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The Signaling Theory of Symptoms: An Evolutionary Explanation of the Placebo Effect

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Abstract

Placebo research shows that the subjective quality of care and social support, as well as the patients' expectations of treatment, influence therapeutic outcomes. However, this phenomenon, known as the placebo effect, does not usually cure the disease, but rather can provide symptomatic relief: It may soothe symptoms such as pain, swelling, or nausea that constitute part of an immune response. The function of this mechanism remains unclear. This article puts forward the Signaling Theory of Symptoms (STS) as a possible explanation. According to STS, discernible aspects of an immune response, such as pain, swelling, or nausea, not only serve a defensive and healing function but also a signaling function: symptoms signal the need for care and treatment to potential helpers. Once help and treatment are granted, the signaling function is fulfilled and the symptoms diminish. This mechanism may have been a significant advantage in preindustrial environments, when sufferers depended on extensive social support and personal treatment. Nowadays, from the point of view of modern materialist medicine, the mobilization of social support no longer seems so crucial, and thus the placebo effect has been assigned a somewhat mysterious quality.

Keywords

placebo effect, signaling theory, evolutionary medicine, immune system, psychoneuroimmunology

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Introduction

The placebo effect has been known for a long time and has been replicated in many studies (Beecher, 1955; Howick et al., 2013). Originally, the term ''placebo effect'' or ''placebo response'' stood for an improvement of the patient's clinical state caused by a physiologically inert treatment (Benedetti, 2014). However, it is not the inert treatment itself, but rather the meaning that it has for the patient, which causes the effect (Moerman, 2013; Moerman & Jonas, 2002). Consequently, the term placebo effect does not refer exclusively to allegedly inert treatments, such as sugar pills or saline injections, but also includes other psychosocial aspects of the medical environment, such as care and a positive doctor–patient relationship (Benedetti, 2013; Hart & Dieppe, 1996; Kelley, Kraft-Todd, Schapira, Kossowsky, & Riess, 2014). New terms such as ''meaning response,'' ''contextual healing,'' ''belief effect,'' and ''interpersonal healing'' have been introduced to capture this broadened understanding of the placebo effect (Chiappedi, 2009; Evans, 2003; Miller, Colloca, & Kaptchuk, 2009; Moerman & Jonas, 2002). However, even if the placebo effect can be powerful, its scope is limited. For example, placebo treatment may reduce cancer-induced pain, but it cannot cure cancer itself (Benedetti, 2014). Most of the time, placebo treatment does not cure the disease, but it reduces the symptoms (Miller et al., 2009; Spiro, 1997). Furthermore, placebo effectiveness is limited to certain conditions such as pain, swelling, depression, and irritable bowel syndrome (Evans, 2005; Howick et al., 2013; Hróbjartsson & Gøtzsche, 2004; Kirsch, 2011; Miller et al., 2009; Miller & Kaptchuk, 2008). Remarkably, most of these conditions are aspects of an immune reaction or are at least closely related to it (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Evans, 2003, 2005; Hart, 1988; Öhman & Simrén, 2010). Still, it remains an open question as to why

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social support and physiologically inert treatments have an impact on these symptoms (Miller et al., 2009).

This article suggests an answer to this question by introducing the Signaling Theory of Symptoms (STS). This theory assumes that easily discernible features of an immune reaction, namely symptoms such as fever, swelling, apathy, obvious signs of pain, and so on, not only serve defense and healing purposes but also signal the need for help and treatment to potential helpers. The stronger the symptoms, the higher their signaling efficacy. Therefore, symptoms are exaggerated to heighten the likelihood of mobilizing help and treatment. Once help and treatment are received, this signaling function is fulfilled and the symptoms can diminish.

First, I will give an overview of previous evolutionary theories on the subject in order to provide a basic framework and draw attention to the open questions. In the following sections, the adaptive problem of infection and injury will be discussed as well as the probable adaptive solutions to this problem, namely the immune system and the help and treatment by others. Against this background, STS will be introduced and developed. A further section will assemble empirical evidence supporting STS, and testable hypotheses will be derived. Finally, the article will be summarized and some implications will be elucidated.

Theoretical Background

Placebo research is rather interested in the proximate mechanism of the placebo effect, specifically in how it is mediated physiologically (Benedetti, 2013). However, research in this field has yet to answer questions concerning the function which this mechanism fulfills and, hence, why such a mechanism exists (Miller et al., 2009).

According to the pain researcher Patrick Wall (1999), pain is not only an alarm system that informs the sufferer of tissue damage, but it also motivates appropriate action. Pain can express the need to withdraw from a harmful situation (e.g., a hot stove), the need to adopt a relieving posture, or the need to seek help and treatment. The mere act of providing help and treatment fulfills the need and allows the pain to fade. Wall's conception suits the evolutionary perspective well, since he regards pain as having the function of motivating appropriate action in case of sickness or injury. According to this theory, the placebo effect can be seen as one small aspect of this adaptation, "[...] the placebo is not a stimulus but an appropriate action" (Wall, 1999, p. 155). The patient, unaware of the physiological ineffectiveness of the placebo treatment, believes that appropriate action has been taken, and thus that the need state has been fulfilled, hence the pain diminishes. However, Wall's theory remains restricted to pain and placebo analgesia.

Humphrey (2002, 2004; see also Humphrey & Skoyles, 2012; Trimmer, Marshall, Fromhage, McNamara, & Houston, 2013) puts forward the theory of the "health management system" or "health governor." Self-healing and defense should not be an automatic reaction to infection and injury. Rather, they should be employed selectively after a cost–benefit analysis: Pain and swelling of the broken ankle should be postponed when a person is in immediate danger from the proverbial lion. Fighting the flu should be postponed when there are immediate options for procreation. Moreover, a lack of food and bodily energy reserves might not allow for a full immune response. Thus, the regulation of self-healing should be based on a calculation of costs, opportunity costs, and potential benefits. This calculation is based on the individual's subjective judgment of environmental conditions, that is, in the terminology of placebo research, on *expectations.* According to Humphrey, the placebo treatment modifies this cost–benefit analysis—it gives the impression that it will assist the immune system and in this way, it improves the prospects of a rapid recovery. The "health governor" assumes that the circumstances have changed for the better and allows a full immune response.

Evans (2003) disagrees with Humphrey's thesis, claiming that the placebo effect is not concerned with enhancing immune activity but rather with suppressing it. Evans observes that the placebo-responsive conditions, such as pain, depression, and irritable bowel syndrome have something in common: They are each symptoms of an acute-phase response or at least closely related to it. Evans regards the placebo effect as a special case of the broad phenomenon of immune conditioning. He refers to evidence from the respective field, suggesting that immune reactions are up or down regulated, depending on environmental factors and previous experience. However, Evans finds more empirical evidence for conditioned immune suppression than for conditioned immune enhancement. Therefore, he suggests that immune conditioning might have evolved as a "[...] protective mechanism, to save the immune system from unnecessary expenditure, and not as a general-purpose learning mechanism to enable the immune system to respond in any way to any psychological input" (Evans, 2003, p. 105).

According to Evans, one opportunity to save resources would occur when effective treatment and care provided by others contribute to a task that the immune system would otherwise perform alone. If extensive care and effective medicine have existed long enough, the selective pressure to save resources could have shaped a mechanism like the placebo effect. Still, Evans' theory does not explain what he also tried to claim, namely why the placebo effect is restricted to symptoms of the acute-phase response. Evans speculates that in some situations, it might be adaptive to suppress the acute-phase response in order to allow an earlier onset of the adaptive immune response. However, he does not elaborate on this further.

Previous evolutionary theory provides foundations as well as open questions for further theoretical development. Wall's theory gives a convincing explanation of pain, but not of other placebo-responsive conditions. Humphrey's theory applies to all placebo-responsive conditions, but it does not agree well with empirical findings. Finally, Evans' theory applies to all placebo-responsive conditions and is supported by empirical evidence, but it does not answer the question of why the placebo effect is restricted to certain symptoms.

The present article will attempt to fill these gaps. Further, it will try to broaden the focus, so that it not only regards the

sufferer who is helped and treated but also others who decide either to help and treat the sufferer or to refrain from doing so. Specifically, it explains the placebo effect as part of an adaptive signaling mechanism.

Just like other theories in evolutionary medicine, STS is based on the assumption that humans are not adapted to their modern environments, but rather to the hunter-gatherer environment, the so-called environment of evolutionary adaptedness (Nesse, 2005; Nesse & Williams, 1995; Williams & Nesse, 1991; Wilson, 1978). As a consequence, in order to understand the regulation of the immune system, and thus the placebo effect, it is necessary to identify how the adaptive problems of illness and injury were solved during human evolution, especially in hunter-gatherer environments.

The Environment of Evolutionary Adaptedness

The risk of injury and infection has been a crucial adaptive problem throughout evolutionary history, and the immune system developed as its adaptive answer (Nesse & Williams, 1995). However, an immune reaction also has substantial costs. On the one hand, there are direct costs, such as higher energy consumption or potential tissue damage due to high fever (Bonneaud et al., 2003; Eraud, Jacquet, & Faivre, 2009; LeGrand & Alcock, 2012). On the other hand, there are opportunity costs. Immune system activation is associated with so-called sickness behavior such as sleepiness, apathy, and social withdrawal, reflecting a motivational shift away from social, sexual, and aggressive behavior that allows maximization of immune activity (Aubert, 1999; Dantzer & Kelley, 2007; Hart, 1988). Due to this change in priorities, sick animals miss out on opportunities for mating, bonding, and fighting for places in dominance hierarchies. Further, avoidant behavior of conspecifics may contribute to these social costs (Avitsur, Cohen, & Yirmiya, 1997). In certain situations, opportunity costs are so high that the immune response is suppressed in order to enable normal behavior (Aubert, Goodall, Dantzer, & Gheusi, 1997; Lopes, 2014; Lopes et al., 2013; Lopes, Adelman, Wingfield, & Bentley, 2012; Owen-Ashley & Wingfield, 2006). For example, male zebra finches whose immune systems were artificially provoked, display symptoms of illness when they are housed in a single cage, but when housed in a group cage, they do not display these symptoms (Lopes et al., 2012). More specifically, when sick male zebra finches are in the presence of a female zebra finch, their symptoms vanish, presumably to enable mating (Lopes et al., 2013).

However, in some species the opportunity costs of an immune system are partly compensated by support of conspecifics. For example, house sparrows breed in couples and feed offspring together. When the female shows symptoms of sickness, the male sparrow collects more food to compensate for her absence (Bonneaud et al., 2003). Hart (1990, 2011) summarizes a series of observational studies about animals helping sick conspecifics. Female chimpanzees reduced their travel speed to let a sick group member keep pace. They also took care of the sick mother's son while she was sleeping. In a group of wild mongooses, an injured group member was extensively groomed and even provided with food. While provision of food to sick group members is observed only in some nonhuman animals, mutual support in case of sickness or injury is a crucial part of life in human hunter-gatherer societies and, moreover, some have conjectured that this social support is one of the reasons for human longevity (Gurven, Stieglitz, Hooper, Gomes, & Kaplan, 2012; Sugiyama, 2004).

In contemporary hunter-gatherer societies, injuries and sicknesses that temporarily keep a group member from gathering and hunting are common (Gurven, Allen-Arave, Hill, & Hurtado, 2000; Hagen, Hames, Craig, Lauer, & Price, 2003; Hill & Hurtado, 2009; Sugiyama, 2004; Sugiyama & Chacon, 2000). However, the resulting temporary inability to join hunting or foraging does not result in the starvation of the sick persons, since their absence from foraging is buffered by the group. Sick and injured group members are provided with food (Gurven et al., 2000; Sugiyama, 2004; Sugiyama & Chacon, 2000), notably, without the possibility of direct reciprocity from the sick person (Sugiyama, 2004; Sugiyama & Chacon, 2000; Tooby & Cosmides, 1996). The altruistic act of sharing food might be explained through delayed reciprocity or improved reputation on the part of the donor (Hawkes, 1991; Nesse, 2007; Sugiyama & Chacon, 2000; Tooby & Cosmides, 1996). Thus, helping can be an honest signal of mate quality and worthiness as a cooperation partner (Barclay, 2012, 2013; Barclay & Willer, 2007; Fehrler & Przepiorka, 2013; Gintis, Smith, & Bowles, 2001; McAndrew & Perilloux, 2012; Sylwester & Roberts, 2013). Helping can also signal indispensability and act as ''insurance'' against the helpers themselves becoming sick or injured (Gurven et al., 2000; Jaeggi & Gurven, 2013; Sugiyama & Sugiyama, 2003). In fact, group members who distributed more food when in a healthy condition receive more support when they are sick (Gurven et al., 2000; Sugiyama, 2004; Sugiyama & Chacon, 2000).

Further, humans have probably had knowledge of simple medical treatments since the time of homo neanderthalensis. There is a wide range of effective herbal medicines and it is possible that some of these might have been in use in ancient hunter-gatherer societies (Halberstein, 2005). Flowers found in a Neanderthal grave have remarkable medical efficacy and might have been chosen as a funerary object on this basis (Lietava, 1992). The use of red ochre is well-documented among Neanderthals across Europe (Roebroeks et al., 2012). Besides for personal decoration and cave paintings, red ochre is used for medical purposes by modern hunter-gatherers and this might also have been the case for Neanderthals (Roebroeks et al., 2012; Velo, 1984). The iron salts in red ochre are antiseptic, can arrest bleeding, and promote the healing of wounds (Velo, 1984).

Further treatments are imaginable, since symptoms have clear demand characteristics: a feverish head demands cooling and a shivering body warmth. Cooling a feverish head could protect the brain from overheating, despite a high fever in the rest of the body. Shivering serves the function of creating heat, and warming may contribute to this adaptive reaction. So, in humans, the opportunity costs, as well as the direct costs of an

immune response, are partly compensated by social support and treatment.

Still, it is important to note that some kinds of help and treatment can be counterproductive. For example, consuming iron-rich food counteracts the body's strategy of sequestrating iron to limit bacterial growth (Nesse & Williams, 1995; Weinberg, 1984). Similarly, certain lipoproteins serve, on the one hand, for the transport of lipids in the blood and, on the other hand, aid the functioning of the immune system (Adamo, Bartlett, Le, Spencer, & Sullivan, 2010; Steiner & Romanovsky, 2007). Thus, a low intake of fat could assist the immune system, whereas high fat consumption could counteract proper immune functioning (Adamo et al., 2010). Also, soothing symptoms such as fever may relieve suffering but at the same time may undermine the immune reaction (Nesse & Williams, 1995). This problem of counterproductive treatment might be partly solved by the sufferer's feelings toward the help that is granted, for example disgust toward fatty or iron-rich food.

Symptoms as Cues

Providing support for sick or injured group members requires others to detect them. Therefore, the seemingly trivial question arises of how sickness and injury are detected. Some injuries can be perceived directly either visually (e.g., blood loss) or haptically (e.g., the unusual mobility of broken bones). Infections, however, can only be directly perceived through modern means: Microscopes make bacteria visible, and antibody tests provide evidence for the presence of certain viruses. Without these modern means, humans have had to rely and still rely on symptoms to detect sickness in people. Accordingly, what we perceive as a sickness in everyday life is not the presence of an infection itself but the easily discernible symptoms, such as pain, fever, cough, sneezing, shivering, loss of appetite, and so on. Notably, these symptoms are not caused by the infection itself but are part of the body's response to the infection. This immune reaction obviously functions as a defense against the infection, as in the example of fever, which creates an uncomfortable situation for pathogens, or coughing and sneezing, which expels them. However, as elucidated above, some aspects of this immune reaction are discernible to other group members: They provide cues which render the sickness perceptible. In other words, an immune reaction not only fulfills the function of a defense against infections but also, as a byproduct, produces discernible symptoms that inform other group members about the need for help and treatment. Along the same lines, Thornhill and Thornhill (1989) suggest that psychological pain has a dual function. On the one hand, psychological pain drives the individual's attention to the source of pain, motivates introspective analysis and, in this way, might lead to a solution. On the other hand, psychological pain serves as a social display of need. Also, Wall regards pain as a need state that drives the sufferer's attention to a possible solution. At the same time, without elaborating on it, Wall makes it clear that pain has two sides: ''private pain and public display'' (Wall, 1999, p. 1).

Cues Becoming Signals

Once the tendency to help the sick appeared in evolutionary history, discernible symptoms of an immune reaction no longer had only a defensive function but also happened to act as cues for potential helpers to discover sick individuals. It might be reasonable to assume that individuals differed in their symptom structure, for example, the peak of their fever, the expression of their pain, the intensity of coughing and sneezing, and so on. As individual immune systems differ in their defensive effectiveness, the discernible symptom structure of immune reactions might also differ in their effectiveness as cues. Some individuals might have had a symptom structure that mobilized support more effectively, while others had symptoms that were less effective in mobilizing help. The former had an evolutionary advantage over the latter since, as described above, mobilizing help is crucial for survival. This would result in a selection pressure for more effective cues. Thus, the immune system, alongside its defensive function, was also selected for a symptom structure that most effectively elicits support from the group. According to the terminology of Williams (1966) and Gould and Vrba (1982), the discernible symptoms of an immune reaction form part of the immune system, that is, a complex set of adaptations for the function of defense, but the discernible symptoms are also an exaptation with the effect of mobilizing help. Thus, there is a second selection pressure for better cues of sickness, which causes the symptoms to turn into a secondary adaptation for this function. However, the initial defense function persists, making the discernible symptoms an adaptation which serves two ultimate functions: defense and providing cues. The symptoms are now also *signals*, since they are shaped by evolution for a communicative purpose.

Presumably, stronger symptoms provide more convincing signals than weaker symptoms. Thus, higher fever, stronger appearance of pain, louder sneezing and coughing, worse anemia, more obvious nausea, and so on should mobilize the most social support. The symptom strength optimal for mobilizing help is probably higher than the optimal symptom strength for defense. Thus, symptoms should be exaggerated above the level that is optimal for defense to improve the chances of receiving social support. Similarly, Trivers (1974) suggests that crying by young infants is not only a cue for need but an exaggerated signal to extract more resources from the parents than they would otherwise give. However, in some severe diseases, optimal symptom strength might be so high that exaggeration is neither necessary nor feasible.

In summary, I suggest that discernible symptoms serve two functions: defense and signaling the need for help. The two functions result in a trade-off. Optimal signaling means suboptimal defense, while optimal defense means suboptimal signaling. In general, trade-offs are a common reason for the imperfections of the human body (Nesse, 2005; Nesse & Williams, 1995; Williams & Nesse, 1991). The double function of discernible symptoms is based on an evolutionary path dependency: a constraint in the terminology of evolutionary medicine (Nesse, 2005; Nesse & Williams, 1995; Williams & Nesse, 1991).

Costly, and Thus, Honest Signals

Generous social support usually entails the problem of free riders, which, within the scope of this article, refers to people faking sickness. However, the symptom signals are quite difficult to fake, since they are highly costly for the sender. First, discernible symptoms like fever are costly in terms of energy (Benhariz, Goulet, Salas, Colomb, & Ricour, 1997; Kluger, 1989; Stettler, Schutz, Whitehead, & Jequier, 1992) and they become more costly the more exaggerated they become. Second, the symptoms not only harm the pathogens but also the body itself (Eraud et al., 2009; LeGrand & Alcock, 2012). Likewise, they do more harm the more they are exaggerated. Third, being sick has opportunity costs which arise from typical sickness behavior: fatigue, lack of sexual interest, and loss of appetite (Dantzer & Kelley, 2007; Hart, 1988). A sick person refrains from social activities that might provide a pay-off in terms of reputation, rank, or mating opportunities. In short, transmitting convincing signals of sickness is highly costly and likely only pays off for those who are really in need of help, not for those who only aim to take time off on full board.

These costs also limit the exaggeration of the symptoms for the sake of signaling. This can be illustrated by an imaginary hunter-gatherer band that features several sick members at the same time. In this case, the sick individuals compete for the help of others. Other factors being constant (like the respective sick individual's reputation or importance within the group), the sick individual will probably receive more support the needier they appear to be, that is, the stronger the symptoms they display. However, other factors being constant (like the energy reserves of the respective sick individual), the sick individuals should only invest as much in the signaling as the hoped-for help is worth. Thus, again, even exaggerated symptoms are a reliable signal for the need for help. Costly signals are honest signals (Spence, 1973; Veblen, 1899; Zahavi, 1977; Zahavi & Zahavi, 1996).

Cost and Benefits of Helping

For the sufferer, sending convincing signals of sickness is highly costly. And for potential helpers, altruistic behavior is costly in terms of the time and resources it takes to feed and treat the sick and to absolve the sick of other duties. Furthermore, contact with individuals who carry parasites bears the risk of contagion. In fact, close contact with sick conspecifics, as compared to contact with, for example sick animals or rotten food, is especially risky, because parasites are adapted to particular species (Curtis, 2014).

There is a great deal of research on adaptations to the risk of contagion, among them the tendency to avoid sick conspecifics. This body of research predominantly deals with the emotion of disgust within the theoretical framework of the behavioral immune system (Curtis, Aunger, & Rabie, 2004; Curtis, de Barra, & Aunger, 2011; Oaten, Stevenson, & Case, 2009; Schaller & Park, 2011; Tybur, Lieberman, Kurzban, & DeScioli, 2013). This behavioral immune system is so sensitive that it not only reacts to contagious conspecifics but also to noncontagious deviations from the norm, such as facial disfigurements, overweightness, old age, and physical disabilities (Duncan & Schaller, 2009; Lieberman, Tybur, & Latner, 2012; Park, Faulkner, & Schaller, 2003; Park, Schaller, & Crandall, 2007; Ryan, Oaten, Stevenson, & Case, 2012).

However, there are some factors that mitigate the drive to avoid sick conspecifics. First, disgust and avoidance are weaker when considering familiar people and in-group members, as compared to out-group members and strangers (Case, Repacholi, & Stevenson, 2006; Curtis et al., 2004; Peng, Chang, & Zhou, 2013). This makes sense from the standpoint of pathogen avoidance, since strangers are more likely to carry novel pathogens for which the immune system is not yet prepared (Fincher & Thornhill, 2012; Navarrete & Fessler, 2006; Stevenson & Repacholi, 2005). Second, the fast automatic reaction of avoidance can be overridden by a slow, controlled, and rule-based process that takes into account social norms and social pressure (Kleck, 1969; Kleck, Ono, & Hastorf, 1966; Pryor, Reeder, Yeadon, & Hesson-McInnis, 2004; Stone & Potton, 2014). One of these social norms might be to help sick group members (Schaller, 2011). Also, helping the sick might be rewarded with especially high social prestige (Schaller, 2011). In fact, helping the sick greatly improves reputation, as reflected in the especially high reputation of members of the medical professions. Rankings of occupational prestige in the United States show physicians ranking first and nurses fifth, while similarly, in Germany, physicians rank first and nurses second (Institut für Demoskopie Allensbach, 2013; Pollack, 2014).

Furthermore, a sick group member could put pressure on other group members who are dependent. Sharing a similar basis, the "social navigation hypothesis" (Watson & Andrews, 2002) and the "bargaining model of depression" (Hagen, 1999, 2002, 2003, 2011; see also Rosenstrom, 2013) explain self-harming behavior in depression from drug abuse to suicide attempts. In interdependent relationships, like the family or a foraging group, harming oneself also imposes costs on others: Other people who usually depend on or cooperate with the depressed individual are left to their own devices when the self-harmer is injured or dead. In this way, self-harming behavior on the part of the depressed individual can put pressure on family or group members to help.

Similarly, exaggerated symptoms may also mobilize help by putting pressure on potential helpers. Exaggerated symptoms may not only be costly to the bearer but they may also impose costs on others who depend on the well-being of the sufferer. Overly exaggerated symptoms are a kind of self-harming behavior that might serve an extortive function to elicit social support from dependent others.

The Regulation of Signaling Symptoms

One of the primary functions of the immune response, and also its discernible symptoms, is fighting pathogens. When the infection is eliminated, this defensive function is fulfilled and

the immune reaction can thus diminish. The same should be true for the hypothesized secondary function, the signaling function of symptoms. Signaling symptoms have high costs in terms of energy and create the risk of tissue damage. Therefore, the signaling symptoms should not be continued longer than necessary. As soon as the status of sickness is acknowledged by the group, once support and treatment is granted, the signaling function is fulfilled and the immune reaction can diminish. As described above, Wall (1999) claims that the mere act of giving help and treatment fulfills the need and allows the pain to fade. From the perspective of STS, the same might be true for any other discernible symptom.

But how does an individual judge (consciously or unconsciously) whether it has been supported and treated properly and, in this way, whether the signaling function of the immune system has been fulfilled? Medical research provides information about the state of the art of treatment for the respective disease and thus makes clear which kind of treatment the sick person should be satisfied with. However, the human body has not yet adapted to modern circumstances, but rather to the environment of evolutionary adaptedness (Nesse & Williams, 1995; Williams & Nesse, 1991; Wilson, 1978). The regulation of the signaling symptoms may therefore still be largely calibrated for a Stone Age environment.

It is not known exactly how medical treatment was in the Paleolithic age, but two self-evident assumptions can be made. First, there was no machinery, so any kind of treatment was done by people and always involved social contact with familiar group members. Second, just like any other part of culture, medication and rituals of treatment probably changed over time and differed between groups. The human need for help and treatment in case of sickness should be shaped accordingly. As there was no effective treatment without extensive personal care, humans should have a universal need for personal care in case of sickness. As medication and rituals of treatment differed between times and groups, humans should have a variable need for medication and treatment that is shaped by their respective medical culture. The regulation of signaling symptoms should be calibrated accordingly. On the one hand, there should be a general response to social support. On the other hand, there should be a rather open response, based on the beliefs of effectiveness of the sick person, shaped by the respective cultural environment.

Empirical Support for the STS

The STS assumes that discernible symptoms of an immune reaction serve a second function alongside defense and healing: namely, signaling the need for help and treatment. Discernible symptoms, such as swelling, apathy, loss of appetite, and the obvious distress of pain, signal to others the need for support and treatment. These symptoms are exaggerated to enhance the signaling efficacy and, in turn, to more reliably mobilize social support and treatment. Once social support and treatment are granted, the signaling function is fulfilled and the signaling symptoms may decline. However, this need for help and treatment is shaped by the selective pressures of the environment of evolutionary adaptedness. First, due to a lack of medical machinery, any treatment had to be performed by people, and sufferers were thus selected for the demand for personal help by actual humans. Second, medical cultures differed between tribes and changed over time, so humans were selected for flexible treatment demands depending on the respective medical culture.

Precisely these two factors—a general response to social support and an open response based on individual beliefs of effectiveness—can be found in empirical studies of the placebo effect. Two factors trigger the placebo effect: on the one hand, *care and social support* (Benedetti, 2013; Kelley et al., 2014; Miller et al., 2009) and, on the other, *the patient's expectation of amelioration* (Benedetti et al., 2003; Stewart-Williams & Podd, 2004).

For example, an early study on the placebo effect used an ultrasound device designed to reduce swellings caused by dental treatment (Hashish, Hai, Harvey, Feinmann, & Harris, 1988). The subjects were treated with the device, and the swelling was reduced, even when the device was turned off—a placebo effect. The placebo effect, however, was found only when an experimenter administered the device to the patient. It did not work when the subject used it alone. This finding points to the significance of social support for the placebo effect. From the point of view of STS, the excessive swelling was a signaling symptom that had fulfilled its function once someone helped the sufferer. The function was not fulfilled when the sufferer administered the treatment alone, in which case the excessive swelling prevailed. In a much more recent study, intranasal administration of oxytocin has been shown to increase the analgesic effect of a placebo ointment applied to the forearm (Kessner, Sprenger, Wrobel, Wiech, & Bingel, 2013). Oxytocin increases trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and in this case it probably raised the subject's trust in the doctor applying the placebo ointment (Kessner et al., 2013). In the view of STS, signaling symptoms should continue as long as the sufferer distrusts the potential helper's intentions. By raising trust, oxytocin may change the appraisal of the situation in such a way that the signaling functions seem to be fulfilled. Similarly, the facial expression of potential helpers might also change the appraisal of the situation. Presenting facial expressions to the subject alters the magnitude of the placebo effect in placebo analgesia (Valentini, Martini, Lee, Aglioti, & Iannetti, 2014). A sad face enhances the placebo effect when compared to a neutral face, but a happy face enhances the placebo effect even more. This makes sense in view of STS, since a sad face indicates that a potential helper empathizes with the sufferer, which can be seen as a precondition of helping. A happy face can be seen as an indicator that help is very likely.

Helping included physical contact in the environment of evolutionary adaptedness (EEA). In contemporary medicine, treatments rarely include touching as part of the treatment itself. However, even the slight physical contact typical of medical settings can soothe pain (Fishman, Turkheimer, &

Degood, 1995). Still, there seems to be a demand for treatments which involve greater physical contact: Many alternative and complementary treatments feature "light touch + a healing meaning" (Kerr et al., 2011, p. 785). Acupuncture, for example, involves significant physical contact and causes a strong placebo effect (Kaptchuk et al., 2006, 2008). From the perspective of STS, these treatments satisfy the patient's general need for helping through physical contact. Once this need is fulfilled, the signaling symptoms can diminish. These examples show that the humane aspects of medicine are crucial for patients' well-being. This observation does not fit with contemporary approaches to medicine, which are entirely materialist, but it fits perfectly well with STS.

The STS further suggests that there is a flexible component of immune regulation that adapts to developments and cultural differences. Patients can learn which treatment is effective and then develop a placebo effect according to this belief. Accordingly, the advertising of a drug—a kind of manipulative teaching—enhances the drug's placebo effect (Kamenica, Naclerio, & Malani, 2013). Similarly, a patient can learn that a treatment is effective from a doctor who is convinced of its effectiveness and, in this way, can exhibit a placebo effect (Gracely, Dubner, Deeter, & Wolskee, 1985). From the perspective of STS, the advertisements or the authority of the doctor teaches the patient which treatment is effective and, therefore, the signaling symptoms diminish once the patient receives the respective treatment. The patients can also learn from their own experiences: Classical conditioning is one of the main mechanisms of the placebo effect (Benedetti et al., 2003; Stewart-Williams & Podd, 2004). Furthermore, culture influences the placebo effect: For 30 years, the placebo effect of antidepressant medication has increased while the treatment effect remained the same (Undurraga & Baldessarini, 2012; Walsh, Seidman, Sysko, & Gould, 2002). This can be interpreted as an effect of learning on a large scale. Slowly, antidepressants have become a part of popular medical culture and it has become a standard means of treating depressed moods (Kirsch, 2011; Moerman, 2013). From the point of view of STS, patients have learned that antidepressants are an appropriate treatment, and thus signaling symptoms are regulated accordingly. Taken together, these examples show that people can learn the meaning, the significance and, in this way, the expectation of medical treatments through advertisement, authorities, and their own experiences. The placebo effect, and hence the regulation of signaling symptoms, adapts to the current medical culture through these mechanisms, as reflected in the growing placebo effect of antidepressants.

This section has shown that STS fits well with the empirical findings of placebo research. In a modern medical environment that owes its advances to a materialist way of thinking, it seems puzzling that patients should respond to treatments that do not have direct physiological effects. However, from the perspective of the STS, the much-discussed but nevertheless poorly understood placebo effect is an adaptation to a medical environment where the social component was much more important for adequate treatment.

Predictions and Testable Hypotheses

The STS assumes that discernible symptoms not only serve defense and healing purposes but also the signaling of a need for help and treatment. Accordingly, signaling makes sense when there are recipients of the signals. Therefore, STS predicts that the exaggeration of the immune reaction should rather take place in the presence of potential helpers.

Hypothesis 1: Patients should show stronger symptoms in a social environment as compared to in isolation.

The hypothesized exaggeration of symptoms within a social environment depends on the behavior of the people who are present. The symptoms should only be exaggerated as long as the other people are passive and do not demonstrate acknowledgment of the status of the sick individual. Once they acknowledge the status and start helping, the signaling symptoms have fulfilled their function and may diminish.

Hypothesis 2: When other people acknowledge the status of the sick individual and start helping, then the symptoms should diminish.

When there is only one sick individual, it is sufficient to convince the helpers of the sickness status. However, when there are more sick individuals and helpers are scarce, competition among the sick individuals would emerge for the support of potential helpers, thus symptoms should be even stronger.

Hypothesis 3: The more sick individuals compete for help and the more scarce potential helpers are, the stronger the expression of symptoms of sick individuals should be.

However, the idea that symptoms serve as signals applies only to discernible symptoms. It does not make sense to exaggerate aspects of the immune response that potential helpers do not notice. Fever, anemia, cough, and sneezing are easily discernible, while the concentration of antibodies is not.

Hypothesis 4: The aforementioned hypotheses (Hypotheses 1–3) should only be valid for easily discernible symptoms but not for indiscernible aspects of the immune reaction.

When testing this last hypothesis, the fact that different aspects of the immune system are closely interrelated must be taken into account. Different symptoms and sickness behaviors, such as fever, swelling, and pain, loss of appetite, loss of sexual interest, and apathy, usually come together and they are of course highly correlated with the high cytokine levels that are causing them. For example, there is a reliable placebo effect for the treatment of stomach ulcers, which would seem to contradict STS. However, stomach ulcers are an inflammatory disease and, therefore, include other discernible symptoms such as nausea, loss of appetite, and abdominal pain. Similarly, depression is hypothesized to be an inflammatory disease, though in this case the cardinal signs of inflammation such as swelling, redness, and heat are not visible. Nevertheless,

sickness behaviors, such as apathy, tiredness, and loss of sexual interest, are very well discernible. So, it might be difficult to separate the discernible from the undiscernible aspects of the immune response.

Further, symptoms suitable for signaling should not only be discernible, they should also cause the least disgust and avoidance in potential helpers. Natural selection should have favored those symptoms for signaling that most reliably motivated others to help, and at the same time prevented disgust that could counteract this motivation.

Hypothesis 5: The placebo effect should rather be found in symptoms that do not elicit disgust in potential helpers.

This hypothesis has the same difficulties as the previous one, as different symptoms that elicit more or less disgust are correlated. Also, there is no research that compares the degree of disgust that different symptoms elicit. Still, the theory of the behavioral immune systems suggests that disgust should be strongest when infection is most likely. So, symptoms of pain and depression should be suitable signals. Accordingly, these are also the symptoms that show the most reliable placebo effects. Following the assumption further, coughing and sneezing should be less suitable signs, as they bear the risk of droplet infection. Still, coughing and sneezing can be viable signals as long as they are only used when the potential helper is distant, but suppressed when the helper comes closer. Conversely, fever would be a better signal when potential helpers are close, because fever is not recognizable from afar and it does not raise the risk of infection. Following this line of thought, the previous hypothesis can be further specified.

Hypothesis 6a: When helpers are distant, the sufferer should have strong symptoms that are recognizable from far, such as noises like sneezing, coughing, and cries of pain.

Hypothesis 6b: When helpers are close, the sufferer should not have symptoms that raise the risk of infection of potential helpers, such as coughing and sneezing. Instead, the sufferer should have strong symptoms, such as fever, that are recognizable from close proximity and that do not raise the risk of infection.

Finally, STS has comparative implications. Signaling need for care makes only sense in species where care for the sick can be found. Notably, this hypothesis is not about the presence of a placebo effect in these species as the placebo effect found in animals is usually based on classical conditioning.

Hypothesis 7: Signaling symptoms should only be found in species, where care of the sick can be found.

Accordingly, the most complex regulation patterns of symptoms of sickness can be found in highly social species (Hennessy, Deak, & Schiml, 2014). However, as mentioned above, the evidence of care for sick conspecifics in species other than humans is scarce. Therefore, the hypothesis might be limited to the comparison of humans with other species. The idea of Hypothesis 7 could apply to further species when it is translated from a comparative into a developmental hypothesis. Maternal care is much more common in nonhuman species than care for the sick is. Therefore, young animals could have signaling symptoms to extract more maternal care.

Hypothesis 8: In species that show maternal care, but not care for sick adults, signaling symptoms should be found in young animals but not in adults.

Conclusion

According to the STS, the human immune system is adapted to Paleolithic times, when medical care consisted of different kinds of social support and when, in case of illness, it was crucial to mobilize this help. Thus, openly discernible aspects of an immune reaction's symptoms have not only been naturally selected for defense but also for their signaling effectiveness. They are exaggerated to mobilize help. Exaggerated symptoms are trustworthy because they are costly. Furthermore, some exaggerated symptoms can be interpreted as a self-harming behavior on the part of the sufferer, which may extort help from interdependent group members. When support and treatment are granted, the function of the signal is fulfilled, and the immune reaction can decrease to the intensity level that is optimal for defense.

STS serves as a theoretical explanation of the placebo effect. Placebo treatment, a good patient–physician relationship, as well as treatments from complementary and alternative medicine might be effective by granting the social support sick humans are selected to demand. Still, STS does not compete with other evolutionary theories of the placebo effect, such as Humphrey's model of the "health governor." The two theories are not mutually exclusive, but complementary, since the term placebo effect probably subsumes numerous different mechanisms (Benedetti, Carlino, & Pollo, 2010).

The STS points to the importance of social support for soothing signaling symptoms and, in this way, promoting well-being and health. In contemporary society, social interaction is an increasingly less important aspect of medical examination and treatment. Certainly, modern medicine can ascertain and treat the material causes of illnesses more effectively than ever before, but at the same time, it no longer fulfills the social needs of patients (Hart & Dieppe, 1996). According to STS, however, these social needs are a crucial part of the regulation of the immune system. Just as symptoms persist when their material cause is not treated, symptoms might also persist when the cause is treated but the evolutionarily shaped need for help and interpersonal treatment is left unsatisfied. The assumptions of the STS could also be developed into an explanation of chronic symptoms that do not seem to have a real material cause, such as chronic pain or irritable bowel syndrome. A hypothetical example for the development of irritable bowel syndrome from the perspective of STS could be the following: Due to a false alarm of the immune system, a person

develops symptoms of abdominal pain and discomfort. The person's spouse does not take the complaints seriously, and the doctor rejects the person's worries about the abdominal pain, a second doctor does the same, and so does a third. In fact, the doctors are right in their diagnoses but they do not satisfy the patient's social need. With each doctor the symptoms worsen, because the signal strength does not seem to suffice to convince potential helpers. The person becomes accustomed to the persistently unsatisfied social need and, hence, might end up developing chronic symptoms, even though a simple acknowledgment and social support might have soothed symptoms at the outset. In the end, the person is treated by a spiritual healer, who takes every complaint seriously, if only to earn money from the patient. Here, the person's symptoms are finally acknowledged and treated interpersonally. Finally, the signaling function is fulfilled and the symptoms soothed.

Certainly, it is no solution to shut down medical labs and switch off medical devices to compensate for this social deficit. Nonetheless, the STS suggests that social support and a good doctor–patient relationship is an important supplement for treatment in the paradigm of western medicine. This position is nothing new, and in fact it is quite common sense. Empirically, it is based on overwhelming evidence (Benedetti, 2013; Hart & Dieppe, 1996). Theoretically, however, it has received little support outside of humane arguments. The STS shows that these ''soft factors'' are crucial for some conditions, rather than just decorative accessory of the materialist approach. By connecting these ''soft factors'' to evolutionary medicine, STS provides the opportunity to argue for them from a more solid scientific foundation.

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