Chapter 8
Making Sense in the Medical System: Placebo, Biosemiotics, and the Pseudomachine

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8.1 Placebo and Biosemiotics

A placebo is, by definition, an inert substance or an inactive procedure. The placebo effect is considered as the reaction following the administration of a placebo. But, as Moerman and Jonas (2002) have pointed out, since there is no active ingredient in an inert substance, it cannot be the placebo itself that is causing the placebo effect. Rather, the placebo effect is due to the many meaningful circumstances of the placebo administration or procedure such as the information given about the likely effect of the substance, the color and branding of a placebo pill, the relationship and interaction with the person who administers the placebo, the medical context, and the background experience a person has with medical interventions in general terms, etc. It is in this sense that Moerman (2013) suggests to speak of *a meaning response* rather than of a placebo effect.

This clarification in terminology makes the underlying scientific problem of any response to placebos obvious. We see changes in the material word, for example, physiological changes as a consequence of mental activities, that is, the creation of meaning. Here we are at the heart of the mind-body problem. This is because we have a severe lack of scientific concepts and models on how these two categorically different levels of description are relating to each other or, to put it simply, how a

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change in meaning is related to a physical change. This is a problem that is usually neglected in the discussion. The problem is the following: Even if we were able to clarify the full causal physiological chain that leads from a belief to an improvement in health, it is still not clear how the very mental act of believing can indeed effect the first physiological change, just as much as it is unclear how neuronal activity creates thoughts, feelings and sensations.

One potential theoretical framework that can find appropriate descriptions bridging this mind-matter gap is *biosemiotics*. It is the application of the theory of signs and sign processes (semiotics) to biological systems. This approach was first conceptualized by Thure von Uexküll, one of the founding fathers of modern psychosomatic medicine (von Uexküll 1982; see also Goli, Raieian and Atarodi in this volume). In semiotics, as developed by Charles S. Peirce, the dyadic relationship between cause and effect in a mechanistic model is replaced by a triadic relationship consisting of a *sign*, an *object*, and *meaning*, in a more general model. According to Peirce, a causal relationship is a special case of this more general paradigm (Walach 2011) (see Fig. 8.1).

Earlier, we have placed the placebo response within this biosemiotic framework and demonstrated that this is a fruitful approach (Walach 2011). A mechanistic model can explain how a pharmacological *active* substance can result in certain physiological changes. But it cannot explain why a pharmacological *inactive* substance can result in similar or even identical physiological changes. In the biosemiotic approach, the placebo administration can be described within the respective

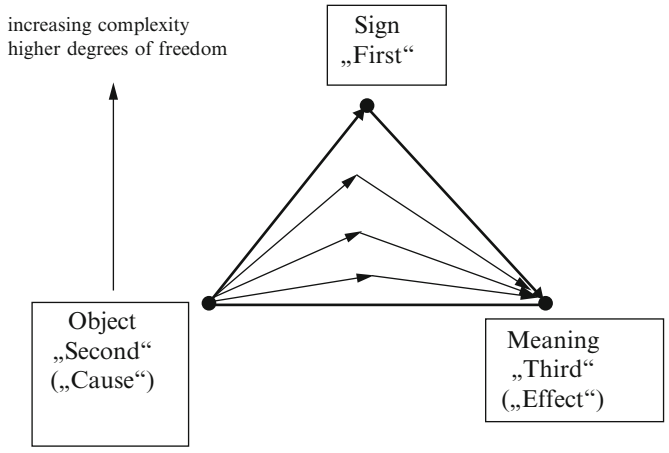

Fig. 8.1 The dual relationship of cause and effect as a special case of the tripartite semiotic relationship between Object–Sign–Meaning according to Peirce: While for simple, deterministic systems with no degrees of freedom, a mechanistic causal relationship between cause and effect is sufficient (base of triangle), systems with increasing degrees of freedom, such as simple biological systems like bacteria, or more complex systems, such as human beings, require a description in terms of a tripartite relationship (increasing angles of the triangle). Here, what may be a cause becomes a sign that produces a meaning, and hence the deterministic relationship is broken up into a relationship that allows for a variety of reactions as a consequence of this meaning-making process

medical context as a complex *sign* which creates a certain *meaning* in the recipient (and also in his or her social environment). The *object* itself is the inert pill with its inert substance (e.g., dextrose). Thus, when administrating a placebo, the object is of minor importance, but it becomes a sign for a more complex context with a certain meaning. On the other hand, when there is a pharmacologically-active substance in the pill, then the object itself is also of some importance. In the latter case we have a twofold pathway towards changes in the physiology. One is the mechanical pathway due to the active substance. Here, the pharmacological molecule becomes a sign for the system with a particular meaning, its physiological consequence. This is dependent on the genetic make-up of the organism with its metabolic specificity and capacity, counter-regulating activity, and the sensitizations history. In parallel, there is the pathway via the psychological context. This context, for instance, a medical treatment facility, becomes a complex sign with a very specific meaning that is dependent on multiple internal processes – some conscious, some unconscious – within the individual. It eventually creates a certain meaning, the complex reaction of the organism.

In a semiotic analysis, these two pathways cannot be seen as independent from each other. This is because in a semiotic model, it does not make sense to separate them, since all effects are always a complexion and a synergistic combination of material-causal and psychological meaning effects. In that sense, each intervention is a complex intervention that generates meaning in the recipient – at least if the recipient is not unconscious – and this meaning *is* the effect. That is the reason why non-active interventions can become harmful, for instance when people fall ill because of supposed and anticipated toxic effects from the environment, or why seemingly non-active interventions can be very beneficial, for instance when they are perceived as such in many cases of complementary or psychotherapeutic interventions. It makes no sense at all to ask whether there is a *real* effect for instance from psychotherapy, complementary medicine or geopathic zones. As long as there is perceived meaning, there will be an effect. This is also the reason why active interventions can lose their effectiveness completely when perceived as not important or not effective. In other words, a semiotic perspective redirects our attention from the material-causal properties of an intervention to the effects it has in the mind of the recipient. This explains why in Africa people may covet blue pills for certain types of diseases (e.g., for pain, and will find them effective), although they may be imbued with completely different meaning (e.g., as aphrodisiacs) in Western countries (Harry van der Zee, 2008, personal communication).

The important issue here is that for the triadic semiotic model *consciousness* is a necessity, yet not for the mechanical dyadic model. The latter will also work in situations where the patient is unconscious. But once the patient is conscious and able to create meaning, the result of this semiotic process cannot be predicted from the equation, since we cannot know all potential parameters entering into the meaning-making model.

One of the major implications of this approach affects our view on the generalizability of scientific statements. *Physiological processes in the human body* can be conceptualized as having a genetically-determined and thus limited variance

between individuals. Of course there are differences with respect to the life cycle, genetic polymorphism, etc. but in general, the assumption is that whatever works in one human body should also work in the other, and all biomedical research is successfully relying on this assumption, at least in very general terms. *Meaning creation processes in the human mind* on the other hand show a large variation. Meaning-making is always an expansion and extrapolation of an already existing model about the world. Large parts of our world model are of course socially mediated and culturally embedded. Yet beyond this rises the individual challenge to make sense out of the world in which one lives, which is intimately tied to the individuality of each biography, its specific opportunities and individual obstacles. The consequence of this, is that in contrast to the biomedical approach, it is not so easy to generalize about individuals and to arrive at uniform statements about certain populations by quantitative research only. Especially more-refined approaches within the biosemiotic framework, as proposed here, will have to address individuality by qualitative research methods. Such an approach is less capable of adding general statements as it is usually expected when speaking about science.

8.2 The Biosemiotic Perspective on Aspirin

We would like to explain this biosemiotic perspective on the placebo response by an example from the placebo literature, Branthwaite and Cooper published a placebo study on the analgesic effects of aspirin as well as drug branding in headache patients in *The British Medical Journal* (1981). In a 2×2 design, 835 women who regularly used painkillers for headache relief received a box of tablets. These were either placebo pills in an unbranded pack (Group A), or placebo pills endorsed with the manufacturer's design in a branded pack (Group B), or 325 mg aspirin pills in an unbranded pack (Group C), or 325 mg aspirin pills in a branded pack (Group D). The resulting mean pain relief 1 h after intake can be seen in Fig. 8.2.

The pain relief of the two active groups (**C** and **D**) was significantly better than those of the two placebo groups (**A** and **B**). Furthermore, branding (groups **B** and **D**) resulted in more pain relief than no branding (**A** and **C**). The interaction was not significant.

This study shows that there are several different effects at work. The first effect is the one we can see in group A. There is a pain relief of 1.78 points 1 h after the intake of an unbranded inert pill. This effect can be due to several sources. It can reflect the *natural course* of the headache which just got better by itself after 1 h. It can reflect the action of taking a pill which would be a *placebo effect*. This effect could be explained, for example, by *expectancy* (cognitive effects), or *learning* (classical condition), in case the person is used to taking (active) pain killers for headache (Benedetti et al. 2011). Furthermore, the effect can also reflect a *change in behavior*. When the participants decided to take a pain killer for their headache, this reflects that they realized in some way that they *have* a headache which is now so strong that some action is necessary. Here the action was to take a pill, but at the

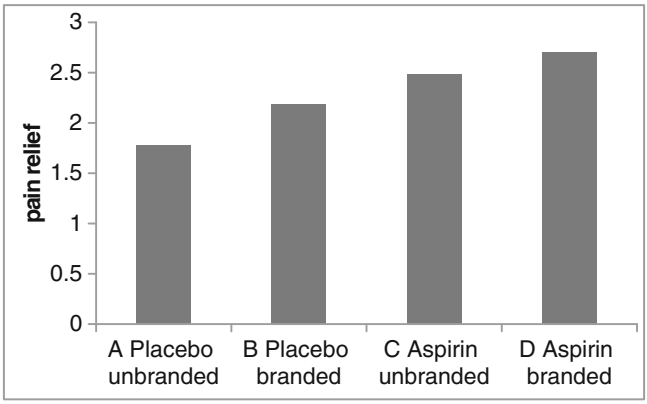

Fig. 8.2 Pain relief 1 h after intake of either aspirin or placebo being either branded or not branded. Pain relief ranges from –1 'worse' to +4 'completely better' with 0 indicating 'the same'

same time this realization may also result in other behavior changes which will help to reduce the headache, for example, drinking some water, taking a break, ventilating the room, or taking a walk in the fresh air.

This process of realization can also be conceived as a semiotic process. Here we could say that the headache is a sign which creates a certain meaning. The object would be, for instance, a dull pain in the left part of the head. The meaning of the headache will of course be quite individual, for example, "this is all too much for me, my head is already aching …", or "I have to admit that I drank too much alcohol yesterday…". Each of these processes can in turn be the starting point for the next semiotic triad. So the realization of having had too much alcohol yesterday can now be a sign to create a subsequent meaningful thought such as "maybe I should stop drinking alcohol for one week", etc.

Next to these three types of effects mentioned here, there may be even more effects at work, with some of them also related to the fact that the data was obtained within a scientific study (e.g., Hawthorne effect). However, we cannot disentangle these different effects (natural course, placebo effect, behavioral change, others) from each other with the study design applied here. One way to assess them would be to have a fifth group in which participants, for example, instead of taking a pain killer, wait for another hour, and then note their pain before taking the pill.

If we now look at group B, we see an improvement of 0.4 points to a mean of 2.18. This is obviously caused by branding the inert pill. This effect cannot be explained within a pharmacological causal framework because no pharmacological agent was present. It is solely due to the semiotic process, which requires a conscious person able to create meaning. Here the sign is the branding, and the object may be the inert pill. The meaning created by the sign will also be individually different, but in this case may go in the direction that this will be a powerful pain killer because the branding is well – known, there is a lot of advertising for the pain

relieving effect of this brand and also many people in the social environment will have given positive accounts after using this brand.

If we jump from group A to group C, we see the effect of the pharmacological drug which raises the pain relief by 0.7 points to 2.48. This effect cannot be explained within a semiotic triadic framework since the difference between groups A and C (both unbranded) cannot be detected by the participants. Thus, this effect needs to be explained within a pharmacological causal framework. In the case of aspirin, the pharmacological active ingredient is acetylsalicyclic acid which suppresses the production of prostaglandins and thromboxanes by inactivating the enzyme COX-1 and modifying the activity of COX-2.

Finally, group D should show all three sources combined, that is, initial effects (group A, placebo effect, natural course, etc), branding effect, and pharmacological effect. Under the assumption that these effects are not interacting, they could be added up. Then D should be $1.78+0.4+0.7=2.88$. The value measured is a little smaller with 2.7, thus reflecting some minor interaction.

The interesting point here is that only approximately one quarter of the pain relief measured in this study can be attributed to pharmacological processes. If we assume that more or less the same mechanisms are at work if aspirin is taken in daily life and not within the framework of a study, then this is an astonishing fact. It reveals that three quarters of the pain relief of aspirin are due to biosemiotic processes beyond the pure pharmacological action of acetylsalicyclic acid. On the other hand, the lay user of aspirin will likely attribute the whole effect to some pharmacological mechanisms which is also of course a semiotic process. This, by the way, tallies nicely with the result of a meta-analysis of all kinds of long-term pharmacological interventions. This resulted in a correlation between improvements under placebo and treatment of $r=0.78$ which means that across different treatments and diseases approximately 60 % of the variance in treatment effects is explained by all sorts of effects, including the meaning effect, and only 40 % of the variance is attributable to a causal effect of the pharmacological intervention (Walach et al. 2005).

8.3 Biosemiotic Pharmacology

If we generalize these conclusions to pharmaceutical therapy in general, then we can assume that a large portion of the therapeutic effects seen in general are misattributed to pharmacological mechanisms only. Or in other words, large parts of the effects are only working in conscious and meaning creating drug consumers, because the consumption of drugs has a certain culturally, historically and scientifically-produced meaning. This means that in order to describe pharmacological effects adequately, the standard dyadic causal models are insufficient. Biosemiotic descriptions are more appropriate since they are able to add meaning to the framework. Let's take a look at some more examples to illustrate this perspective.

Both of the two following examples employ the so-called open/hidden design. The standard design of the randomized controlled trial cannot determine the size of

the placebo effect. Even the above presented 2×2 design of the aspirin study is not able to do so; this is why we have suggested a waiting condition. Another option to assess the size of the placebo effect is the open/hidden design (Amanzio et al. 2001; Bingel 2013; Levine et al. 1981). Here the same pharmacologically active ingredient is given either openly in full view to the participant, or in disguise. The difference between these conditions represents the placebo effect; the pre-post difference in the hidden condition represents the pure drug effect.

Benedetti et al. (2006) investigated placebo effects in patients suffering from dementia due to Alzheimer's disease in an experimental pain paradigm (venous puncture). If large parts of drug effects are due to semiotic processes, then they should decline with ongoing dementia. Thus, Bendetti et al. correlated the size of the placebo effect to pain application with cognitive status as measured with the Frontal Assessment Battery. The placebo effect was measured by applying a local anesthetic to the skin either openly in full view of the patient, or covered with a tape. Thus, in both conditions patients received the same analgesic treatment (and the same pain stimulus), but only in one condition were they aware of this fact. The results of their replication testing 1 year after a first test when Alzheimer patients showed further cognitive impairment can be seen in Fig. 8.3.

The cognitively not-impaired controls showed a pain reduction of 66 % in the open condition. The hidden condition reveals that only 16 % of this reduction is due to the pharmacological substance, and the remaining 50 % is due to the placebo effect. Like in the Aspirin study, approximately three quarters of the overall pain reduction cannot be accounted for by the causal effects of the drug. In Alzheimer patients, the reduction due to the drug in the hidden condition is 23 %, but the placebo effect is obviously reduced, with only 41 % pain reduction in the open condition. Furthermore, there was a significant correlation between cognitive status and

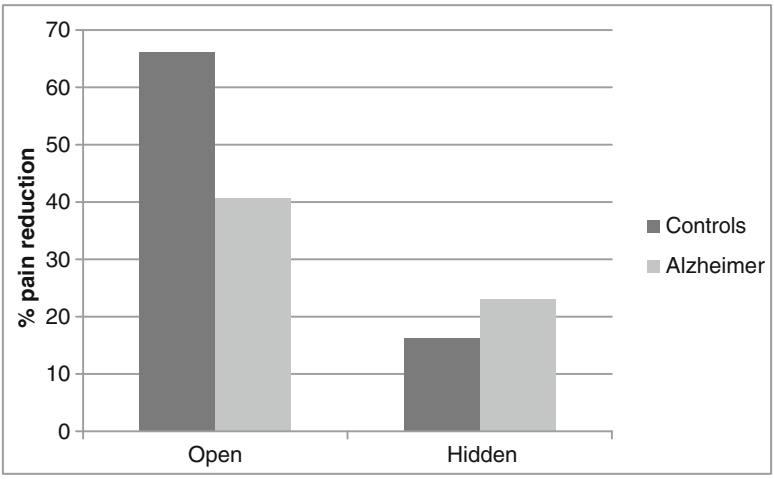

Fig. 8.3 Self-reported pain reduction in venous puncture by an analgesic that was either openly administered or covertly applied. Patients were either suffering from dementia due to Alzheimer Disease or healthy controls with no dementia

pain reduction in the open condition of $r = -45$, indicating that with a more impaired cognitive status, the pain reduction declines. These findings clearly underline the assumptions that large parts of pain relief after pharmacological therapy is due to meaning creating processes in conscious patients.

In a second study, Colloca and Benedetti (2005) also applied the open/hidden design, this time for the assessment of the placebo effects in analgesic drugs on postoperative pain. Patients after a thyroidectomy were randomized in two groups, and both groups received the same analgesic treatment. In the open condition, a doctor injected it in full view of the patient. In the hidden condition, the same dose of the same drug was administered by a computer controlled infusion pump at a preset time unknown to patients and careers. In addition, two analgesic drugs were compared regarding their ability to reduce postoperative pain after surgery – Metamizol, also known as Novalgin, and Buprenorphine, an opiate. The results can be seen in Fig. 8.4.

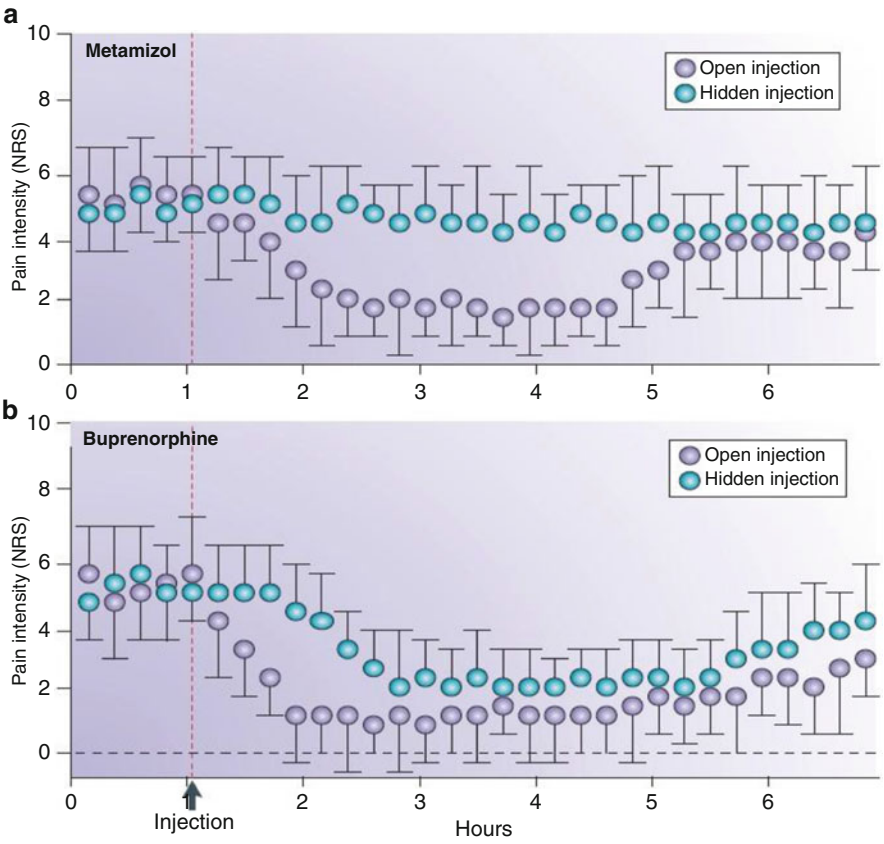

Fig. 8.4 Pain intensity rating on a numerical rating scale (NRS) from 0 to 10 in patients suffering from post-operative pain. The time course of the pure pharmacological effect of either Metamizol (**a**) or Buprenorphine (**b**) is reflected by the hidden injection. The placebo effect can be inferred as the difference between the open and the hidden injection (From Colloca and Benedetti 2005, p. 550)

On the lower panel, Buprenophine shows an overall drug-induced pain relief of approximately 2 points on the numeric rating scale (NRS) in 12 patients, 2–4 h after the injection in the hidden condition. If the same drug is given in full view of the patient (open injection) the analgesic effect starts much earlier and causes a placebo effect of approximately 3 points 1 h after the injection. The pharmacological drug effect is obviously much slower in onset than expected. If Burprenophine results in instant relief, this is mainly due to a placebo effect. On the upper panel, one can see that there is hardly any pharmacological effect in ten patients receiving Metamizol in the hidden condition. Pain reduction takes place only in the open condition when the patients are aware that they are indeed receiving a painkiller. Based on this data, one could conclude that Metamizol, which is a frequently-used analgesic medication, has no specific, that is, pharmacological effect at all, at least in patients with post-operative pain. This is a rather unexpected finding since Metamizol is a well-studied standard analgesic.

For a proper interpretation, it is, first of all, important to realize that these data have to be seen as preliminary in some respect. There are 22 patients in two groups, the study has not yet been replicated so far, and the publication lacks most of the methodological details. In another study applying the open/hidden paradigm, Metamizol showed a small drug -related effect in post-operative pain after 1 h (Amanzio et al. 2001). However, there are no data reported on pain relief beyond the first hour.

But let us assume that the data of Colloca and Benedetti (2005) are reliable. How can this complete lack of a pharmacological effect be explained? Since Metamizol is a licensed analgesic drug, we can infer that it has demonstrated a significantly stronger effect than a placebo in some randomized controlled trials (RCTs). So how can it be more effective than placebo in an RCT, but on the other hand, show no specific effect in the open-hidden-design? The authors suggest as an interpretation that the drug itself has no analgesic effect but enhances the release of placebo induced endogenous opioids. In other words, the idea is that this substance improves the placebo effect and thus, can only work when the patients are consciously aware that they receive a drug. Again, a pure pharmacological model cannot explain this finding. It can, however, be described within a biosemiotic framework. The other important point that can be drawn from this example is that drug and placebo effects are not necessarily independent, but may interact with each other. On the other hand, the RCT, which is the standard design to demonstrate specific effects of pharmacological substances, relies exactly on the assumption that placebo and verum do not interact, but are simply additive in effect. But from the data presented here, and many others (Kleijnen et al. 1994), we have to conclude that this assumption of additivity and a lack of interaction is wrong.

Finally, a third example investigates the interaction between pharmacological and placebo induced effects more formally. This is the field of *active placebo*, which is still underrepresented in the currently fast-growing placebo literature. An active placebo is defined as a pharmacologically-active substance used as a control condition in an RCT. This can be best explained by an example. Antidepressant medications have very clear and well-known side effects. Thus, in RCTs of such agents, the

participants are often unblinded during the course of the trial, because they can infer from the presence or absence of the side effects whether they have been randomized to the verum or placebo condition. To avoid this unblinding, researchers apply active placebos in the placebo condition, which are able to produce similar side-effects but lack the specific pharmacological substance (Enck et al. 2013).

But this logic of the active placebo can also be applied for investigating the placebo effect itself. In such an active placebo design, a pharmacologically-active substance is given which results in some physiological effects that can be noticed by the participants of these experimental studies (Flaten 2013). In addition, this drug administration is also combined with different types of information regarding the effect of the drug. The idea here is that the process of sensing the physiological effect of the drug in the body will interact with the information given.

Flaten et al. (1999) administered Carisoprodol, a centrally-acting muscle relaxant which induces drowsiness. They combined the administration of the drug with the information that this is (1) a relaxant, (2) a stimulant, and (3) no information on the drug was given. Three more groups also received the capsules of the same form and color with the same information, but in this case, the capsule contained only lactose and acted as an inactive placebo. The resulting changes in difference between the self-reported relaxation and tension, measured on a visual analog scale (VAS) for all six groups can be seen in Fig. 8.5.

One can see that participants of the "no information" and the "relaxant information" group showed some relaxation in the course of 2 h following the administration of either placebo or carisolprodol. But the most interesting finding is the group which received the active placebo and the information that it was a stimulant drug. They showed a compatible strong increase in tension while receiving at the same time apharmacological substance acting in the opposite direction. This third example

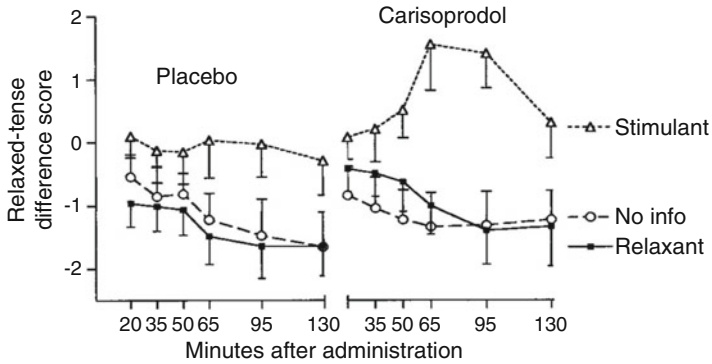

Fig. 8.5 Self-reported change regarding relaxation and tension after the administration of either a placebo (*left panel*) or a muscle relaxant, Carisoprodol (*right panel*). Data of six different groups are displayed. They received in a 2×3 design either placebo or carisoprodol with the additional information that this would be either a stimulant, or a relaxant drug, or they received no information at all (From Flaten et al. 1999, p. 253)

shows, once more, that the standard model of simple pharmacological effects which are not mediated by any context factors can no longer be maintained. Furthermore, the difference between the two groups getting the information that they have received a stimulant demonstrates that placebo effects are larger if any kind of physiological effect of the drug is noticed at the same time. This show, like in the other examples, that pharmacological and placebo effects interact with each other. Thus, they cannot be conceived as being independent from each other.

8.4 The Pseudomachine

We have seen that the biosemiotic process of assigning meaning is a powerful factor in inducing physiological changes in relation to either a pharmacological substance or to the administration of an inert pill, and that this process is governed b y a somewhat complex dynamic. We have also seen that a simple dyadic cause-effect model is not able to explain these processes. Interestingly, the patients and participants in these studies are very often making simple causal assumptions regarding their effects, which is a biosemiotic process in itself. In the aspirin study, the women taking the drug most likely may have assumed that aspirin works because there is a pharmacologically active agent, which in some physiological cause-effect mechanism unknown to them, eliminates the physical cause of the headache. It is less likely that they assumed that the simple effect of taking a pill, may it be inert or not, will substantially reduce their headache anyway. So the causal assumption of the consumer is only partially correct if an active substance is taken; it is completely incorrect if an inert pill, that is, a placebo is taken. However, it is exactly this causal attribution towards the pill which is responsible for the resulting effect to a large extent.

What is happening here is that people make incorrect assumptions about the causal mechanism of some treatments. This attribution process in turn results in effects confirming their causal model. The headache disappears because of the belief in a causal pharmacological process, although there was no such process in the case of a placebo.

Walter von Lucadou (2002), a German physicist and psychologist, calls this process a *pseudomachine.* He differentiates between machines and pseudomachines. A machine – by his definition – is a technical device or a causal process having a well-defined goal, and mostly amplifying or transforming properties, for example, a snatch pulley. In some machines like in hair dryers, bikes, or cars, their mechanisms are obvious to the user. In other machines, for example, in computers or microwaves, the mechanisms are more complex, and many users will not understand how the effect comes about in detail. It is especially this latter aspect that allows for the attribution of some causal effect to a device although we do not understand its precise mechanism. Such complex machines seem to be magic in some respect. They heat our dishes although they do not get hot themselves or they fly through the sky although they are very heavy. According to von Lucadou, it is mainly this latter

experience which results in the *attribution* of causal effects to machines that are not able to causally affect them in reality. Von Lucadou's real world example of a pseudomachine is a magnet attached to the fuselage of a car sold for the purpose of fuel saving when driving a car. According to the "scientific" description of the manufacturer, the magnet "aligns the molecules of the fuel" so that hidden energy potentials can be used once the magnet is fixed to the gas tank. However, this assumed mechanism is impossible from a physical point of view, and the underlying theory is flawed. Nevertheless, people buying the magnet and attaching it to the gas tank, report needing less fuel when driving. The mechanism behind this effect is most likely that the car-drivers buying such a magnet change their driving behavior with respect to fuel consumption. Sometimes such a magnet is even sold together with a CD providing information about fuel saving by changing one's driving style. So the magnet does indeed do what the drivers expect. It helps in saving gas, but the attribution of the effect is incorrect. The effect is actually caused by psychological processes, not by physical mechanisms. This is what von Lucadou calls a *pseudomachine*. Important for the function of a pseudomachine is that the effect is attributed externally to the machine and not internally to the user. Furthermore, it is important that the attributed mechanism is confirmed or at least partially confirmed in reality to maintain the attribution pattern.

From the perspective of learning theory, this would be a kind of operant conditioning. We know from learning theory that next to regular enforcement, an intermediate enforcement works best to maintain the attribution. Operant conditioning is often made responsible for magical thinking. An ill person gets an amulet, which has, according to the person handing it over, magical powers. The person recovers and attributes the healing to the power of the amulet, and, lo and behold, another pseudomachine is born.

Von Lucadou further separates between *classical* and *non-classical pseudomachines*. In classical pseudomachines, the physical and psychological effects can be clearly separated from each other. The magnet and the amulet are such examples, but also the intake of an inert placebo, especially when there is a learning history as per the aspirin example. A non-classical pseudomachine, on the other hand, is a procedure or apparatus where the physical and psychological effects may interact with each other or are entangled, and where it is not so easy to describe the effects of the "machine" in solely-physical or psychological terms. An example here is the active placebo where the physical sensing of the carisoprodol was related to larger change according to the (incorrect) information that the drug is a stimulant.

As we have seen above, each drug intake by a conscious and meaning-making consumer will result in some effect due to the interaction between pharmacological and psychological mechanisms, and thus the very process of taking a pill can be described as a non-classical pseudomachine. This concept of the pseudomachine is a fruitful one for describing all kinds of activities within the medical system, not only for oral medication, which served as a blueprint here. One may justly ask whether some kinds of operations, such as arthroscopic knee surgery for osteoarthritis (Moseley et al. 2002), or some instances of stent operations for stable angina (Stergiopoulos and Brown 2012), should not be conceived as pseudomachines.

Within complementary and alternative medicine, there are many "magic" devices sold, for example, machines measuring the "energy of meridians" by applying electrodes to various acupuncture points or machines on computerized biocommunication, or for measuring the "energy field" of the body. While the users report very good effects and are convinced by the practical results of applying the machine, double-blind testing reveals often that no physical effects are involved in this process, so they can be considered classical pseudomachines.

On the other hand, a recent meta-analysis revealed that the analgesic effect of acupuncture seems to be a non-classical pseudomachine. Until recently, the literature showed contradictory evidence for acupuncture having specific physiological effects. Specific effects were, for example, demonstrated in a model on blocking adenonsin receptors in mice (Cressey 2010; Goldman et al. 2010). On the other hand, there are several clinical studies in which sham acupuncture proved to have the same analgesic effects as real acupuncture (Cherkin et al. 2009; Haake et al. 2007). Sham acupuncture is a treatment that tries to mimic acupuncture (McManus et al. 2007), for example, in the German Acupuncture Trials (GERAC) where acupuncture needles were placed in purported "inactive" points rather than in specified acupuncture points (Diener et al. 2006; Haake et al. 2007; Witt et al. 2005). In a study on back pain, Cherkin et al. (2009) applied toothpicks on the back which do not penetrate the skin. The individual patient data meta-analysis by Vickers et al. (2012) was large enough to demonstrate that both mechanisms contributed to the overall analgesic effect of acupuncture. Since real acupuncture resulted in significant analgesic effects compared to sham acupuncture, a specific effect can be assumed which is beyond placebo effects. On the other hand, comparing acupuncture to standard treatment or usual care showed larger effects than in comparison to sham control; this points towards the interaction of placebo and "real" effects of acupuncture.

8.5 External Causal Attribution as a Special Biosemiotic Process

What we can learn from these examples and the fruitful concept of the pseudomachine is that human beings are clearly looking for (external) causal mechanisms and explanations regarding inner states in general and their health status in particular. The causal pattern is one of the most basic cognitive patterns in order to create meaning. Furthermore, ascribing a certain causal mechanism to a certain procedure may result – similar to a self-fulfilling prophecy – in the expected effect although we can show from a mechanistic point of view that the attributed causality is wrong. The strongest changes seem to occur in cases where the procedure or machine to which the causality is attributed does indeed show some small causal effect, especially with respect to bodily sensations. Such sensations seem to function as a kind of proof for the assumed causal mechanism and can thus act as a powerful amplifier. In this case, it is even possible that the causal effect can be overridden by the semiotic attribution processes in the opposite direction, as has been shown in the Carisoprodol example.

In this sense, making causal external attributions can be considered as a special type of a semiotic process, that is, a special type of creating meaning in the world. In the case of a pseudomachine, classical or non-classical, the "machine" or procedure can be seen as the sign, which will result in this special causal and external attribution type of meaning.

At this point, we have to take care that we do not fall into the trap of conceiving this meaning pattern as individually invariant. We can assume that many of our causal attributions are deeply rooted in our culture, for example, that taking a pill will result in a physical change, and that it will be almost impossible to escape from this pattern. We know from cultural studies that the only way to do so is to become aware of one's own inculturation, which is not an easy process. On the other hand, we have to see that on a more refined level of attribution, people will be different from each other with respect to which attributions are meaningful for them. Within some native cultures from the Amazon, there will be hardly any possibility for an individual to escape the idea that an amulet will have powerful forces. Within a more Western industrialized culture, the opinions will be split. Many will consider attributions towards amulets as superstitious, but others will stick to them although they will not always disclose this. As with any semiotic process, one's individual internal model of the world will be the starting point, and the individual will only construct attributions that fit this mod el. On the other hand, we have to acknowledge that large (if not all) parts of an individual's world-model are due to his or her cultural embedding.

The culturally most independent part in this process is the causal pattern itself. Inferring linear causal connections is one of the earliest cognitive patterns resulting from sensorimotor integration in the newborn. Indeed, it is likely to be rooted in the evolutionary success of our whole heritage as mammals and primates. It was William Ockham, and later on Hume, who argued convincingly that the cause is not necessarily a mechanical event taking place in the outer world, but a cognitive inference of the human mind connecting regular and contingent observations.

According to Ockham, causality is not a property of things, but a result of observations of regularity and hence a property of our mind. We only observe correlations: "Where smoke is, there is fire", we infer and attribute a causal property to the fire itself, although all we observe is the correlation (Goddu 1984). Hence, Ockham (1957) defined a cause as something given that it is taken away, the supposed effect does also not happen, and given it is, the effect happens (p. 629). Hume (1977), later in the eighteenth century, took up the same line of argument postulating that the idea of a cause is an abstraction of our mind. It is formed once we observe that (1) causes precede their effects, (2) in close proximity, and (3) and regularly. Thus, the concept "cause" is formed in our mind. But it is important to realize, according to Hume, that there is no cause in the outside world, but only in the model we construct of it. Kant, disturbed by this analysis, considered causality a condition of our mind and a precondition for understanding. With the advent of evolutionary theory, we can assume that the concept of causality is something which is an evolutionary a-priori of our existence. It helped us to understand contingencies, avoid dangerous ones

and exploit propitious ones, and hence made us what we are. But we should not forget that the causality we attribute to the world is in fact one constructed by us.

If children or members of aboriginal cultures show what is usually called superstitious beliefs or magical thinking by ascribing causality to processes which have no causal connection from the perspective of modern science, we smile at this because we assume we have a superior and more refined understanding. If within our societies, some people believe in the healing powers of certain machines and healing rituals which we consider to be inert and of no mechanical causal relevance, we also react with depreciation since we assume that – from a scientifically informed world view – any effects due to these procedures are "nothing but" mere suggestion and self-deception and cannot compete with a "real" healing process employing physiological causal processes explained in scientific terms.

But let's step back for one moment from this line of reasoning. If the dominating scientific model in the medical science is looking for the "real" causal pattern, then what is the difference from the lay person making their own causal attributions of the world? Isn't it the case that this type of science replicates the same intrinsic nature of us humans on a larger scale to find meaning by creating causal descriptions of the world? Or in other words, by explaining effects in the field of medical science with simple mechanic linear cause and effect descriptions similar to the ones of physics? One would argue that the difference here is that the causal mechanisms can be proven by experiments. For instance, it can be demonstrated by a double blind randomized control trial that an effect is taking place which cannot be related to the mindset of the patient if the blinding was appropriate. But let us come back to our first example, the aspirin study. We have seen that only approximately, one quarter of the pain relief can be unequivocally attributed to the pharmacological process. What about the other three-quarters? In the case of pain relief, these three-quarters are the crucial part. The mechanistic biological model usually attributes all effects related to drug intake to the pharmacological process and neglects or ignores any placebo or biosemiotic effects. But isn't this also a crude misattribution? Isn't this just a replication of the laymen's behavior of looking for simple mechanistic cause-effect models and to ignore the more complex relationships? Obviously, the difference between the native attributing pain relief to the amulet and the scientist attributing it only to the COX-1 inhibition is not as big as expected after all.

From the point of view of semiotics, we could reframe science, like many have done before (Foucault 1991; Latour and Bastide 1986; Latour 1999; Shadish and Fuller 1974), also as a social meaning creating process rather than a procedure in order to find the truth about the world. It is obvious that science – as it is conducted today – is a social practice governed by certain rules and basic assumptions. It is also clear that many of these rules are due to social agreement rather than due to objective proof (whatever that could be). Take for example the rule that values smaller than or equal to .05 ($p \leq 0.05$) are considered as significant while larger p-values are indicative of no significant finding. We all know the importance of this fine line. But of course this is not a given fact, but simply a social agreement. Or as Rosnow and Rosenthal put it: "God loves the 0.06 nearly as much as the 0.05" (Rosnow and Rosenthal 1989, p. 1277). Of even larger importance is that at the very heart of our

modern science, there are many basic assumptions which are unproven (Walach and Schmidt 2005). And some of them are relating directly to our topic, for example, the assumption that all effects in the world are of a mechanical nature. This implies that all changes are brought about by the local impact of material parts which is efficient causation. But this presupposition that the world is mechanical and causal in its core is unproven. If we take this for granted and make causal explanations to a criterion for scientific proof, we are creating a dogma (Sheldrake 2013). In this case, an unproven presupposition turns into a belief and science shifts towards scientism.

From such a philosophy of science point of view, there is space to complement the mechanistic causal explanation pattern with a semiotic one. The first one may be the more dominant one when dealing with unconscious items such as in physics, but the latter may likely give us the better explanations in all instances when consciousness kicks in. The field of medicine surely belongs to the second group.

8.6 Healing Due to Semiotic Processes: Is It Allowed?

The dominant mechanistic model in the medical sciences, combined with the assumption that all change is due to direct causation, results in another strange misconception. Healing processes that cannot be explained within such a causal model are not taken seriously. If somebody underwent some medical procedure unable to be explained currently within such a framework, any resulting healing process is depreciated, if not negated. If somebody benefits, for instance, from a treatment in homeopathy, or from a visit to a spiritual healer they will often hear comments like: "Well, of course you might feel better, but that is *only* a placebo effect". What happens here is that the ability of finding a scientific explanation is rated higher than the benefit of the patient, or the experience of an individual. If we do not understand how a placebo effect works, then benefiting from a placebo is considered as being not real. Or, in other words, the dominating scientific model discriminates between accepted and unaccepted healing processes, which is rather strange from the patients' perspective and may also in part explain the longstanding debate about the role of complementary and alternative medicine in our society.

The blueprint for this line of reasoning is that the placebo-controlled RCT is the standard to evaluate the efficacy of any drug or procedure. Here, the idea is to control against the placebo and this means that only the difference between the placebo effect and the verum effect is taken seriously while everything else is ignored. You may benefit 90 points from a placebo and additionally 10 points from the verum. Then only the 10 points are considered to be a 'true' improvement while the other 90 points are neglected. We have shown elsewhere that this line of reasoning may even result in the strange case that a more efficient procedure is neglected in favor of a less efficient one (efficacy paradox, see Walach 2001, 2011).

But meanwhile, the climate is changing ever so slightly. Since the since the mid-1990s, researchers have started to recognize the power of the placebo. The placebo concept is now shifting from being a control condition that needs to be ruled out in

order to find a 'true' effect, towards a valuable treatment in itself. This also has to do with the discovery that placebo effects are mediated by neurobiological processes, for example, by neurotransmitters binding to the same receptors as pharmacological substances (Benedetti et al. 2011; Colloca and Benedetti 2005; Price et al. 2007). Hereby, large parts of the placebo response can be incorporated into the mechanistic model. The distinction between so call ed 'specific' and 'unspecific' effects slowly melts away (Linde 2006). If after the intake of an inert pill, the idea of having received an aspirin results in the release of endorphins and thus analgesia, this may be considered a very specific process.

8.7 Is the 'Open Placebo' the Future?

If we extrapolate this development for another 20 years, we may imagine a medical system that makes heavy use of the large potential of semiotic processes, for example, by designing hospitals and procedures which optimally support healing processes (see, e.g., Jonas and Chez 2004; Ulrich 1984), or by developing communication and treatment strategies which are known to maximize placebo effects by initiating positive semiotic processes and meaning constructing. This sounds promising, but there is one major problem associated with many of these ideas. Once we have understood that a positive semiotic process might be due to certain causal assumptions about the world which cannot be maintained from a physical point of view, it will not be ethical to communicate them any longer. Or, in other words, if we start to understand that some classical pseudomachine is at work, then we have the ethical obligation to inform the patient about this fact, while this may at the same time result in the placebo effect to disappear. Going back to von Lucadou's example of the magnet, it will be fine to sell these magnets if you are personally convinced that they have a causal effect. But once you are aware that the description of the magnet aligning the molecules of the fuel is wrong, you should no longer tell this to your customers since this is deception. In the same line, psychiatrists should no longer tell their patients that selective serotonin reuptake inhibitors (SSRI) will improve depression once they have understood that almost all of their effects cannot be attributed to the process of serotonin reuptake inhibition (Kirsch et al. 2008). But, on the other side, being honest here is to the disadvantage of the customer or the patient. It looks like two ethical principles are in contradiction here, that is, being honest and acting in the patient's best interest (Kaptchuk 2002).

The solution of this dilemma may be a surprising one: "the so-called open placebo". In 1965, Park and Covi published a paper entitled "Nonblind Placebo Trial" (1965). In this study, 14 patients attending a psychiatric outpatient department were offered to take a sugar pill which is as they were told "a pill with no medicine in it at all" (p. 337). This offer was combined with the statement "…Many people of your kind of condition have also been helped by what are sometimes called 'sugar pills', and we feel that a so called sugar pill may help you, too" (p. 337). After 1 week the patients showed reasonable improvements on a symptom check list and a

generic self-report scale. This is a surprising result, since it is usually assumed that a placebo will not work anymore once it is known to be a placebo. But this assumption may be wrong. It took 45 years until this finding was replicated in a more stringent study. In 2010, a publication by Kaptchuk et al. (2010) reported about a randomized open placebo trial in 80 patients suffering from Irritable Bowel Syndrome (IBS) . They were either randomized to a no treatment control condition or to an open placebo condition receiving "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind–body self-healing processes" (Kaptchuk et al. 2010, p. 1). Patients in the open placebo arm showed significant improvement compared to controls in the main outcome criteria (symptom severity, global improvement).

How can these results be explained? Until now, there is no conclusive model that can account for these findings. So far we thought that placebo effects were elicited by the expectancy that one would receive a powerful drug. But in the case of the open placebo, the deception that is usually employed to convey the expectancy was disclosed. Obviously the authors of these two studies were able to maintain positive expectations despite the lack of deception. When reading the two statements, one can see that both are relying on prior positive experiences with treatment or placebo by telling the patients that these sugar pills have helped many other patients before. So it looks like the expectation this time is not tied anymore to some assumed pharmacological process, but to the placebo itself. What is conveyed is the message "this placebo will help you because it is a placebo and we know that placebos are very powerful". This is the pseudomachine reloaded by itself and back onto itself. One can furthermore assume that the powerful ritual of taking a drug which is very well established in our society also assisted the process through unconscious learning processes (Jensen et al. 2012). Or to put it the other way around, the idea that taking a pill will result in no change at all seems to be nearly impossible.

If we try to interpret this finding from a semiotic point of view, we can see that certain types of expectations, once they are out in the world, cannot be just switched off like in a causal model. This is, in fact, a situation that is seen very often. There are some ideas about certain mechanisms in circulation but one tends not to believe them, for example, amulets protecting from evil. Nevertheless, it proves difficult to eliminate these ideas completely once they are known to be there or shared by others. This is often reflected in statements of the type "Actually I don't believe in x but why not give it a try?" Obviously, meaning making processes do not follow linear models but integrate many different perspectives and they can also take up ambiguities and contradictions and still come up with a coherent view. Here we are only beginning to understand how humans, based on their prior experience and their world models, create meaning and how this meaning making then interacts with physiological indicators. Based on other research (Jensen et al. 2012), we also can assume that this is not an entirely conscious activity but will also tightly interact with many non-conscious processes.

At any rate, this perspective and the empirical data to support it have shown that a semiotic model is more useful for understanding therapeutic effects in humans

than a causal-mechanistic model. Thus, the placebo effect teaches us, and medicine at large, that humans are not machines, that therapy is not a reparation process, and that it is clever to understand and appeal to meaning-making processes also in the treatment, if not in the understanding of disease.

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