Reconstructing the Meaning Effect

- The Capacity to Self-Heal Emerges From the Placebo Concept

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Introduction

Arguably the most important conceptual development in the area of placebo research in recent times was the redefinition of the placebo effect as an "effect due to the meaning of an intervention" (Moerman & Jonas, 2002). The placebo effect was reframed from a nuisance to a potential resource. When Martini in Germany (Martini, 1932) and Beecher in the US (Beecher, 1955; Lasagna, Mosteller, von Felsinger, & Beecher, 1954) started discussing the placebo-effect in the 30ies and 50ies it was a conundrum. Clinical pharmacology set out with the promise to find ever more specific treatments for diseases. This project assumes that through scientific knowledge we will unravel the causal network of diseases that can then be specifically targeted through clearly designed drugs with specific, known and targeted causal pathways of efficacy. This is theory. Or shall we say poetry and fantasy? Following this theory, everything that is not causal can only be background noise

and a nuisance (Grünbaum, 1989). And hence the placebo-effect, as it showed in clinical trials that were necessary to prove the specific efficacy of these interventions, was considered a nuisance and, technically speaking, error variance to be minimised. Research and clinical experience showed how powerful such effects can be in practice. The redefinition by Moerman and Jonas captured this cultural move: the placebo-effect grew from a nuisance to be avoided to a resource that can be very helpful (Walach & Jonas, 2004).

In this contribution I would like to take this development one step further and argue that this effect is actually the most important therapeutic effect of all. All so called specific effects, causal interventions etc. are only maneouvres that help marshal this most powerful therapeutic ally: the self-healing response. And so my thesis is that behind the placebo-effect we see self-healing at work. I am advocating a kind of figure-ground perceptual change: What has been considered the background, even background noise, namely the placebo-effect, I would hold to be the most important element. It should move to the foreground and become what it actually is: the most important component of every therapeutic system (Wampold, Minami, Tierney, Baskin, & Bhati, 2005). That does not negate that there are specific effects, like in life-saving surgeries in cases of emergencies or when resecting tumours. But they are the background that only allow the figure to emerge: the individual self-healing trajectory.

The Conceptual Problems of the Specificity-Non-Specificity Distinction

The standard paradigm of clinical pharmacology and modern medicine assumes that the way to cure is to understand the pathological cause of illness and then to intervene at the causal point of pathogenesis. This reasoning follows from the assumptions of cellular pathology introduced by Virchow in the 1850ies and followed through until today (Uexküll, 1982; Uexküll & Wesiack, 1988). The paradigmatic idea behind this notion is that the body is a causal (classical) biological machine with understandable causal relations. It turned out that this was an extremely useful abstraction from the complexities of human life when we are dealing with emergency situations and acute problems, as was the case for most of the 19th century and roughly until the 1950ies. Until then the major problems were to understand and contain the large epidemics - cholera, typhus, tuberculo-

sis, polio, smallpox, etc. - and to provide emergency relief for the casualties of the large wars from 1914 to 1919 and from 1939 to 1945. And for all those problems it is very useful to abstract from complexities and view the human body as a causal biological machine, find the point of maximal causal disruption and treat it. The discovery of potent anesthesic substances supported this reasoning in a powerful way (Alkire, Hudetz, & Tononi, 2008; Woolf & Butcher, 2011). The large scale synthesis of morphine in 1827 by Merck and other opiates in its wake, as well as cocaine (Stachowske, 2002), seemed to pave the way for very powerful and reliable alteration of human conscious experience of pain and psychological well-being. So why not also for the treatment of diseases and cures for headaches, stomach pain, and the like?

Enter a new rogue and a new jester. The rogue: multicausal, complex, life-style dependent diseases and functional, psychosomatic problems taking centre stage from the middle of the 20th century onwards. The jester: systems biology and non-linear systems theory.

The new challenges of our times are increasingly complex and difficult to understand using theoretical models that have been developed to deal with acute problems. The huge problems of the future are diseases like

- depression, forecasted by the WHO to be the number 2 reason of life-long disability worldwide as of 2020, as well as anxiety and other psychological disorders

- metabolic syndrome, the ground state of more than half the population of the US and a growing proportion of the populations of Western societies and affluent strata of societies in Asian countries, and the precursor to serious diseases like coronary artery disease, artherosclerosis, myocardial infarction, diabetes type 2, and a risk factor for stroke, cancer and myocardial infarction

- heart and vascular diseases

- cancer

- dementia

- chronic pain syndromes.

Most of these diseases cannot be cured using the paradigmatic model of emergency medicine. We can contain some of them, prevent acute exacerbations, and cure some in early stages, such as cancers or coronary artery disease. But in order to really cure them, these diseases demand a broad, multicausal approach. And

cause number three of all premature deaths in the Western world even is a direct consequence of the very therapeutic model adopted to cure such diseases: side-effects of medications (Gøtzsche, 2013).

Systems biology has developed in niche areas of basic research. Neuroscientists and biologists, as well as immunologists have shown that the human organism can be modelled more adequately if we understand it not like a classical linear causal system, but as a self-organising, complex, non-linear system that regenerates its own integrity and keeps its boundaries against the environment stable at a state far from thermodynamic equilibrium (Barabasi, Gulbahce, & Loscalzo, 2011; Hyland, 2011; Pincus, 2012; Pincus & Metten, 2010; Pincus & Walach, 2012). This technical lingo expresses three simple facts:

- Our organism is an active system that is creative and generative, generating health as a result.

- It produces its conditions of flourishing and living autonomously, independent of and despite, sometimes even because of, disturbances coming from the environment.

- Whenever you disturb the system, it will self-actively react and create a response, either reconstituting its integrity or recalibrating.

A corollary to this is the observation that multiple causes can lead to very similar outcomes, such as diseases, and multiple stimuli can lead to similar endpoints, like cure. To use an example:

We can become depressed because our food does not contain enough omega-3-fatty acids and hence our fat-metabolism, including our immunological status, is in a dysbalance. Insufficient amounts of phospholipids are generated, and thus precursors to neurologically important substance are lacking. In addition, our immunological state may shift to increased activity of the pro-inflammatory axis, promoting cytokines like Il1 and Il6 that lead to behavioural withdrawal (Horrobin, 2001). We might also become depressed because of a severe personal life-event, or because we have an epigenetically inherited disposition from past traumata that becomes relevant, when a crisis hits us. Some people become depressed because they lack a purpose in life, and some because their social networks break apart. So many causes can lead to just one, phenomenologically similar, outcome. In the same vein, some therapists might choose to treat a depressed patient by pharmacological substances, some use nutritional interventions and exercise, or

social activation, or meditation, or psychotherapy, and all have a – probably very similar – chance of treating depression (Barth et al., 2013).

Both, the challenge of multicausal, functional and psychosomatic, chronic diseases, and the understanding that the organism is a highly complex, self-regulating, autonomic system pose severe conceptual challenges to the received paradigm of linear causation and specific causal cure.

The Fallacy of Separability and Isolation of Causes

Both the pathological model and the curative model of standard pharmacology assume that we can make out the major cause of a disease, and isolate it from other, less important, causes, in order to target it. In addition, it assumes that we can separate out and quantify the specific effects of an intervention against its non-specific background. Both assumptions are wrong, I contend. At the very best they are abstractions and conceptual crutches, but they are very far from producing a realistic picture. Let's again use depression as an example. The standard model of biological psychiatry assumes depression is a biological disease that arises because important transmitters are not available readily enough, usually serotonin, but often also noradrenaline, or a dysbalance between systems is discussed (Fava, 2006). By isolating a "rogue" system it can be pharmacologically targeted, usually by substances that alter the chemical balance and make serotonin available through blocking re-uptake into synapses. Following this reasoning, the new generation of drugs that do exactly this should have been hugely effective, and so they were, initially at least. A powerful myth was created around those "happy pills" that lead to a brutto-effect of antidepressant treatment of 2.5 standard deviations, if we compare pre-treatment scores with post-treatment scores (Rief et al., 2009). The only problem is that this effect is mimicked by placebo. Or shall we say: The major part of this huge effect is driven by placebo? For the specific effect, or net-effect of those drugs against placebo is only about d = 0.32 or a third of a standard deviation difference (Kirsch et al., 2008; Kirsch, Moore, Scoboria, & Nicholls, 2002; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Thus, a small specific effect drives a huge therapeutic effect, the largest part of which is due to non-specific effects of expectation, hope, relief of being in treatment, etc. Would it make sense to therefore prohibit the dispensing of serotonin-reuptake-inhibitor drugs for the treatment of depression? But this were to negate that patients have huge benefits from taking these drugs. It does not make sense to separate out the specific effect from the total effect that also includes the placebo effect. This is,

because these effects are not separable and additive, but, technically speaking, multiplicative and synergistic (Walach, 2011, 2013).

What does that mean?

In a linear system you could separate out the specific effect, say of the pharmacological part of the happy pill, from its psychological or non-specific part, i.e. the placebo-component. This is how our standard way of reasoning operates. We assume that the placebo-effect, i.e. the background noise, across studies, is constant and behaves similar to error variance, i.e. is negligible. But this is wrong in several ways:

1. Placebo-effects are not constant across studies

2. Treatment- and placebo effects are highly correlated

3. Strong non-specific treatment components drive the full therapeutic effect and can enhance it despite a small specific effect, and strong specific components can also enhance or diminish non-specific components, depending on parameters such as context and expectation.
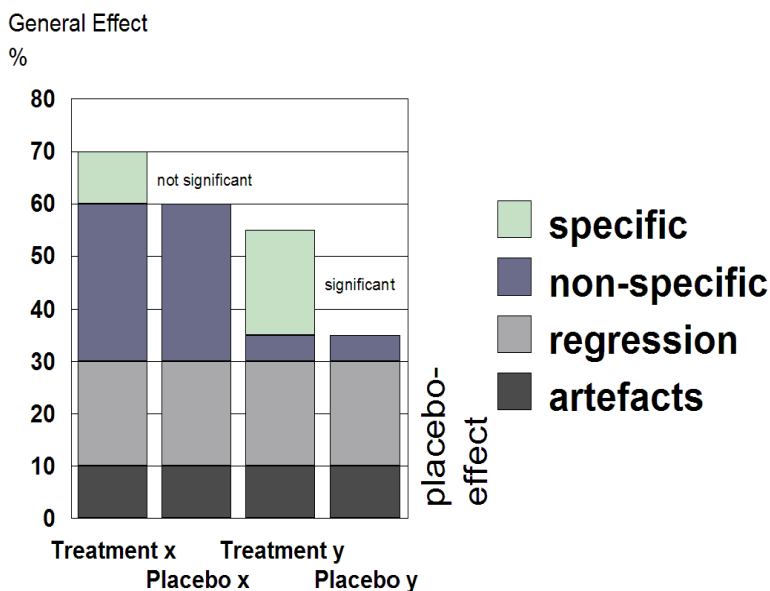

Figure 1 – Illustration of the Efficacy Paradox: treatment x is not statistically superior to placebo x and hence is called inefficacious, while treatment y is statistically superior to placebo y and hence is called efficacious, yet placebo x is, overall, more effective than efficacious treatment y

Consider the illustration in Figure 1 (Walach, 2001; Walach, Falkenberg, Fonnebo, Lewith, & Jonas, 2006). We assume we have two placebo controlled treatment studies in the same condition with similar patient populations. The first study, treatment x against placebo x, we assume, is not significant, because the specific component is very small and cannot be shown to be statistically different against its placebo control. The placebo controlled arm contains various components, some of which we assume to be constant: statistical regression to the mean and natural regression of the disease (both captured in the part of the column labelled "regression"), as well as measurement artefacts because of unreliability in our measurements (labelled "artefacts"), and another component we assume to be variable. It is called "non-specific" here and captures all those effects that are variable and dependent on the context, such as psychological effects of hope and expectation and the like.

The second study of treatment y against placebo y, we assume for argument's sake, is statistically significant against its placebo, because the specific effect is stronger. We call study x and treatment x not efficacious, while we call treatment y efficacious. We see immediately that something is wrong here. For the overall effect of treatment x is much larger than that of treatment y, even so that placebo x produces a larger effect than treatment y. This is what I call the efficacy paradox. It illustrates a situation where a placebo-treatment can be more effective than a proven, efficacious specific treatment, precisely because the non-specific component is not constant across treatments (see point 1 above), and because some treatments maximise non-specific effects and can therefore, despite producing only a small specific effect, be overall much more effective (see point 3 above).

Let us make this more concrete: The efficacy paradox is a thought experiment. But there has been one empirical situation that comes close to it. This is provided by the German acupuncture trials (GERAC trials) (Diener et al., 2006; Haake et al., 2007; Scharf et al., 2006). These studies are the largest studies of acupuncture to date in general practice. Each of the three studies comprised around 1200 patients, randomly allocated to three groups. One group received true acupuncture, one group received sham acupuncture, i.e. shallow needling in the back into points that were considered non-therapeutic with no manual stimulation. And one group received best-practice conventional medicine, following guidelines. All of the latter was evidence-based i.e. proven efficacious in previous studies. Two of these GERAC studies, the ones in chronic low back pain and in osteoarthritis pain (Haake et al., 2007; Scharf et al., 2006), demonstrated nearly twice as large an improvement of both acupuncture and sham acupuncture against proven, evidence-based

conventional treatment, and in the third study on migraine prevention all three groups were similar (Diener et al., 2006). Acupuncture and sham-acupuncture were not different in any of the studies, like treatment x in Figure 1. But in two of the three studies sham-acupuncture was twice as effective as proven conventional treatment, comparable to the difference between placebo x and treatment y in Figure 1, only much larger.

Why is this so? There have been many explanations for this strange result. One can be found in the patient information that generated expectation and constituted the context. The patients all came from insurance companies that advertised acupuncture as part of their portfolio within this study. So patients agreed to enrol with the hope to receive acupuncture. Both types of acupuncture were framed as "two different types of acupuncture with unknown efficacy" Thus, patients were led to expect two different types of true acupuncture, not one true and one sham acupuncture. Since most patients had already experienced conventional treatment that did not help their problems, being randomised into the conventional care arm might have produced only low expectations of improvements. Thus, the studies probably reflect internal processes of patients: expectancy and hope in the case of the two acupuncture arms, true and sham, and disappointment or disillusionment in the case of the conventional arm.

Thus, the efficacy paradox has to some extent been empirically validated. It illustrates that placebo- and verum components of treatments or specific and non-specific effects are not additive, but multiplicative and synergistic. This means that a small specific effect can multiply a large non-specific effect. Take 2 and add it to 10 and you receive 12. Take 2 and multiply it by 10 and you receive 20. A good example of a synergistic system is a skilled child rider: The child can make the horse do things that the horse by itself would not do, and the child by him- or herself could not do either. But both together can jump high hurdles or broad ditches and run quite fast. In the same way, small specific effects can maximise non-specific effects, through the myth that is created and surrounds the treatment, through the expectation or other parts of the therapeutic ritual.

The Meaning Response Illustrates the Complexity of the Human Organism – Some Examples

I would like to illustrate this with a couple of pertinent and classical examples.

The Importance of Context Effects

The difference in the power of non-specific effects arises from contextual effects. It is an implicit assumption of the crypto-positivist view of pharmacology and most of medicine[1] that the context of research and discovery is irrelevant. Once we know the true effect size of an intervention, to be discovered by experiment, we can apply it and it will, by and large, remain the same. This assumption of additivity has rarely been tested, and where tested, has been found to be wrong. Here are four typical examples.

One is a classical study by Thomas (1987): Being positive. Thomas randomised 200 patients that walked into a GP clinic with non-specific, functional symptoms into two groups, each of which he either treated randomly with placebo or did not treat. Half of the patients received a "negative" communication. They were told that it was "unclear what was the matter" with them, and that "further testing" was necessary to determine the condition, before better or true treatment could be initiated. This, clearly, set up anxious apprehensions. The other half of the patients received a "positive" communication. They were told that their condition was likely harmless and self-limiting, that, to make sure, some more tests will be done, but everything will surely be gone come next week. Both groups then either received a placebo or not and were seen again in a week. Their symptoms and their sense of being understood was measured. Not surprisingly, the patients who had received a negative communication felt less understood and had more symptoms, while those who had received a positive communication felt much better understood and had nearly half the symptom severity compared with the other group. Interestingly, it did not make a difference, whether patients received something, a placebo, or not. Thus the activity of the intervention was modulated by the context of the communication quite impressively.

When there still was a time when informed consent was not always necessary, Bergmann and colleagues conducted a four armed trial in cancer patients in a hospital, who normally received naproxen as their bedside pain medication (Bergmann et al., 1994). Within that trial they randomised patients into two larger groups. One group was told that they would be part of a placebo-controlled trial of pain medication and would either receive medication or placebo. Another group of the same patient population did not receive that information but received naproxen as bedside medication, or placebo, also in a blinded, randomised manner. Patients in the placebo-arm of the declared study improved more in their pain than patients in the napoxen arm of the study who were unaware that they

are part of a trial. The two naproxen arms were significantly different, with those patients knowing that they received naproxen improving nearly twice as much as those receiving naproxen as part of the normal bedside ritual. Again, this study shows that the context – study or normal routine – can modulate the pharmacological effect dramatically.

A third example is a four armed trial by Colloca and Benedetti, in which no placebo was involved, only active pharmacological agents (Colloca & Benedetti, 2005). Instead, knowledge about the application was manipulated. Patients who had received thyroidectomy surgery and were recovering received pain medication. The medication was either an opiate, buprenorphin, or an NSAID, metamizol, better known as novalgin. All patients received medication. But in each group half was told about the moment, when it was injected into the i.v. port, and half the group knew that they would receive the drug, but it would be administered by a computer according to a random allocation mechanisms within a certain time window. This allowed the researchers to study the effect of knowledge without withholding any medication. While in the opiate group both groups received adequate pain relief, the group that did not know about the moment of application reported pain relief only 2 hours after application, while the group that knew about the application experienced pain relief immediately after the injection. The relief itself was comparable. In the group that received metamizol there was a pain relieving effect only in the group that knew when the application was delivered, but not in the group that knew that they would receive a drug, but not when.

The context is often not constructed by the therapist or the study alone, but also by the patient. This is commonly termed faith or belief. This can be nicely seen in our study on distant healing (Walach et al., 2008). We enrolled 409 patients with severe chronic fatigue syndrome into a study of distant healing. They either received distant healing immediately by three healers unknown to them and without any contact, or they had to wait for their treatment for six months. Again, half of the patients were informed about the group allocation, such that we had patients who were treated and knew about it, patients who waited and knew about it, and patients who were either treated or had to wait and did not know it. The overall result of the study did not provide any evidence that distant healing had an effect, except that all those groups that were either treated or did not know about their allocation had about one third of a standard deviation improvement over the control group that knew they had to wait for treatment. But the more interesting finding was the discovery that about 8%, 35 patients in all, had strong improvements. Analysing all those patients' improvement that also provided data after a one year

follow-up revealed that the decisive variable was not whether they were treated but whether they believed they were treated and received healing, whether true or wrong was irrelevant. Effect sizes were large and approached a standard deviation (d = 0.95). A qualitative post-hoc study using interviews revealed that most of these patients had made a leap of faith and at some point started to believe that something would happen (Güthlin, Anton, Kruse, & Walach, 2012). Thus, important parameters might reside in the patient's consciousness. It is the meaning that triggers the meaning response.

The Meaning Response: The Evasiveness of Meaning

Meaning is a semiotic category. Following Peirce, one of the grand theoreticians of semiotics, meaning is produced by signs in the mind of a recipient or interpreter of these signs (Peirce, 1931). While we normally apply this only to human beings and their capacity to understand cultural signs, such as language, one can actually make a point that this is an ubiquitous paradigm (Sheriff, 1994). Thus in principle anything can become a sign and create meaning (Uexküll, 1982, 1995). Even the antigen can become a sign for the immune system and the immune response is an answer to the meaning this sign creates (Blalock, 1994; Jerne, 1985). In a more mundane way, a medical intervention is a sign for an organism that can understand signs with a certain meaning – not a causal stimulus that elicits a uniform answer from a biological machine. Let us use an examples to illustrate this. It is reported by Bernard Lown, a famous cardiologist, inventor of the pacemaker (Lown, 2002). He reports that he once saw a patient on the ward who was close to dying, his heart being locked in a steady, quick beat that cardiologists call "galloping rhythm". He demonstrated this patient to his students on the ward round, and in order not to frighten the patient he said nothing about the patient's dire prognosis but used the chiffre of the "galloping rhythm". This, for medical specialists, had the meaning of "badly damaged, close to death". But for the patient it had the meaning of "super strong, still being able to gallop". So when Lown came the other day he found the bed empty. Assuming the patient had died he made inquiries only to find that the patient had dismissed himself from hospital. He met the patient later and he told the doctor that with a heart that was so strong as to still gallop he thought he might have quite some time to live and indeed did live for a couple of more years.

Here we see how a certain meaning, generated by communication, can produce quite different or unexpected outcomes. And we might want to add some reflec-

tions on how normal communicative skills of doctors do not optimally make use of this meaning making capacity (Colloca & Finniss, 2012; Lang et al., 2005).[2]

A good therapist will reconstruct the inner world of meaning a patient experiences with his or her disease and will offer interventions that fit. Hence, part of this semiotic approach to therapy that includes the individual meaning of a situation for a patient and of a therapy is to create a fit between therapeutic offer and the patient's universe of meaning. This is likely different from patient to patient, and this is the reason, why non-specific effects cannot be handled and distributed like pills (Schonauer, 1994). They demand communicative skills and explorations and they challenge the therapist to become a communicative partner of the patient, to enter his or her world in order to find maximally fitting interventions or narratives for the interventions on offer.

This highly individualised universe of meaning is probably the reason why the mainstream community is still a bit puzzled about placebo and placebo effects. There is no clear cut quantifiable recipe for action except the generic and tricky one: try to understand the universe of meaning your patient lives in including the disease, and find an intervention that can take advantage of this universe of meaning, brings a fit and activates the patient's positive expectations.

Placebo and Treatment Effects are Correlated

The neglect placebo effects have suffered from the mainstream community for a long time is due to a theoretical assumption in addition to the other conceptual reasons we have already discussed. This theoretical assumption assumes that placebo effects are constant and uncorrelated with treatments across studies. In statistical terms: Placebo effects are conceptualised as error variance. Error variance is always random, uncorrelated and roughly constant across individual instances. Put differently: the causal model of clinical pharmacology assumes that the "true" or "real" effect is causal, while placebo-effects are simple remnants of an unknown source and strictly speaking should be completely uncorrelated with treatment, if the treatment is fully effective and placebo-effects in trials are simple error variance. It turns out that this assumption is not only wrong, it is capitally mistaken.

We conducted two meta-analyses which, originally, were set-up to test whether the placebo-effect would decrease with time, i.e. would be smaller in studies with longer duration. Thus, we collected long-term trials and correlated treatment and placebo-responses with the duration of the trial. While the first study was un-

systematic (Walach & Maidhof, 1999), based on an ad-hoc sample, in the second study we used clear inclusion and exclusion criteria and operated according to a pre-defined protocol (Walach, Sadaghiani, Dehm, & Bierman, 2005). We hand-screened one year of four major medical journals (New England Journal, JAMA, Lancet, BMJ), searched databases and other secondary sources to find as many trials of pharmacological interventions against placebo that had a study duration of 12 weeks or longer. We included 141 publications with 144 studies. Our initial hypothesis that studies with longer duration would exhibit smaller placebo-effects did not bear out, on the contrary. Duration of the trial correlated significantly positively with the therapeutic effect in the placebo-arm (r = .41), even more than with the verum treatment (r = .29). This means: Longer trials reveal larger treatment effects, but in longer trials the placebo effect is disproportionately larger than the treatment effect. While our original hypothesis did not bear out, we discovered something much more interesting (in our view at least): The improvement with placebo was strongly correlated with the improvement under treatment with r = .78. Evans had previously reported a correlation of r = 0.55 in pain studies (Evans, 1974). This correlation changed only slightly, when we tried to clarify it using a regression approach. Prevention trials produced stronger placebo-effects, and anti-dementia or anti-tumour therapies produced smaller effects. Methodological quality clarified only some of the variance, and more than half the variance remained unaccounted for by predictors like methodological quality, type of study and disease.

This result is puzzling and not easy to understand. If all treatments were ineffective then the correlation between treatment and placebo healing rates would be perfect. The fact that it is not perfect, but "only" r = .78 shows that there is some – small – specific element in all the treatments covered. But it also shows that most of the variance between groups is in common and the more effective a treatment is, the more effective is also the respective placebo. Or should we turn it the other way round: The more effective a placebo is, the better the effectiveness of the treatment? It is difficult to tell on the basis of correlational data which is the driver and which is the consequence. But it is clear that the assumption is plain wrong that placebo effects in studies are just error variance, uncorrelated and negligible.

There are at least two ways to explain the correlation: The correlation occurs due to the fact that there is a strong tendency of diseases to just run their course uninfluenced of any therapeutic strategies, treatment or placebo alike. Treatment only alters this natural trajectory slightly; hence the small difference and the high correlation. This "natural history of diseases" hypothesis is intriguing and would

in fact smother our therapeutic enthusiasm of "ever better, newer and more powerful" treatments and that of powerful therapeutic non-specific rituals alike. In this scenario, treatments are only small players on the stage of diseases in life. The other interpretation would assume that placebo-effects are quite powerful, in fact so powerful that it is very difficult to show an additional benefit of treatment on top of it. This would then mean clinical trials are actually powerful therapeutic rituals.

Thus, placebo-effects in trials are not just noise and negligible waste products. If we think treating is helpful then we are committed to assuming placebo – and whatever this stands for – is also helpful, not quite to the same degree perhaps but nearly so.

Placebo Is Indeed Therapeutic in Trials

There has always been a minority debate around the question whether placebos are truly effective or whether placebo effects in clinical trials are only artifacts that arise from flawed reporting, uncritical belief in badly documented anecdotes, measurement artifacts, regression of the disease and the like. The first analysis developed its arguments along the lines of Beecher's influential paper (Beecher, 1955; Kienle & Kiene, 1997). While it succeeded in showing that Beecher made a stronger point than supported by the data he had, it failed to convince, because there have been other data since Beecher, and a large number of experimental studies (Hull & Bond, 1986), that produced strong evidence for the power of contextual and information effects.

Placebo effects are more than artifacts. This conclusion seems to be inevitable, if we consider the full range of evidence, part of which is also the neurobiological evidence that has arisen since the beginning of the new millennium. I will return to that shortly. Another important piece of evidence is the distinction between experimental trials that study placebo-effects directly and try to maximise it, and clinical trials that use placebo just for control purposes and try to minimise it (Vase, Riley, & Price, 2002). Using trials that compared placebo interventions to no-treatment controls in clinical pain trials versus experimental pain trials, Lene Vase could show that in clinical trials such placebo-effects compared to no-treatment are comparatively small (d = 0.15). But they are very large, sizeable, and thus clinically important in experimental pain studies (d = 0.95). This finding is in good accord with a widely quoted analysis that found little evidence for a strong

placebo effect in three-armed clinical trials that also included a no-treatment control group (Hróbjartsson & Gøtzsche, 2001). Only trials with subjective outcomes, mainly pain, showed a small, significant effect size of d = 0.28, i.e. less than a third of a standard deviation. But trials with dichotomous outcomes did not show significant placebo effects.

A re-analysis of practically the same data-base of three-armed clinical trials changed the perspective dramatically (Howick et al., 2013). These authors conceptualised treatment effects as differences *within* studies and made those differences the unit of analysis. That is, in each trial, they calculated the difference between placebo and no treatment as the placebo-effect and the difference between treatment and the placebo-arm as the treatment effect and estimated the difference of these differences as a true treatment effect. That is, they tried to determine the component of specificity in each trial and averaged those across trials. The first important finding from this analysis is: Placebo-effects are clearly different from no treatment. They are small: across all trials they are d = 0.25, and d = 28 for subjective outcomes while they comprise d = 0.18 for objective outcomes. They are all significantly different from zero. Treatment effects, across all trials, are larger and also significant (d = 0.36 for all trials and outcomes, d = 0.48 for objective and d = 0.30 for subjective outcomes). Interestingly, treatment effects are not significantly different from placebo-effects across trials. Only for objective outcomes and for very few conditions were treatment effects significantly different from placebo effects. This finding supports our own results: treatment effects and placebo effects are highly correlated. What the analysis of three-armed trials adds is that placebo-effects are indeed different from no-treatment controls.

Two recent studies using open label placebo illustrate the therapeutic power of placebo. These studies are important for two reasons: They were conducted against no-treatment controls, and they used placebo openly, i.e. employed the semantic and potentially associated automatic and unconscious processes of learning proactively. The two studies had a commonality: they advertised open placebo-treatment with full disclosure right from the start of the trial. Patients were briefed extensively about the fact that they were being enrolled in a trial where only placebo (trial 1) would be dispensed (Kaptchuk et al., 2010), or where (trial 2) they would receive various substances, among them potentially placebo and were told so (Kam-Hansen et al., 2014). This was a conceptual replication of an amazing finding by Park & Covi in 1965, where the authors reported good success with placebo, openly given to anxiety patients. In the first of the recent open placebo studies 80 patients with irritable bowel syndrome were enrolled that either received

open placebo or were in the no-treatment control group (Kaptchuk et al., 2010). The effect size after three weeks of open placebo treatment against no treatment was more than a standard deviation (d = 1.14), and the difference significant. In the more recent trial 76 migraine patients were enrolled in a intraindividually controlled experiment and documented 7 migraine attacks, one without treatment, and six with treatment (Kam-Hansen et al., 2014). In half of the situations they received a powerful anti-migraine drug, a triptan[3], for the other situations they received placebo. Sequencing was randomised and counterbalanced such that each person served as his or her own control. The delivery of both placebo and the triptan was accompanied by different information. Either the information was true - "you will now receive a medication" or "you will now receive a placebo", or false (placebo dispensed as true medication, true medication dispensed as placebo), or information was withheld, similar to the blinding in a blinded trial. This study is extremely interesting in two ways: First, it reproduced the finding of the previous study that placebo can be clinically active, even if given openly. There was a clear and significant effect for open placebo. Second: the difference between the true drug, dispensed as placebo, and the placebo, dispensed and labelled as triptan, was small and statistically not different. While there was a statistical and clinical difference between triptan and placebo overall, due to the difference in the blinded conditions, this difference was gone when the substances were labelled differently and thus, we can assume, perceived as something different.

This finding was recently dramatically supported by a different study that used brain imaging to trace the effects of a powerful opioid-agonist, remefentanil, and positive or negative expectancy in an experimental pain model (Bingel et al., 2011). Here volunteers underwent various procedures after experimental pain induction through heat. They received the opiate with a neutral expectancy induction, with the expectancy that the intervention would be positive and with the expectancy that it would actually enhance pain. The dramatic finding was that psychological expectancy could override the pharmacological effects of the opiate and that this was actually verified not only through subjective reports, but through brain imaging.

Thus, even if given openly, placebo has therapeutic effects. And if given with a different label that is perceived as signifying powerful action it can produce effects as strong as a true medication depleted of its mythological status by a wrong label.

Placebo Is Not Just Imagination And Indeed "All in Your Head"

Older arguments often repeat an adage that placebo effects are just imaginary, i.e. not "real" but only "in your head", or, even worse, faked and the result of wishful thinking. This argument has been definitely proved wrong by neuro-imaging studies. They show: placebo-effects are accompanied by appropriate and theoretically meaningful changes in brain metabolism (Amanzio, Benedetti, Porro, Salermo, & Cauda, 2012).

Earlier studies by Levine and colleagues in the 70ies have used pain paradigms, placebo interventions and naloxone, an opiate antagonist, to show that placebo induced analgesia that was replicable across studies could be reliably blocked if, unknown to participants, naloxone was given (Gracely, Dubner, Wolskee, & Deeter, 1983; Levine & Gordon, 1984; Levine, Gordon, Bornstein, & Fields, 1979; Levine, Gordon, & Fields, 1978, 1979; Levine, Gordon, Jones, & Fields, 1978; Levine, Gordon, Smith, & Fields, 1981). It is known that naloxone blocks mu-opiate receptors in the brain. Since naloxone by itself does not increase pain, but is able to reverse placebo-induced analgesia, this is a sure sign that endogeneous opioids were likely responsible for the analgesic effects of placebos. This meant that pain was in fact decreasing through placebo-interventions, because a participant's brain would produce endogenous opioids, most likely beta-endorphin. A systematic review of these studies reached in fact this conclusion (ter Riet, de Craen, de Boer, & Kessels, 1998). Thus, it was not a long shot, when imaging methods became available to verify this using imaging techniques.

One of the pioneer studies used positron emission tomography (PET) to monitor regional cerebral blood flow as an indicator of metabolic demand and thus neuronal activity (Petrovic, Kalso, Petersson, & Ingvar, 2002). It could show that an opiate given in an experimental pain paradigm influences a large opioid network that is active in pain processing and pain control, comprising areas of the orbito-frontal cortex, the insular cortex, the cingular cortex and deeper brain stem areas in the periaqueductal grey, where afferent pain signals are processed and opioidergic neurons originate. This study could also show that the same network was activated by placebo interventions, in good placebo-responders more so than in non-responders. Especially areas in the rostral anterior cingulate cortex and again in the periaqueductal grey of placebo-responders are active, the very same centres that show the highest activity in opiate induced analgesia. These findings were extended and corroborated by more recent data that prove that the descen-

ding pain control system that operates via endogenous opioids down to the spinal cord is responsible for and active in placebo analgesia (Eippert et al., 2009; Eippert, Finsterbusch, Bingel, & Büchel, 2009).

The first imaging study was actually published one year previously. It used PET in Parkinson patients (de la Fuente-Fernández et al., 2001). In this case PET was actually used not to measure blood flow, but with a radioactive ligand for dopamine receptors, raclopride. Since in Parkinson's disease the dopaminergic neurons in the basal ganglia become less effective, the disease is treated in early stages with a dopamine-agonist, apomorphin, that enhances dopamine availability. The researchers expected that when patients would expect medication they would also generate an expectancy induced rise in dopaminergic activity. Following this reasoning the PET-scans should show reduced activity, because raclopride is dislocated from its bindings through endogenous dopamine, reducing the PET signal following a placebo administration that is expected to be actually apomorphin by the patients. And indeed the researchers could show a highly significant reduction of the signal in the basal ganglia proving that even in Parkinson's patients expectancy can activate the endogenous dopamine production.

Meanwhile a wide array of findings have documented that practically all important transmitter systems – the endorphin system (Amanzio, Pollo, Maggi, & Benedetti, 2001; Colloca & Benedetti, 2005; Eippert et al., 2009; Johansen, Brox, & Flaten, 2003; Lichtigfeld & Gillman, 2002; Pollo, Carlino, & Benedetti, 2011; Sauro & Greenberg, 2005; Scott et al., 2008; Zubieta et al., 2005), the dopaminergic system (de la Fuente-Fernández, Schulzer, & Stoessl, 2002; Fricchione & Stefano, 2005; Hall et al., 2012; Pollo et al., 2002; Volkow et al., 2006), most likely also the opiate system (Scott et al., 2007, 2008; Zubieta et al., 2005), the serotoninergic system (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008; Mayberg et al., 2002), and the endocannabinoid system (Benedetti, Amanzio, Rosato, & Blanchard, 2011) – can be affected and show changes depending on the model used. These studies also show that not only conscious expectation and labelling processes influence the experience of symptoms, but also unconscious processes that are most likely the result of conditioning.

This was experimentally shown in a study that employed a conditioning paradigm (Jensen et al., 2012). Volunteers were shown two different faces, one of which was consistently paired with a rapid application of a strong pain stimulus, a heat shock, while the other one was paired with a minimal pain stimulus. After this conditioning, two experimental runs were conducted. In the first, the same faces used for conditioning were presented for a period long enough to be consciously

recognised, paired with a moderate pain stimulus, together with a neutral face. Participants were asked to rate their pain experience. Those who had previously experienced a stronger pain stimulus paired with the face rated the moderate stimulus much more painful and those who had previously experienced a minimal pain stimulus paired with the face rated the second, moderate stimulus, less painful. The interesting bit happened in experiment two, where the same faces were presented subliminally, i.e. only for 12 milliseconds such that they could not be perceived consciously. While the effects were a bit smaller, they were in essence similar to the ones with consciously perceived faces. This shows clearly that unconscious processing can be very powerful, and likely also affects the way humans react to medical and ritual interventions.

Mechanisms and Triggers of the Self-Healing Response

This leads us to one of the questions that are most important for practitioners: How does it work and how can we optimise and utilise these effects? We saw that important brain systems are implicated in generating effects of meaning. One important variable has not been studied well enough, it seems, namely the therapeutic relationship. One experimental trial tested this directly (Kaptchuk et al., 2008). Ted Kaptchuk randomised 262 patients with irritable bowel syndrome into three groups. One had to wait, one received placebo-acupuncture but only minimal contact, and one group received the same sham-acupuncture but with extensive contact. Those patients with augmented contact had the largest improvement after three and six weeks, one standard deviation difference against wait-list, while the group with sham intervention but less contact also improved substantially, but less than the augmented contact group.

This study demonstrates two things: Expectancy alone is a powerful driver of such self-healing responses. Patients in this trial did not know, after all, that they would receive a sham treatment. They were expecting real treatment by acupuncture. But it also shows that human contact is an important element of this effect as well. We know from other studies how important human trust is. It is associated with the release of oxytocin (Brüne, 2012; Grewen, Davenport, & Light, 2010; Kanat, Heinrichs, & Domes, 2014; Klimecki, Leiberg, Lamm, & Singer, 2013). Peripherally, oxytocin is known as a hormone that triggers birth and lactation in

pregnant women. But centrally it is a very important neuropetide that is relevant for human bonding, and bonding in other mammal species as well (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Donaldson & Young, 2008; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and, importantly in our context, it is a direct antagonist to central stress-associated agents like cortisol and norepinephrine (Porges, 2001). Thus, oxytocin can be considered the neuropeptide centrally associated with parasympathetic activation.

This leads to the question how this can all be connected. A powerful model has already been presented by Jerome D. Frank in his generic model of healing which I have exytended somewhat in Figure 2 (Frank, 1961).
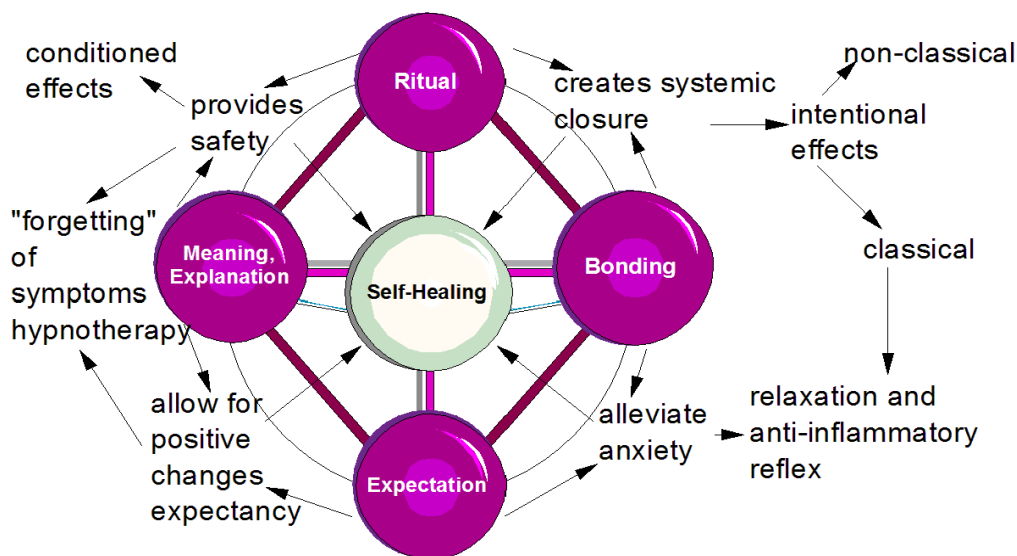

Figure 2 – Revised Generic Model of Self-Healing Following Frank

Jerome D. Frank has originally stipulated that all therapeutic systems can be characterised by four components: They provide an explanatory model, a world model or a cosmology of health and disease. In our modern medical model this is the narrative of causal pathology and treatment. Therapeutic systems equip their healers with insignia of power. The shaman has his drums, masks, feathers, and amulets. Our modern shamans wear white coats and stethoscopes, and display

multiple diplomas and prize certificates in their offices. Each system has its rituals that are sometimes painful, or cumbersome, or both, to suggest potential effectiveness. The shaman goes into an extensive trance, dances and plays the drum, has the participants of the ritual ingest potions or undergo other rituals. The medical shaman has his minimalist ritual of taking his pen and giving out a prescription, or, if serious, can marshal a whole operating theatre. In all this the healer creates relationship and bonding. Through these processes he induces a trusting relationship that alleviates anxiety and instils hope. It sets potent alternative cognitive and implicit processing cycles into motion that replace the detrimental ones sustaining disease. Positive expectations and thereby therapeutically active strategies are generated. The ritual together with the explanatory myth and the expectations might even work in the manner of hypnotherapy: through subconscious, implicit processing or what Milton Erickson termed the "forgetting of symptoms" (Erickson & Rossi, 1993). We know from social cognitive theory that positive expectations make it more likely that positive consequences happen and this might indeed be an important mechanism (Kirsch, 1978, 1997; Kirsch & Baker, 1993).

But we should not forget all the implicit, autonomic and subconscious elements. Bonding, feeling safe and understood in a relationship triggers a generic relaxation response and counteracts sympathetic tone with parasympathetic activation. Centrally, this might activate the oxytocin system that counteracts stress experience and helps building trust. Peripherally, parasympathetic activation leads to what has become known as the inflammatory response. This is a little known neuroimmunological axis: Each activated macrophage expresses acetylcholin-receptors. As acetylcholin is the major transmitter of the parasympathetic system, parasympathetic activation that happens as a consequence of relaxation and relief leads to a release of acetylcholin peripherally, which in turn downregulates the immune response or inflammatory response mounted by macrophages (Black, 2002; Tracey, 2007). Thereby we have an immediate potential axis of influence that connects generic relaxation and parasympathetic activation with immune modulation. This might explain therapeutic effects for the majority of chronic diseases, most of which have an inflammatory component. Apart from that, relaxation counteracts the stress-associated effects, such as overstimulation of the PA-axis, or the direct stimulation of the adrenal gland (Pacheco-López, Engler, Niemi, & Schedlowski, 2006).

Ritual and bonding create systemic closure. This term, stemming from systems theory, describes the fact that rituals create temporary systems, for instance patient-healer, with a specific micro-environment inside the system that allows the patient to explore new avenues of being, at least mentally and temporarily. It may create this creative empty space that is necessary for a little miracle to happen (de Shazer, 1994). And it may stimulate such self-healing processes in still unknown ways, which I have described in Figure 3 as "non-classical effects". This is currently only a terminological gatekeeper for effects that follow a different logic than the causal ones we are currently exploring (Walach, von Ludacou, & Römer, 2014).

Interestingly, self-healing is not really possible, I assume, for oneself and by oneself alone. So it is in fact a misnomer, if it is understood as a solitary achievement. Very likely, it is most often triggered within a ritualistic context of human bonding and relationship, since we humans are social beings. But once it is triggered – through ritual, trust, alleviation of anxiety, instilment of hope, bonding, and a relaxation of tension and stress – within a therapeutic system of any kind, the processes seem to happen quite endogenously, without any further causal intervening in the system from outside. Thus we have a puzzling paradox here: Self-healing is autonomic but does usually not happen in isolation. Placebo effects are good specimens of self-healing responses, but do by no means exhaust this category. But what the discussion around placebo-effects teaches us is that those generic, seemingly non-specific effects are ubiquitous and very powerful. Perhaps some specific effects however minute need to be present, or have been in the past, to generate a positive experience and to instil hope.

Thus specific and non-specific effects only come in pairs. I would like to use a well known image to illustrate this: In the cathedral of Chartres there are famous stained glass windows showing dwarfs sitting on the shoulder of giants. This is an illustration of the medieval concept that temporary writers felt like the dwarfs on the shoulder of giants, the age-old tradition, and this is why they could see farther. John of Salisbury had devised that image in the 11th century, according to his disciple Bernard of Chartres (Klibansky, 1936). I would like to recycle that image to describe the relationship between specific and non-specific or self-healing effects:

Generic self-healing effects are a little bit like the giants on whose shoulders the dwarfs, the specific effects sit. This is, why they reach so far. Without those giants they would not be so powerful. But perhaps without those dwarfs on their shoulders the giants would be without direction. Thus, it does not really make sense to emphasise one against the other, or negate one of them. They belong together, implicate and mutually strengthen each other.

But what this discussion might have shown is: The label of "placebo-effects" should be abolished. Instead we should start thinking and speaking about these effects as effects of a self-healing capacity which needs to be further elucidated, which can be and should be used in therapy and is in fact used by many, if not all, therapeutic systems more or less directly and explicitly. And it would be a wise move for our modern medical system to stop denigrating these effects and to stop marginalising systems that have made an art of maximising such self-healing responses. For else the "placebo-argument" currently used to ostracise medical systems or interventions that do not fit the mainstream narrative might come back one day like a boomerang when slowly the insight emerges: most of what we do is "placebo", after all.

Notes

1: I say "crypto-positivist" because this stance is underlying most medical research and is hardly ever reflected upon. Some rare examples of theorists discuss this critically, but mostly these are not influential, powerful figures in the research community, which happily follows along such a positivist path, assuming that they discover innocent truths sitting out there in reality to be discovered like ripe fruits that can be plucked from trees. Reflections on the social contingencies of such discoveries or the social determinants of science as have been elaborated by Fleck or Latour do hardly tinge the refreshingly naive view that we only need more research "to know it all" and, of course, to treat it all.

2: Some oncologists have a notorious reputation for saying things like "It is time to make your testament; you have three more months to live" or "There is nothing we can do for you" instead of using some more constructive strategies that are equally true like "On average, patients with a condition similar to yours live three months, but there is a wide uncertainty, and some have even recovered completely. Miracles are always possible." or "While we cannot do anything for you currently, you can do a lot such as eating healthy, enjoying your life, finding out what purpose or meaning this disease has in your current situation."

3: Triptans are serotonin agonists that are supposed to counteract the causal pathological trigger of migraine attacks, the changed tone of cranial vessels with a rapid switch from tension to dilation because of serotoninergic imbalance. The pharmacological rationale is to enhance the bioavailability of serotonin to change the tone of the vessels. When triptanes were introduced beginning of the 90ies they were advocated as wonder drugs that would get rid of migraine pain for good.

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