placebo}}{\text{(Number of patients with unwanted outcome / total number of patients) No treatment}}$$

$$\text{Standardized mean difference} = \frac{\text{mean values for unwanted outcomes in placebo group} - \text{mean values for unwanted outcomes in untreated group}}{\text{pooled standard deviation}}$$

A negative value indicated a beneficial effect of placebo both for binary and continuous outcomes.

The placebo did not have a clear effect in the group with binary outcome but showed a heterogeneity of effect larger than would be expected only by chance. The authors did not find a significant effect of placebo in the three independent binary outcomes studied: nausea, relapse after cessation of smoking and depression; but the confidence intervals were wide.

Concerning continuous outcomes, an effect of placebo was noted for trials with a subjective outcome but not for trials with objective outcomes. Furthermore, the significance of the results, as shown by the magnitude of the placebo effect, was lowered by the increase in sample size. Which could indicate that even those results could be, in part at least, due to the effect of sample size and indicate a bias.

No effect of placebo compared to no treatment was shown when conditions such as obesity, hypertension, insomnia and anxiety were taken separately either, but the confidence intervals were once again wide. The only exception noted was concerning the treatment of pain, which showed a significant effect of the placebo compared to the no treatment group.

The authors concluded that the fact that the effect was not significant in quantifying objective outcomes could show a reporting bias when reporting subjective outcomes. Compared to no treatment, the placebo group thought they were being treated and possibly want to please the investigator by reporting improvement when none actually occurred. However, it would be

presumptuous to assume, based on those results, that subjective placebo results should be dismissed as biased. In fact, there are numbers of studies showing the effect of subjective results, such as pain, in an objective matter, such as activation of cerebral pathways liked to analgesia in brain imaging (Benedetti, 2009).

Another bias discussed by the authors may be due to the fact that the no treatment group may be more prone to seek a treatment outside of the experiment and thus reduce the amplitude of results of the placebo group. This also implies that in trials where groups were receiving no treatments, the nature of the trial could not be double blinded, which may have had an influence on dropping rates or other effects that are not possible to account for in such a study.

Finally, the care effect, the effect of the relationship between patient and therapist, could not be evaluated with such a trial. This effect can largely be independent of the placebo effect per-se, even if, depending on how the placebo is defined, it holds similarities (Thomas KB, 1987).

## IV.II The powerful placebo

The previous study did not take in account that the placebo effect could have non-uniformity in its effect depending on the disease considered. The meta-analysis was based on a wide range of clinical conditions without taking in account that some conditions might respond better to the placebo effect than others. “Generally, the presence of anxiety and pain, the involvement of the autonomic nervous system, and the immunobiochemical processes are believed to respond favorably to placebo, whereas hyper acute illnesses (i.e., heart attack), chronic degenerative diseases, or hereditary diseases are expected to resist” (Papakostas YG & Daras MD, 2001). If "drowned" in the middle of a multitude of conditions, it is probably that the placebo effect would mathematically show to be nonexistent.

It also has been suggested that the placebo effect might be more effective in improving physical parameters than biochemical parameters in multiple conditions such as Crohn's disease, heart failure, urinary tract infections and venous leg ulcers (Meissner K et al., 2007). Furthermore, the placebo effect is not as powerful in the context of randomized clinical trials, as the patients know they might either get a real treatment or a sham one. In contrast, when studied with the appropriate tools, the strength of the placebo can be revealed, its effect on some conditions such as pain, has been shown to be significant in balanced placebo studies where patients take a placebo with the false affirmation that it is an actual treatment (Vase L et al., 2003). Suggesting that instead of being powerless, the

placebo effect is directly linked with the awareness of the patient of the administration of treatment and the similarity of the placebo with the treatment itself. That is yet another problematic of the study from A.Hrobjartsson and P.C. Gotzsche, as it is quite difficult to take in consideration the multiple facets of what influences the efficacy of the placebo effect (patient and physician expectations, healing context, cues and factors that can influence the effectiveness of a therapeutic intervention (Benedetti F, 2002)). And beyond this, if the patient remains unaware that a treatment, sham or real, has been administrated, or if the placebo is by any ways distinguishable from the treatment (by side effects for example), then the effects of the placebo would be reduced.

It is fair to assume that there is an effect of the placebo in some conditions as there have been neurobiological changes associated with the administration of a placebo in a variety of diseases. This will be discussed later on in this work. It is however necessary to keep in mind that what has been traditionally called the placebo effect cannot easily be separated from the pure effect of care and willingness of the patient to please and to some degree to spontaneous remissions or regressions to the mean.

## V. Types of placebo:

### V.I Placebo without deception

For long, it has been thought that in order for the placebo to have an effect, the sham aspect of the treatment had to be concealed to the patient. However, recent research points towards the idea that there might be clinical benefits of the administration of placebo without deception.

A study on the effect of placebo on migraine (Kam-Hansen et al., 2014) has looked into this question with interesting results. Two groups of migraine sufferers were asked to evaluate their attacks. Subjects were recieving either an active drug or a placebo labelled "rizatriptan", "placebo" or "rizatriptan or placebo". The order of efficacy of the treatment was as followed: rizatriptan labelled as such, rizatriptan labelled as placebo and placebo labelled as rizatriptan, placebo labelled as such and at last, no treatment. This study shows that an open label placebo has, contrary to what is usually believed, more efficacy than no treatment.

Another study, this time on irritable bowel syndrome (Kaptchuk TJ et al., 2010), looked at eighty

women for a duration of three weeks. The placebo pill was introduced as an inert substance that had been shown to improve symptoms of irritable bowel syndrome through "mind-body self-healing processes". They compared the group receiving the placebo without deception to the group receiving no treatment other than the same interaction with the care provider and found open label placebo to have better efficacy in symptoms reduction than no treatment. The group receiving the unconcealed placebo reported twice the improvement as the untreated group. The importance of labelling is discussed in more details in section VIII.II of this work.

## V.II bottom up and top down

Arguably, it is relevant to separate the placebo effects in top down and bottom up mechanisms. Sensory information conveyed from the peripheral nervous to the central nervous system are the foundation for symptoms perception. This mechanism is called bottom up process. On another hand, the sensory information is processed and interpreted, forming what is called a top down mechanism and constituting the uniqueness of the symptom perception for a given patient. In this model, the experience and perception is based on expectations from the top, which influences lower areas. This process can be influenced by psychological, cultural or social factors.

Conditioning seems to have an effect that can be seen in animal models as well as humans, and analyzed in a thorough way. As a consequence of the initial effect of expectation, real physiological changes take place, following a bottom up mechanism. Immunological placebo effects have also been observed in animals. Aderan Cohen injected mice with a sodium saccharin solution after having had repetitively paired it with cyclophosphamide, an immunosuppressive drug. The immune function of the subjects was assessed by interleukin-2 and interferon-gamma mRNA expression levels. After initial conditioning, the simple sweet taste of the saccharin drink was enough to trigger a suppression of the immune functions (Goebel MU et al, 2002). Similar findings have been observed in patients. In a study on multiple sclerosis, patients received four injections of cyclophosphamide that was associated with an anise-flavored syrup. On ten patients receiving this treatment, eight displayed decreased peripheral leucocytes counts following the administration of the syrup alone (Giang D.W et al, 1996). Such findings have their importance in clinical practice. They could potentially allow for an extension of the treatment effects of the drugs and a maintenance of the therapeutic benefits of this

one with a reduction of the side effects. The learned placebo response could be successfully used in clinical practice as part of the pharmacotherapeutic protocol, reducing cost of treatment and its dangerosity while preserving its efficacy (Colloca L, Miller FG, 2011).

A placebo that would keep working when the patient knows it is a placebo could be considered to have a bottom up effect. Indeed, it can be argued that the socio-cultural and expectancy factors are, to some degree, deleted or at least lessened by the open label. A team lead by Schaffer S.M (Schaffer SM et al. 2015) shook the consensus implying that belief in the effectiveness of the drug is essential in obtaining a placebo effect. The effects of long (4 days) versus short (1 day) term conditioning to placebo treatment were analyzed in two separate patients groups. After the initial conditioning, it was revealed to the patients that they never received an active drug. In the long term conditioned group, the placebo analgesia persisted. These findings show that, however consequent the feeling of expectation might be in the strength of placebo response, it is not necessary to obtain such a response after a couple of days of conditioning.

## V.III Conditioning and suggestion

The psychological mechanisms responsible for the placebo effect are often separated in conditioning and suggestion.

Conditioning has been illustrated and shown to work since the work of Pavlov. By having previously been exposed to an active drug, the patient will experience better subsequent effect of the so called inert substance. The importance of conditioning has first been shown in the 1960s, (Herrnstein, 1962). Rats, after an injection of scopolamine, showed motor changes that were also observed if an injection of saline was performed after the scopolamine treatment.

The effect of conditioning on the efficacy of the placebo was shown in a multitude of clinical trials. In a laboratory setting, electrical stimulus was applied to patients after administration of a placebo analgesic cream. As expected, some participants responded to the placebo, but the study aimed at the exploration of another group. The researchers tricked a number patients into thinking the cream was a very powerful analgesic by diminishing the intensity of the electrical stimulation after application of the inert cream. These patients became strong placebo responders (Voudouris et al, 1989). We can conclude from those experiments that conditioning facilitates the placebo effect, helped by the positive expectation of pain relief brought by past positive experiences. Expectation and conditioning

are both recognized of importance in the mechanism that induces a placebo response (Price et al., 2008). However, even if the placebo response is considered to be cognitive, there is evidence in humans of the importance of unconscious conditioning as well in the placebo response, particularly in those that involve unconscious physiological functions. In this case, what is usually called "expectation" (i.e the conscious thought that the drug will bring relief) doesn't appear to play a role any longer (Benedetti et al., 2003).

Some studies even showed the possible unconscious effect of the placebo in analgesia. Jensen et al (Jensen et al, 2012) tried to assess if conditioned placebo and nocebo responses to analgesia could be obtained in non-conscious exposures. To investigate this theory, the team separated patients in two groups. One group was exposed to clearly visible cues used to conditioned a placebo or nocebo response, while the second was exposed to masked cues. They observed a placebo and nocebo effect in the masked exposure group, indicating that there was an effect of the placebo outside of simple expectation.

The conditioned expectation of relief from receiving a medication has been shown to activate reward mechanisms in the brain. As we've seen in the previous section, patient having been conditioned for longer periods (4 days) have been shown to have a lasting placebo effect, even when it was revealed that they were taking a placebo all along (Schaffer SM et al. 2015). The length of conditioning seems to play a more important role than the overt nature of the treatment in the efficacy of the placebo effects.

Suggestion, also has been used for a very long time, as is illustrated by the already mentioned Mesmerism or the Coué method. More recently, Thomas (1997) followed 200 patients divided in four groups. One group received a placebo, the other no treatment. Each of those groups received either positive or negative consultations (either certainty or uncertainty concerning the diagnosis and healing). After two weeks, 64% of patients having received a positive consultation improved, compared to only 39% in the group receiving a negative consultation but he found no difference between placebo and no treatment. The improvement they found was then concluded to be due to suggestion alone.

## VI. Neurobiology of the placebo and nocebo effect

This investigation into the placebo effect would not be complete if were only observed the psychological mechanism that mediate between the context of care and the development of a therapeutic effect. There are different biological mechanisms capable of, in turn, causing physiological changes in the biochemistry of the brain and producing measurable results. Such results can be either interpreted in term of neurochemical changes or neuroanatomic changes.

VI.I Neuroanatomy of placebo and nocebo effects:

There has been number of imaging studies made on the placebo and nocebo effect, especially concerning pain conditions. The effect of a placebo in pain is thought to work through the activation of the expectation pathways.

In order to properly understand the mechanisms underlying the placebo and nocebo effects, it is interesting to investigate the link between the two. It seems intuitive to consider that both are two sides of the same coin and that similar neuroanatomical pathways are triggered to inhibited depending on expectations of pain worsening or relief. However, such an intuitive theory have been investigated and its validity seriously questioned. A study conducted in 2015 (Freeman S et al., 2015) investigated the mechanisms contributing to placebo and nocebo analgesia. It compared the response to subject's expectations after having received three types of placebo creams. One was labelled "Lidocaine" (positive expectation), one "Capsaicin" (negative expectation) and the last one "control". The expectation of pain intensity change was triggered by previously conditioning the patient by changing the intensity of pain stimulation (decreasing, increasing or not changing respectively) after the application of each creams. The aim was to discover if placebo and nocebo analgesia were manifestations of the same type of brain network activating or de-activating or if they were two separate cognitive constructs. As to understand the complex relation between placebo and nocebo effects, the team compared fMRI signal changes associated with the administration of identical pain stimuli to the 24 study subjects before and after the administration of one of these three creams. They found no common brain regions associated with both "Capsaidin" and "Lidocaine" conditioning even though both triggered significant nocebo and placebo effects respectively. The nocebo effect triggered changes in the insula, orbitofrontal cortex and periaqueductal gray. On the other hand, the expectation of pain relief triggered activations in the striatum. This study suggests that there is a distinct neural pathway for placebo and nocebo analgesia. However, it is generally accepted that there

is a significant overlap in the zones activated during a placebo or nocebo response. This makes sense when considering that both trigger expectation and sensory sensations are linked to pain.

However, it is important to remember that this fact influences not only the administration of a pure placebo, but also the mechanism of action of potentially active drugs. Benedetti and his team (Benedetti et al., 1995), conducted a trial that showed the importance of "active" drug interactions with the expectation pathways. The trial was conducted with the administration of cholecystokinin (CCK) antagonist proglunide in the context of postoperative pain. Proglumide was shown to be better than the placebo in pain reduction. However, if the injection of proglumide was given overtly, the drug showed no effectiveness whatsoever. Therefore, it is likely that the active drug's mechanism of action is linked with the expectations pathways which in turn enhance the placebo analgesic effect. Proglumide enhances analgesia only when associated with a placebo procedure (the non-overt administration of the drug).

VI.II Theories in neurochemistry:

As is going to be further explored on the section on pain (see section IX.I), endogenous opioids play a crucial role in the placebo modulation of painful sensations. It is relevant to notice the overwhelming importance of context in relieving pain, and it was hypothesized that endogenous secretions of opioids was the cause of this observed effect. Levine and his team, (Levine et al, 1981) illustrated this hypothesis by studying the effect of morphine and intravenous placebo in 74 post-operative patients. Two hours after the administration of anesthesia, all patients received an open injection of placebo. By open is meant that the patient saw and had interaction with the staff for the placebo administration and this one was not performed by a pump with no intervention of caregivers. An hour after, the patients received either another open placebo or a hidden (with a pump) injection of morphine. Fifty minutes after, the level of pain of each patients was evaluated by the means of a visual pain scale so the effect of the placebo could be compared to an exact dose of morphine. It was found that the placebo was equivalent to a dose of 4-6 grams of morphine.

The neurotransmitter dopamine has also been widely investigated. Its effects have been noticed during the study of Parkinson's disease, caused by a degeneration of dopaminergic neurons and resulting in a dopamine deficit in the nigrostriatal pathway manifested by the well-known movement disorders that follow. De la Fuente-Fernandez and colleagues (De la Fuente-Fernandez et al., 2001)

used a radionucleotide capable of binding to dopamine receptors to detect the effect of placebo on the dopaminergic system with a PET scan. The patients received an injection of levodopa or placebo. They found that the placebo triggered substantial release of endogenous dopamine in the brain highlighting the importance of dopamine in understanding the placebo effect.

Serotonine also has been studied. Mayberg (Mayberg et al., 2002) carried out a double blind test on patients taking fluoxetine against placebo. They scanned the patients before treatment, a week later and finally six weeks later. They found an equal number of patients improvement in each groups and those patients showed increased activity in the part of the brain associated with emotions. The placebo effect seems to be able to stimulate the serotoninergic system as well, even though further studies need to be done to further understand to which degree and reliability its action stands.

## VII. Responders to placebo

### VII.I Personality and the placebo effect: a case for optimism

The two main phenomena explaining what makes a placebo work are, as we have seen, expectations and conditioning (Price DD et al., 2008) but there are many other possible ways a placebo response can be triggered, such as the care effect, the healing ritual and potentially the personality of the subject (Jaksic et al, 2013).

In the scientific literature of today, there is a debate on whether personality plays a role in placebo responsiveness. Personality as a criterion has often been found to be unreliable (Vallance 2006), the personality being constant but the placebo response variable for the same individual.

However, some studies linked responsiveness to hypnosis (suggestibility) with responsiveness to placebo (De Pascalis et al., 2002) and personalities such as optimistic or pessimistic with its strength (Geers et al. 2005).

Geers and his team made an experiment in which they assigned optimists and pessimists randomly in three groups. The first group was given a pill with no active substance but with a negative association. In this case the researcher told them the pill would make them feel an unpleasant sensation. The second group was informed they would either ingest an inert pill or an active pill. The

third group was the control group and was told that they would receive a placebo. In the first group, pessimists responded more to the negative expectation associated with the pill, but in the second group no significant difference between personalities could be revealed. Conditional expectations were therefore reducing the strength of the placebo or nocebo effect. This study points towards the fact that both personalities and situational variables play an important role.

In a relatively small study on 50 healthy controls, Pecina and his team (Pecina et al., 2013), compared psychological traits with their physiological response to placebo analgesia. This was done by measuring μ-opioid neurotransmission as well as changes in serum cortisol levels during a painful stimulation. Traits such as resiliency, altruism and straightforwardness have, in this study, been shown to be positively associated with a better placebo response compared with the angry hostility personality trait. Of course such a study only gives an indication on the possible link existing between personality traits and placebo response.

### VII.II Genetics and the placebo effect: "the placebome" (Hall KT et al., 2015)

The effect of the placebo and nocebo have been shown to be encored in the brain, mediating neurotransmitter pathways. Genetic variation in these pathways could have an influence on the effect or strength of the placebo or the nocebo. The research on the matter could potentially lead to an improvement in the efficacy of randomized controlled trials, cutting costs of design, as well as of treatment of patients. The importance of considering the potential genetic variations influencing the placebo arm of a randomized controlled trial is evident when thinking about how to estimate the efficacy of a drug, this one being defined as the difference in outcome between drug and placebo. If genetic variability to placebo response can be estimated in both placebo and drug arms of a trial, this would result in a reduction of potential bias in the interpretations of results of such trials. Furthermore, knowing the susceptibility of each patient to the placebo/nocebo effect could, as well, change the approach to the therapeutic relationship and potentially decrease the titration of some drugs in strong responders.

Different polymorphisms could play a role in the genetics of placebo response. Based on the current literature, the culprits of interest are the dopamine, serotonine, opioid and endocanabinoid pathways as well as correlation between those. All of those potential candidates will be analyzed in the text that follows.

### VII.II.I Placebo pathway: Dopamine

| Gene name/ symbol | Placebo SNPs | Subject(s) of studies | Results |
|---|---|---|---|
| Cathecol-O-methyltransferase : COMT | rs4680<br>rs4633 | 1)Symptoms relief in IBS<br>2)Acute-pain relief<br>3)Symptoms relief in | **Homozigotes** (met/met)(low activity allele): greatest placebo response.<br>**Homozigotes** (val/val) (highest activity allele): lowest placebo response; highest nocebo response.<br>**Heterozigotes** (val/met): intermediate response |
| Monoamine oxidase: MAO-A | rs6323<br>rs6609257 | Depression | **Low activity MAO-A**: higher placebo response<br>**High activity MAO-A**: lower placebo response |
| Dopamine Receptor 3: DRD3 | rs6280 | Symptoms relief in schizophrenia | **Homozigotes (ser/ser)**: higher placebo response |
| Dopamine Beta Hydroxylase: DBH | rs1611115<br>rs2873804 | 1) Alcohol dependence<br>2) Depression | **Homozygotes** (CC genotype): better placebo response |
| Brain-derived neurotropic factor: BDNF | rs6265 | Pain relief | **Homozygotes** (val/val): increased placebo induced D2 and D3 activation but no repercussion on placebo response. |

The particularly strong link between pain response and efficacy of the placebo effect, points towards dopamine and the reward system as major in the pathophysiology of the placebo and nocebo responses. A variety of genes influences factors linked to dopamine levels, either by affecting its metabolism, as it is the case for modifications in COMT, DBH or MAO-A, or by changing the affinity of its receptors, as it is the case for modifications linked to DRD3. Dopamine's role in inducing changes in the brain related to learning and response to reward, are also influenced by the neurotrophin BDNF. Its SNP, rs6265, represents yet another possible candidate for a gene in relation

to placebo and nocebo response.

Investigations concerning COMT

A single nucleotide polymorphism named rs4680, in the cathecol-O-methyltransferase (COMT) gene, is of great interest. COMT is part of the enzymes involved in the metabolism of cathecolamines such as dopamine, epinephrine and norepinephrine.

Rs4680 reduces enzymatic activity by three to four folds by encoding a valine to methionine change at the codon 158. It is then understandable that homozygotes for a less active met allele would have a higher dopamine level in the prefrontal cortex, a region thought to be linked to the placebo pathway (Meyer-Lindenberg I, et al., 2005).

Such a response has been observed in different trials focusing on the reduction of symptoms in irritable bowel syndrome (Hall K.T., et al., 2012), schizophrenia (Ehathena A, et al., 2013) or acute pain relief (Yu R, et al., 2014). This last one showed the linear correlation between suppression of pain and the number of rs4680 alleles. And, as the pain stimulation was short lasting, it reinforces the idea of the importance of rs4680 in the strength of answer to the placebo, as it eliminates confounders as spontaneous remission or diminution of symptoms as part of the normal course of the disease.

Going along with this hypothesis, the study on IBS not only showed the potential difference of strength of the placebo effect in association with the different alleles expressed, but also the correlation of the high activity Val allele and the nocebo effect. These results were reinforced by yet another trial demonstrating a potential link between the SNP rs4680 high activity Val allele and the nocebo effect in learned immunosuppression (Wendt L et al., 2014).

MAO-A

Similarly, other polymorphisms linked the dopamine metabolism seem to be playing a role in the placebo response. One that is of interest is the MAO-A gene, which is X-linked. The SNP rs6323 results in 75% reduction in the activity of the enzyme in females homozygotes and males heterozygotes for T allele. Multiple trials on depressive illness showed that low-activity genotypes have a higher placebo response (Tiwari A.K. et al., 2013). This makes sense because MAO-A works similarly to COMT as it catalyzes monoamines like dopamine and metabolizes serotonine. Another SNP rs6609257, associated with dopamine basal tone, also was also significantly associated with the placebo response.

DBH

DBH is an enzyme converting dopamine to norepinephrine, synthesizing the latter inside the vesicle and being found in noradrenergic nerve terminals of central and peripheral nervous systems. It is associated with decision making and addictive drugs, such as alcoholism (Mutscher J et al., 2012), and psychiatric illnesses (Cubells JF et al., 2011) such as depression and schizophrenia.

DRD3

A variation in the dopamine receptor DRD3 encoded by Rs6280 (serine to glycine coding polymorphism) changes the affinity of the receptor for dopamine. Homozygous for the serine allele have been found to have significantly better placebo response in the treatment of schizophrenia (Ehathena A et al., 2013). It is not difficult to extrapolate that other conditions linked to abnormal DRD3 expression such as Parkinson's disease (Guillin O et al., 2003), drug addiction (Sokoloff P, et al., 2002) or other psychiatric disorders would also be affected by the placebo effect in a different manner than healthy subjects.

BDNF

Brain-derived neurotrophic factor (BDNF) is a polypeptidic factor uptaken by the nerve terminal and transported retrogadely to the cell body. It was initially thought to be involved in learning and memory through neuron proliferation, differentiation and survival. We now understand that BDNF is also transported anterogradely and released upon neuron depolarization being, by this mean, responsible for inducing the expression of dopamine receptors D2 and D3.Guillin O et al. showed in a research on mice with lesions and gene-targeting mice lacking BDNF the potential importance of this neurotrophin in long term neuronal adaptation both in development and adulthood (Guillin O et al., 2001).

The rs6265 SNP in BDNF encodes a valine to methionine substitution at codon 66, a variation in rs6265 val allele homozygotes compared to Met allele carrier shows a greater placebo-induced dopamine receptors D2 and D3 activation that, however, did not show correlation with placebo induced analgesia reduction (Pecina M, et al., 2014).

Discussion

These data suggest that individuals with higher dopamine levels might be more sensitive to placebo response, without either being completely conclusive. More research on the subject of dopamine

expression comparing differences in response of placebo to non-treatment group should be performed to have a clearer understanding.

### VII.II.II Placebo pathways: opioids

| Gene name/ symbol | Placebo SNPs | Subject(s) of studies | Results |
|---|---|---|---|
| Opioid mu rereptor: OPRM1 | rs1799971 | pain relief | **Asparagine homozygotes**: greater placebo pain reduction |

The opioid Mu receptors are critically involved in response to analgesia and pain modulation. The SNP rs1799971 codes for an adenine to guanine transition at position 118 of the OPRM1 gene coding for aspargine to aspartic acid substitution. The aspartic acid variant, has been shown to reduce receptor function (Kroslak T et al., 2007). Placebo-induced activation of dopamine neurotransmission in nucleus acumbens showed to be greater in aspargine homozygotes compared with aspatic acid allele carrier (Pecina M et al., 2015).

This points at opioid receptor genes as yet another candidate in the determination of the influence of genes on the answer to the administration of a placebo.

### VI.II.III Placebo pathway: endocanabinoids

| Gene name/ symbol | Placebo SNPs | Subject(s) of studies | Results |
|---|---|---|---|
| Fatty acid amine hydrolase: FAAH | rs324420 | pain relief | **Homozygotes Pro129/Pro129**: higher placebo response |

Fatty acid amine hydrolase is an enzyme involved in the degradation of endocannabinoids. The endocanabinoid system is thought to be of importance in the reward mechanism and analgesia. The SNP rs324420 of the FAAH gene encodes a Pro129Thr missense substitution, decreasing the activity of the enzyme and leading to a higher endocanabinoid concentration (Chiang KP et al., 2014). FAAH

Pro129 homozygotes have, by this mean, chronically increased levels of endocanabinoid in the brain in response to painful stimulation. This result was shown to occur both right after the analgesic stimulation and 24 hours after this one, when asked to recall and grade the painful experience (Pecina M et al., 2014).

### VI.II.IV Placebo pathway: serotonine

| Gene name/ symbol | Placebo SNPs | Subject(s) of studies | Results |
|---|---|---|---|
| Tryptophan hydroxylase : TPH 2 | rs4570625 | social anxiety disorder: symptoms reduction | homozygous for both pathways |
| Serotonin transporter linked polymorphic region: 5-HTTLPR | variable tendem nucleotide repeat | | |

A small study showed a significant reduction of symptoms associated with social anxiety disorder in homozygotes for two serotonine pathways (Furmark T et al., 2008). Patients were genotyped with respect to the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter, both characterized by a reduction in stress-related amygdala activity. These results occurred only in homozygous patients for the long allele of the 5-HTTLPR polymorphic region or the G variant of the TPH2 G-703T polymorphism, and not for short or T alleles carriers. It seems like the genetic effect linked to symptomatic improvement of SAD is mediated by its effect on amygdala activity. However, given the size of the study and the fact it did not include a non-treatment group, it is difficult to make definite conclusions about the importance of the serotonine pathway in placebo induced stress reduction in the context of psychiatric disorders such as social anxiety disorder.

## VIII. Maximizing the placebo effect

As previously discussed, the placebo effect is particularly noticeable in relieving subjective symptoms, such as pain, anxiety or depression. The strength of the placebo, nocebo and care effect is directly dependent on the type of conditions, but there are other factors influencing it, perhaps the most important of which is belief. When thinking about what influences belief, we are rapidly faced with a myriad of possibly countless factors that have to be taken in account. In the following sections of this work, we will try to summarize part of the literature on what influences expectations and beliefs in a drug or a treatment, and by such, placebo efficacy.

### VIII.I Doctor patient interaction and care effect in healing

The care provider has an essential role to play in healing or worsening of the disease. Words used around the patient induce an expectation of therapeutic benefit which at term triggers a placebo effect. In 1955 already, Balint (Balint,1955) was putting the emphasis on the atmosphere around the treatment. Care givers, may they be nurses or doctors, can convey a number of information to the patient by their words, attitudes and behavior. Kaplan himself (Kaplan et al., 1989) found that specific aspects of the doctor-patient relationship, specifically communication, were having consistent influences of blood pressure, blood sugar and overall health status of the patients.

Number of studies have shown the importance of patient-doctor relationship in health improvement. The mechanisms of which could be linked with a better compliance. The Coronary Drug Project (1980), puts a certain emphasis on the importance of compliance in healing. The project had the shape of a double blinded randomized placebo controlled trial. Its aim was to evaluate the efficacy of lipid lowering drugs in the context of long-term treatment of coronary heart disease. Good adherers in the drug arm of the treatment, those that were found to take at least 80% of their medications had a 15% lower mortality than poor adherers. The surprising fact was that in the placebo arm, very similar findings have emerged. The mortality in good adherers in both groups turned out to be almost the same, 15% in the drug group and 15.1% in the placebo group, as for poor adherers, 24.6% in the drug group and 28.3% in the placebo group. This suggests that the placebo has had an important effect in this study and this one may be linked very closely to compliance to the treatment, may it be sham or not.

It is thus interesting to pay further attention to how exactly the relationship between therapist and patient influences the outcome of the treatment. Prior research from the field of social psychology have helped to shine some light on the subjects (Sliwinski J, Elkins R, 2013). Three factors have been identified as relevant in the enhancement of the placebo effect: priming, client perception and the theory of planned behavior.

Priming can be defined as the effect of memory on behavior. Recent exposure to a stimulus makes it more available cognitively and triggers a response in concordance with the stimulus. During a study conducted by Webb (Webb et al., 2007), subjects were presented with either simple packets containing information on smoking cessation or ones giving the appearance of being individually tailored to the participant by the inclusion of personal information, such as name, age and preferred brand of cigarette. Half of the participants of both groups also received a priming letter informing them of the benefits of the booklet that was to follow. The researchers found that participants receiving the priming letter found the information in the packet to be of higher quality, had more consistent intentions to stop smoking and retained the information contained in the packet better than those who did not receive the priming letter. This was observed in both groups, regardless of the tailoring or lack thereof of the packet sent.

The second factor, client perception, is changing treatment outcome by changing the perception the subject has of the therapist or therapy being offered. Different studies have put emphasis on the importance of warmth, empathy and interpersonal connections in the process of healing. The context of hypnotherapy is relevant concerning the placebo effect, responders to hypnosis being often the same patients than those that respond to placebo. In a study by Lynn et al. (Lynn et al., 1991), 12 highly hypnotizable 10 low-hypnotizable subjects were given instructions aiming to increase the interpersonal relation with their therapist. Two other groups, composed 12 highly hypnotizable and 11 low-hypnotizable people, were given instructions that minimized interpersonal rapport. The group affected to the therapist encouraging interpersonal interactions eye contact and the importance of the patient's involvement in the treatment were emphasized. Furthermore, the patients were told about the interest of the therapist for the research and for hypnosis in general, as well as his expertise in the area. The other group received none of those cues. Such experience showed that in the context of already highly suggestible individuals interpersonal context had no importance. However, in the group where the subjects showed low hypnotic abilities, interpersonal context had an impact on increasing their hypnotisability, as was calculated using the Standford Hypnotic Scale Form C.

The theory of planned behaviour (Ajzen, 1991) highlights the importance of personal belief in the efficacy of a treatment. The decision of an individual on whether or not to engage in a behaviour depends on a combination of normative, behavioural and control beliefs. Normative believes influence a behaviour by the thought the individual has about how his or her behaviour will be perceived by others. It is, in a way, a control of behaviour linked to social recognition and the importance of being part of a group. Behavioural beliefs are related to the expectation of an outcome and can be summarized as an "if...then" mode of thinking. If the outcome expected is positive, the subject is more likely to engage in the behaviour. It is a control of behaviour linked to the personal expectation of a positive or negative outcome. Finally, control beliefs are the presence or absence of facilitating or impeding factors in the accomplishment of the behaviour. A study by Sun et al. (Sun et al., 2011) on 201 depressed patients showed that a variance of 16.4% in antidepressant use could be explained by attitudes towards antidepressants only.

This highlights the fact that psychosocial factors have to be taken in account in order to maximize the placebo effect by mean of the care effect. The patients-doctors relationship influences the quality of care of the patients treated. Knowing how to manage patients' beliefs and limiting beliefs can have a true impact on the management and outcome of the disease.

## VIII.II Forms/price/shapes/labels

### Labelling

As was previously overviewed in this work, a study on the effect of placebo on migraine (Kam-Hansen et al., 2014) showed the role played by labelling in the outcome of the treatment. A cohort of sixty-six migraine sufferers had to document seven of their migraine attacks. The first one was to stay untreated and act as a control, the following six attacks were randomly assigned wither rizatriptan or placebo treatment labelled either as "rizatriptan", "placebo" or "rizatriptan or placebo". While the active treatment showed better efficacy than the placebo, labelling had an impact also. The placebo had more effect when concealed under the drugs name, but had an important effect even when labelled as such (30.9% compared to 51.6% when named as the active treatment) and the order of efficacy of the treatment was as such: no treatment, placebo labelled as placebo, placebo labelled as rizatriptan and rizatriptan labelled as placebo, rizatriptan labelled as rizatriptan. This shows on one side how open label placebo is superior to no treatment and on the other how the treatment labelled

as the placebo is as effective as the placebo labelled as the treatment. These findings point once again towards the effects of expectancy in the healing process and the answer to a treatment protocol. The fact that both mislabelled drug and mislabelled placebo had the same efficacy in migraine reduction also shows that labelling can reduce the efficacy of an active treatment.

The label has its importance in the efficacy of the drug as shown by the fact that a placebo labelled as a drug has more efficacy than a placebo labelled as such. It is then logical to investigate the effects of publicity on the strength of the placebo. Kamenica and his team (Kamenica et al., 2013), lead an experiment which aimed to examine the impact of advertisement on the efficacy of a branded drug. They compared physiological effects of Claritin, an antihistaminic medication, after having watched either Claritin commercials or Zyrtec commercials. To do so, the subject were randomly assigned to a group and watched a movie spliced with advertisements for Claritin or for Zyrtec. The researchers found that in the group that was exposed to Claritin commercials and did not have allergies, Claritin had better efficacy in reducing wheels size after histamine injection than in the group that was advertised Zyrtec. In patients that had allergies, such difference was not found. The publicity increased the belief in the drug's efficacy, which seems to have increased the efficacy of the drug in turn.

Price: is an expensive medication a better placebo?

If a medication's efficacy is dependent on people's beliefs, it would then be expected that not only publicity, but also price would have an impact, the price of a medication being a feature of the patient's perception and expectation. To investigate if commercial features influence the therapeutic efficacy of a medication, a team of researchers (Waber RL et al., 2008), explored the influence of pricing on 82 subjects. Each participants had previously been informed by a brochure about the drug, advertised as a new opioid analgesic similar to codeine but with faster onset of action. However, the pill was, in reality, a placebo. Half of the participants were randomly assigned to a group where the price of the pill was said to be $2.50 per pill, the other half of the participants believed each pill to cost $0.10 instead. Painful electrical stimulation was then applied to the wrist of the subjects and pain rating was obtained before and after the administration of the placebo pill. Pain reduction was found to be more important with the placebo of higher price concerning all voltages tested and main pain reduction.

The price of the medication seems to be of importance when trying to maximize the expectations concerning a medication and thus the placebo effects, even though similar results would have to be obtained on larger populations for reaching a definitive conclusion on the matter.

Is subcutaneous treatment better than oral treatment?

Even though it is difficult to make generalisations because of the small number of specific studies on the route of administration of placebo, it is an interesting area of investigation. In a meta-analysis of 22 clinical trials on migraine, a team of researchers (de Craen et al., 2000) found a difference in symptom alleviation depending on the route of administration. If the patients were treated with an oral regimen 25,7% reported mild or no headaches 2 hours after placebo administration, however, if the patients were administered a subcutaneous treatment the percentage increase significantly to 32,4%. This suggests that there is a symbolic value attached to the route of administration of a drug, which could potentially be extrapolated to other conditions than migraines.

Is a physical treatment better than an oral treatment?

To investigate the idea that a physical treatment, meaning a treatment that includes a physical contact with the patient has more impact than a simple pill, Kaptchuk TJ and his team (Kaptchuk TJ et al., 2006), compared sham acupuncture to an inert pill in 270 adult patients with persistent arm pain. The pain, measured on a ten point scale, showed a greater downward slope per week and greater decrease in severity on the sham acupuncture compared to the pill treatment. No significative difference was found concerning grip strength or on the function scale, however, in the light of the results in pain reduction, it can be hypothesized that the complexity of the treatment ritual maximises the placebo effect.

Does the frequency of administration play a role?

There have been some efforts to understand how the quality of care influences the strength of the placebo effect. We have seen the importance of the care effect and know that the placebo can be triggered by the expectation of pain relief. The expectation of relief, in turn, has different triggers, one of which seems to be the frequency of administration of a drug. In trials on patients suffering

from ulcerative colitis (Ilnyckyj et al., 1997), and Crohn's disease (Su et al., 2004), the analysis of duodenal ulcer seem to suggest that, truly, the healing rate can be increased by the number of placebo received by the patient. Under a placebo treatment, the healing rate of patients suffering from duodenal ulcers has long been shown to vary largely across randomized controlled trials (Gudjonsson and Spiro, 1978; Poynard and Pignon, 1989). In comparing the number of times a day the placebo was administered, Craen and his team (Craen et al, 1999) found surprising results. They conducted a systematic literature review, in which 79 randomized placebo-controlled clinical trials were analysed based on the frequency of placebo administration. They found that there was a significant drop in healing rate in trials that gave a twice a day regimen of placebo (28 trials, 1504 patients) compared to trials giving a four times a day regimens (51 trials, 1821 patients). The healing rate in the high frequency group was 44.2% and decreased to 36.2% in the low frequency group.

Another systematic review (84 placebo-controlled clinical trials) by Pitz and his team (Pitz et al., 2005), investigated the effect of frequency of drug administration in IBS. Once again, the decreased rates of abdominal pain was correlating to the frequency of placebo administration. The team found that the average frequency of placebo administration changed in history. Trials lead before 1999 had a mean placebo pill per day of 2.7 times, and studies done between 1999 and 2004 had a mean placebo pill per day of 2.0 times only. Supporting the hypothesis that there is a link between frequency of placebo administration and clinical improvement, the decrease of abdominal discomfort in patient being assigned to the placebo group went from 31.2% in studies done before 1999 to merely 20.6% in studies done between 1999 and 2004.

The most impressive the better?

We have until now discussed the fact that a multitude of factors influencing the belief of the subject concerning the treatment were potentiating the placebo response. It is then interesting to investigate how the impressiveness of the treatment affects the strength of the placebo. As far as impressiveness goes, surgery seems to be as good as it gets. Forty years ago, a team investigated in this way internal mammary arteries ligation (Dimond EG et al, 1960). The surgery was thought to be very effective at the time for relieving the painful symptoms of angina. However, when incisions were made without touching the arteries, very similar success rate were met. The sham operations proved so successful that the procedure was abandoned and is not practiced today.

More recently, sham surgeries showed effectiveness in osteoarthritis of the knee. At the time preceding the study, it was unclear whether the benefit of the surgery was due to the debridement or the lavage of the joint, both being done during the intervention. The aim was then to assess function and pain over a 24 months period after either debridement, lavage or placebo surgery. To make sure the patient was blinded and rule out bias in case the anesthetized patient could still hear during the surgery, the surgeon performed the sham surgery as if it were real, handling instruments and ordering nurses (and interns), but simply made a small incision that was then later surutred.165 patients were assessed in this trial and showed an improvement that did not exceed the placebo surgery for neither function nor pain reduction (Moseley BJ et al, 2002). The effect of the placebo had been so potent that before comparing sham and real interventions, it had been unimaginable that such results could be derived out of the belief of the patient only.

Another example of the importance of expectation in surgery was exemplified during a trial on embryonic cells transplantation for the treatment of Parkinson's disease (McRae et al., 2004). Once again, it was found that there was improvements in both surgery and sham surgery groups on several outcome measures such as physical and quality of life scores.

The physiology behind the beneficial effects derived from surgery had always seemed straight forward, but the power of the placebo to alleviate symptoms and restore function is not to be underestimated. In the future it may be interesting to further investigate what parts of surgery show a greater efficacy than placebo and what parts do not. Not only such research permits us to better understand and tame the placebo effect, so to be able to use it in clinical work more efficiently, but also to decrease healthcare costs and further scientific understanding of human health and psychology.

## IX. Placebo, nocebo, neural basis in common conditions

Many conditions are influenced by the placebo effect. I have in this work mentioned some of them already but will investigate in greater details a couple of them. This following chapter is a non-exhaustive list of commonly studied conditions that have shown to have an interesting link to the placebo, nocebo and care effects.

## IX.I Pain

Today, we understand that there is not a simple pain center in the brain, but an array of cortical and subcortical areas often referred to as the "pain matrix". The lateral system is involved in a bottom up mechanism of pain sensation, specifically its sensory and discriminative aspects. It is responsible for the discriminative sensation of pain, the feeling of intensity of this one, its localization and duration in time. This system involves part of the spinothalamic tract, the lateral thalamus and its projections to the first order somatosensory area (Benedetti F, 2009). We also know that there is a number of neurotransmitters involved in the regulation of painful sensation and the relief thereof. In this section, we will go through some of the research that has been led so to understand the role of opioids, endocanabinoids and different physical areas of pain regulation in the central nervous system and its relation to the placebo and nocebo effects.

The medial system also plays a role in pain perception and is representing the affective component of pain. Structures involved in the medial system are the medial thalamus, the insula and the parietal operculum, the prefrontal and orbitofrontal, as well as the anterior and posterior cingulate cortices (Benedetti F, 2009). This system is involved in the social and psychological perception of pain, suffering, without which it is difficult to define a painful perception as such. Its function is to give information on how acceptable the pain is and how long it can be tolerated, this system represents the top down mechanism of pain perception.

Placebo analgesia is strongly connected with the above mentioned structures. As will be discussed later on in this chapter, placebo analgesia has been shown to produce activity in the dorsolateral prefrontal cortex, the anterior cingulate cortex and subcortical regions including the amygdala and the periaqueductal grey (Colloca L, Grillon C, 2014). The placebo analgesic response is initiated by the dorsolateral prefrontal cortex and then modulated by the periaqueductal grey and the anterior cingulate cortex. At the same time, activities linked to pain perceptions are suppressed at the level of the thalamus, insula and somatosensory cortices (Bingel U et al, 2006). Nocebo effect, in contrast, is highly associated with the hippocampus and other anxiety-related brain regions (Gondo et al., 2012). There is therefore a neural correlation to the subjective feeling of pain reduction or augmentation. However, when comparing placebo and nocebo effects in absence of active treatment, the specific pattern of pain activation or reduction triggered by expectation of pain relief or worsening showed to

be in part two distinct neural pathways. As previously mentioned in this work (section VI.I), a study realized by Freeman in 2015 (Freeman S et al., 2015), compared fMRI images of placebo, nocebo and neutral cream. This study design permitted to eliminate bias linked to the fact that both positive and negative expectancy were linked to reported changes in pain intensity in the neutral cream group. When the response to the neutral cream was held constant, analysis of the difference in brain activation with placebo and nocebo analgesia showed both overlapping and non-overlapping brain activation regions for placebo and nocebo analgesic responses. With this study design expectation of pain was specifically correlated with changes in the insula, orbitofrontal cortex and periaqueductal gray and expectation of relief was shown to produce specific changes in the striatum.

Furthermore, a team lead by Eippert (Eippert F et al, 2009) showed, using functional magnetic resonance imaging, that the spinal cords nociceptive processing was reduced by placebo analgesia, showing the importance of spinal inhibition as one of its mechanisms. Psychological factors can then be said to modulate pain perception at even the earliest stages of pain processing in the central nervous system by a top down mechanism.

Pain is a relevant subject in placebo studies for multiple reasons, the obvious being that the reaction to pain is hugely influenced by social and psychological factors. Individual experiences of painful sensations are derived by many psychosocial factors. We can observe that the expectation of analgesia can trigger pain relief and this one can be enhanced by conditioning. Compared to verbal suggestion alone, analgesia after conditioning is both stronger and longer lasting (Colloca F, Benedetti F, 2006). It has been shown in multiple studies that the strength of placebo relief during a painful stimulation is influenced by previous experiences. As previously discussed (section V.III), even unconscious conditioning elicits analgesic responses. When the patient is conditioned with a repetitive pharmacological treatment, the placebo effect takes the shape of the drug action, triggering drug-like physiological effects. As such, a patient conditioned analgesia with ketorolac will have a placebo effect mimicking the action of ketorolac, same goes with other types of painkillers such as opioid analgesia (Amazio M, Benedetti F, 1999).

Colloca and Benedetti (Colloca L, Benedetti F, 2009) showed that even second hand conditioning, by observation of the beneficial action of the pill in another person, may facilitate placebo analgesia by building up positive expectation concerning the drug. In this study, the magnitude of the placebo analgesia in subjects conditioned by observation of the drug's effect on others was comparable to what is expected with traditional conditioning. Similarly, the nocebo effect could also be triggered if

the subjects were observing another person in pain. This highlights the importance of social interactions and observations in the strength of both the placebo and nocebo effects.

Colloca and his team (Colloca et al, 2010) investigated the strength of conditioning by administrating painful and non-painful stimuli to the dorsum of the foot. In this study, subjects were placed in front of a system of colored lights. They were told that a red light would indicate that the treatment would increase the intensity of the painful perception, while the green light would reduce it and the yellow light was used as a control. They were then separated in two groups, one receiving one session of conditioning and the other four sessions. Interestingly, the group receiving one session of conditioning showed a nocebo response but no placebo response when no painful stimulation was given, and both placebo and nocebo responses to painful stimulation. This effect disappeared over time. On the other hand, the group receiving four sessions of conditioning showed placebo and nocebo responses to both painful and non-painful stimulation that were lasting over the entire duration of the experiment. This suggests that the strength of learning plays an important role in the sensation of pain and pain relief.

Even when conditioning is performed, the nocebo and placebo effects depend on expectation of pain or relief of it. In another study, Benedetti and his team (Benedetti F et al, 2003) preconditioned subjects with ketorolac during two consecutive days. Ketorolac was then replaced by a placebo accompanied by a verbal suggestion of analgesia. As expected, a consequent analgesic response was noted. However, a second group, also conditioned with ketorolac was switched to placebo on the third day with a verbal suggestion of hyperalgesia. Not only did the verbal suggestion in the second group block the analgesic effect of placebo conditioning, it also produced a hyperlagesic effect. We can thereby appreciate the role of suggestions and belief even when conditioning is previously performed.

A way to show the relevance of the placebo effect in clinical practice is to observe its influence on the efficacy of treatment. To do so, studies have been made in which a painkiller treatment was given either overtly or not.

Bingel and his colleagues (Bingel U et al, 2011) did a study that showed that when patients expected to receive an opioid analgesic (remifentanil), the painkiller effect before receiving it, was greater than if the administration was overt (if the patient thought he was getting saline but was administered remifentanil). Another way to produce an overt administration was to tell the patient the treatment

would be interrupted but keep the administration of remifentanil going. In this group, the analgesic effect of remifentanil was abolished. Looking at fMRI responses, the zones corresponding to the enhancement of analgesia could be seen as the condition was associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex. On the other side, negative expectation of interruption was associated with activity in the hippocampus.

The fact that a drug is more efficient if it is given with an open label points towards the idea that the total effect of a drug is the added pharmacodynamic action and psychosocial effect linked to the expectation of symptoms alleviations. The placebo effect seems to have its importance in both phenomena. Some studies showed the action of the placebo as a mediator of endogenous nociceptors (such as opioids), others point towards the importance of expectations in the strength of its effect.

To understand how the placebo analgesia work, different approaches have been used. On one hand, functional imaging permitted to literally see brain activity occurring during analgesia and compare placebo with active drugs. On the other hand, antagonists have been used to try to pinpoint the neurotransmitters that could be culprits for self-triggered pain reduction.

On the surge for understanding the pathways linked to placebo analgesia, multiple theories have emerged. The action of the endogenous opioid system in regulation of pain has been demonstrated by Levine et al.. In their study, pain suppression was induced by placebo and in turn, blocked by nalaxone, an opioid receptor antagonist (Levine J.D. et al., 1978). This permitted to emit the hypothesis that both placebo and morphine share a common opioidergic mechanism. It was estimated by the same team that the placebo analgesic effect to be equivalent to up to 8 mg of morphine (Levine, J.D. et al., 1981).

In 2002, Petrovic and his team (Petrovic et al, 2002) showed a common array of activity in the brainstem and cerebral cortex in both a placebo group and a group taking a rapidly acting opioid agonist remifentanil. This pointed towards the idea that there might be a related mechanism in both placebo and opioid induced analgesia. The administration of a placebo was shown to activate the rostral anterior cingulate and orbitofrontal cortices, further changing the activity of the lower pons and medulla as well as periaqueductal gray.

To understand how and by which means the placebo effect was taking place in the brain, a series or researches have been led using antagonists and analyzing whether or not they would block the analgesic effect of a placebo pill. Following a preconditioning with morphine, the response to the

placebo has been shown to be totally antagonized by naloxone. However, if the conditioning is made with a non-steroidal anti-inflammatory drug such as ketorolac, the post conditioning administration of nalaxone only partially blocked the placebo analgesia in case it had been accompanied by expectations cues, while ketorolac conditioning alone proved to be insensitive to naloxone. These results show that while purely cognitive factors, such as the expectation of pain reduction, are associated with the activation of endogenous opioid systems, conditioning is, on the other hand, able to produce other analgesic mechanisms depending on the conditioning agent (Amanzio and Benedetti, 1999). The passive expectation of pain relief seems to be able to trigger opioid analgesia, while conditioning, on the other hand, triggers specific subsystems. The action of the placebo effect on the endogenous opioid system has also been investigated with indirect pharmacologic approaches, showing that placebo analgesia can be antagonized by naloxone, an opioid antagonist, and that such reactions could be confirmed by fMRI and PET studies (Colloca L, Grillon C, 2014).

Similarly, the endocanabinoid system has been investigated with a canabinoid receptor 1 blocker, SR 141716A, after administration of the NSAID ketorolac. After a period of conditioning with the non teroidal anti-inflammatory medication, the patients were administered a cannabinoid receptor blocker. The antagonist blocked the analgesic effect of the placebo, suggesting an action of the endocanabinoid system in the regulation of pain triggered by the placebo effect (Benedetti et al., 2011).

On the other hand, as was previously mentioned in section VI.I on neuroanatomy of the placebo effect, the cholecystokinin system influences the expectation pathways, mediating both the nocebo and placebo effects. This system is known to have an influence in the regulation of anxiety and hyperalgesia and by blocking cholecystokinin A and B receptors with proglumide, nocebo hyperalgesia subsides (Colloca L, Grillon C, 2014).

## IX.II Depression

The response to placebo in antidepressant trials is impressively high. In patients with mild to moderate depressive symptoms, SSRIs, the drug of choice for the treatment of such diseases, shows a disappointingly moderate to null effect. In fact, the difference between the treatment arm and the placebo arm of trials is so small, that they did not exceed the National Institute for Health and Clinical Excellence (NICE, 2014) for a "clinically significant" effect.

The problem linked with the efficacy of antidepressant medication goes even further, the supposed effectiveness of these medication being the primary evidence for the serotonin theory (Kirsh I, 2014).

It makes sense for depression to be hugely influenced by the placebo effect: one of the major symptoms of depression is hopelessness and, as described by the British psychologist John Teasdale, there is this phenomenon of being depressed about depression; a vicious circle in which the disease itself is a cause of the disease, or the worsening thereof (Teasdale, 1985). It is not surprising then, that the simple fact of initiating treatment could dramatically reduce the feeling linked to the disease by the simple action of replacing hopelessness with hopefulness (that is, being hopeful about recovering from the disease).

Kirsch and his team (Kirsch et al, 2002) used the Food and Drugs Administration unpublished and published data from clinical trials for six new generations antidepressants, under the Freedom of Information Act. This is a relevant point because, according to the author, the drug companies do not publish nearly half of the clinical trials they sponsor.

All FDA trials used the Hamilton Depression Scale as a measure for depression, which made a meta-analysis possible as the diagnostic tool is comparable between different studies. When taking into account published and unpublished trials, only 43 % showed a statistically significant effect of the drug over the placebo. Kirsch and his team evaluated the percentage of placebo to the response to antidepressant to be an impressive 82% and the mean difference between drugs and placebo was less than two points on the Hamilton Depression Scale. The scale is based on a questionnaire on which patients can score between 0 and 53 points. By simply improving sleep quality, one can diminish their score by 6 points. It is then easy to understand how the authors conclude that a difference of two points is not a very strong predictor of the drug efficacy. The previously mentioned study of the National Institute for Health and Care Excellence (NICE, 2004) found a difference of 3 points on the Hamilton Depression Scale between drugs and placebo, indicating the importance of the placebo effect in depression. The same study also showed a very small difference between long term and short term trials, indicating that the length of the depression was not affecting the quality of the placebo effect.

It is widely accepted today that antidepressant have a higher efficacy on severely depressed patients (Thase, 2002). Nonetheless, even though antidepressant efficacy is higher in patients scoring higher than 28 on the Hamilton Depression Scale, the mean difference for this group of "severely depressed"

patients was 4.36 points and stayed below the level of statistical significance.

However controversial these meta-analysis might be, it highlights still the importance of the placebo effect in the treatment of this psychiatric illness. Kirsch and his team (Kirsch I and Sapirstein G, 1998) have found a very high correlation between the placebo effect and the drug effect, indicating that even variations to the drug effect size was due to the placebo component. It is then interesting to evaluate how much of this placebo arm remission is due strictly to the placebo effect and how much is due to the natural course of the disease. To do this, they used psychotherapy trials, in which it was easier to find non-treatment groups, and estimated the pure effect of the placebo. They found that in clinical trials for major depression, one-quarter of the effect of treatment can be attributed to the specific action of the active medication, one-quarter to other factors (spontaneous remission) and one-half to a placebo effect.

It is also worth noting that there is an association between the expectation of relief from the antidepressant treatment and the efficacy of this one. In a 9 weeks single blind experiment, patients were given riboxetine and asked to rate their expectations about the drug effectiveness. Patients with higher pre-treatment expectations had substantially better response to the drug (Krell HV et al., 2004). This perfectly exemplifies how expectations can have a direct impact on the strength of the placebo effect and by this mean, on the effectiveness of the drug or treatment.

Investigating the placebo effect in depression is problematic. One of the reason is that the treatment of depression does not work acutely, which means that an investigation concerning its effects has to last multiple weeks. If it is decided to compare the placebo arm to a non-treatment group, this requires some of the patients in the trial to receive no treatment for a long period of time. Considering those ethical limitations, it is understandable that depression has not often been used as a model to investigate placebo effect.

In 2002, the first attempt to determine the neurological mechanism underlying the placebo effect in depression was made (Leuchter AF et al., 2002). Leuchter and his team set up a small experiment in which fifty-one subjects suffering from major depression were involved in one of two independent nine weeks double blind randomized controlled trials. One group was given fluoxetine, the other venlaflaxine as the active medication and the patients went serial quantitative electroencephalography measurements during the length of the trial. They showed that after 9 weeks, subjects that showed improvement on the placebo arm of the study were characterized by an increase in prefrontal

cordance that was not seen in either placebo non-responders, medication non-responders or medication responders. This was particularly marked in the right hemisphere and started early in the treatment. Medication responders, on the other part, showed decreased cordance in the prefrontal area. This is suggesting, with all the cautions conclusions on a study made with such as small population deserves, an independent and distinct physiological action of the placebo.

In a subsequent study (Leuchter AF et al., 2004), efforts were made to further identify the placebo response occurring during the treatment of depression and what was the specificity of placebo responders. Placebo responders showed to be different from drug responders, and to a lesser extend from all other groups, in that they had lower pretreatment frontocentral electroencephalographic cordance in the theta-frequency band. They also showed lower reporting of late insomnia and faster cognitive processing time. After having made a logistic regression analysis, the authors found that these three pretreatment measures accurately identified 97.6% of eventual placebo responders. Once again, however, the population studied was small (51 subjects) and further, larger, trials would be needed to make definite conclusions on the particularity of the placebo response and placebo responders.

Another group of researchers, carried a study in 2002 investigating cerebral changes of glucose metabolism seen on positron emission tomography during a 6 weeks trial on male patients treated with fluoxetine (Mayberg HS et al., 2002). They observed changes in the brain of the placebo responders, specifically regional metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula and posterior cingulate as well as metabolic decrease in the subgenual cingulate thalamus and parahippocampus. The interesting point of this study is that it shows that responders to the drug had the same PET scan change patterns than placebo responders, with a generally greater magnitude and some additional changes (subcortical and limbic changes in the brainstem, striatum, anterior insula, and hippocampus). At six weeks, no regional changes specific to placebo was noted. Furthermore, at week one was seen unique ventral striatal and orbital frontal changes in both groups that was not seen in neither placebo non-responders, nor drug-non-responders. These changes had occurred before any benefit from the treatment was observed. This could reflect anticipation of clinical benefit and reflects results obtained in other trials, in which the ventral striatum was involved as well after the administration of reward mechanisms in the placebo response (Scott et al., 2007). The ventral striatum involvement is not surprising, the nucleus accumbens being recognized as one of the main regions involved in the reward mechanism, and

specifically the anticipation of reward (Knutson B et al, 2001).

## IX.III Anxiety

There is evidence that expectations induced by the introduction of treatment, may it be sham, has an important role in anxiety management. A study on overt and covert administration of diazepam in postoperative patients has been led (Benedetti et al., 2003). In the group that was administered diazepam with an open label, there was an important reduction of the anxiety level, as was expected, but in the group where the administration was hidden, the drug was shown to be completely ineffective. The relapse of the anxious symptoms has also been studied and showed that when the drug was knowingly discontinued, anxiety reoccurred, but it didn't if the drug was discontinued without the patient's knowledge.

This points towards the idea that not only the effect of diazepam was a placebo effect, but also that the effects linked with the cessation of the mediation (re-apparition of the anxious state) was a nocebo effect.

The effect of the placebo on brain function has been investigated by neuroimaging studies (Petrovic et al., 2005). As with most neuroimaging studies, the sample size was quite small (n: 15) and it is difficult to make definite assumptions based on the results, but they show interesting trends that deserve to be further discussed and examined. Petrovic and his team treated the subjects of this experiment with either the benzodiazepine midazolam or flumazenil (benzodiazepine receptor antagonist) and showed them unpleasant pictures. On day one, they found that midazolam's action reduced the feeling of unpleasantness and that flumazenil cancelled this effect. On day two, the subjects were put in an fMRI machine and underwent a similar test. They were first informed that they would receive a drug, either flumazenil or midazolam, then shown unpleasant images and asked to rate their felt degree of unpleasantness. Before the images were shown, it was indicated to the patient which one of those two drugs he supposedly was receiving. Unknown to them, however, subjects received only placebo. The effect of expectation was investigated in this way and the results showed an important placebo response when patients thought they were receiving midazolam and no response when they believed to have received flumazenil. The imaging studies showed that, very similarly to the neurological effects of placebo analgesia, there was regional changes in the anterior cingulate cortex and lateral orbitofrontal cortex. In this experience, the placebo effect seem to be

modulated, emotionally as well as physiologically by the patient's expectations from the treatment.

As mentioned earlier, Furmark and his colleagues (Furmark, 2008) showed on brain imaging studies that the amygdala, that plays an important role in the sensation of fear, is overly activated in patients suffering from social anxiety disorder (SAD). Some healthy subjects having certain variations in genes regulating serotonine also had more active amygdalas. The team ran a placebo controlled trial on 108 subjects that had a previous diagnosis of SAD. Brain activity was assessed by positron emission tomography during a stressful task where they had to prepare and deliver a speech in front of a small group of people, before and after 8 weeks of treatment or placebo. Of the 25 patients receiving the inert pill, 10 reported a reduction in their anxiety level that correlated with a reduced activity of their amygdala. They also found a genetic marker associated with this effect and it would be tempting, if these results were to be confirmed on a larger population, to screen patients for this genetic variant of tryptophan-hydroxylase-2 promoter, to improve the treatment of anxious disorders.

The same group also investigated the similarities between SSRI and placebo response with a similar study setup (Faria V et al., 2012). They proceeded in a double blind manner, giving one group a placebo and the other an SSRI and assessing their brain function by PET scans before the treatment and after 8 weeks during an anxiogenic task. They observed a similar pathway of attenuation of regional cerebral blood flow in the left basomedial/basolateral and right ventrolateral amygdala in both placebo and drug arm of the trial. These physical changes were correlating with the subjective feeling of reduction of anxiety and differentiated responders from non-responders. No differences were found between SSRI and placebo responders. From these data, we can appreciate how drugs and placebos act on common amygdala targets in the reduction of anxiety.

Similarly as for conditions such as pain, the placebo effects seems to act in reducing the activity in the amygdala and insula. This shows how placebo-induced expectations can use common mechanisms across different conditions (Benedetti F, 2009).

## X. Conclusion: Clinical relevance of the placebo effect

The placebo, nocebo and care effects are all three of major interest in clinical practice. The belief, genetics and personality of the patients, as well as the rituals surrounding treatments have been

shown to influence the outcome and relief linked to treatment. In different conditions, the placebo, nocebo and care effects have different strength, however, pain and discomfort, may they be physical or psychological, are important part of the treatment of any diseases. It then seems relevant to try to not maximize the placebo and care effects and minimize the nocebo effect.

From a scientific and human perspective, it makes sense to consider the brain as having the potential to relief distress with no use of externally administered chemicals. Not only would the generalization of such practices decrease costs of healthcare, but also have the potential to decrease side effects linked to medications. However, a change in attitude might be needed. The placebo, as understood and used in today's medicine, is too often considered as a "sham" treatment, and the neural and physiological changes it induces generally ignored. This leads to common confusions and misconceptions, for example, the belief that someone responding to the placebo was not really sick to start with. The major effect of overt placebo compared to open label placebo might have to do with how, as medical professionals, we present the subject to our patients. Admitting that we do not hold complete knowledge about what determines the efficacy of drugs, and recognizing the part of mystery linked to the brain's ability to, to some degree, self-heal, might be a first step towards making the placebo effect clinically relevant in the everyday practice of medicine.

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