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Research

The placebo effect and the autonomic nervous system: evidence for an intimate relationship

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For many subjectively experienced outcomes, such as pain and depression, rather large placebo effects have been reported. However, there is increasing evidence that placebo interventions also affect end-organ functions regulated by the autonomic nervous system (ANS). After discussing three psychological models for autonomic placebo effects, this article provides an anatomical framework of the autonomic system and then critically reviews the relevant placebo studies in the field, thereby focusing on gastrointestinal, cardiovascular and pulmonary functions. The findings indicate that several autonomic organ functions can indeed be altered by verbal suggestions delivered during placebo and nocebo interventions. In addition, three experimental studies provide evidence for organ-specific effects, in agreement with the current knowledge on the central control of the ANS. It is suggested that the placebo effects on autonomic organ functions are best explained by the model of 'implicit affordance', which assumes that placebo effects are dependent on 'lived experience' rather than on the conscious representation of expected outcomes. Nevertheless, more studies will be needed to further elucidate psychological and neurobiological pathways involved in autonomic placebo effects.

Keywords: placebo; nocebo; verbal suggestion; autonomic nervous system

1. INTRODUCTION

The last decade has seen an increased interest in the occurrence of placebo responses in various conditions. However, the vast majority of studies examine placebo effects in subjectively experienced outcomes, such as pain and depression. Relatively little is known about the capacity of placebo interventions to alter objectively assessed endpoints. Based on the meta-analyses of Hróbjartsson & Gøtzsche [1–4], a general view has arisen that placebo interventions do provide symptomatic relief but do not modify pathophysiologal processes underlying the disease. However, such a conclusion may be premature. For example, a subgroup analysis showed that physical outcome parameters modulated by the autonomic nervous system (ANS), such as gastric motility and lung function, improved in placebo-treated patients when compared with untreated controls [5]. Furthermore, the latest update of the meta-analysis of Hróbjartsson & Gøtzsche [4] showed a significant pooled placebo effect on lung function in asthma trials beyond regression-to-the-mean, although results still carried the risk of bias. Thus, there is some evidence from systematic reviews that parameters controlled by the ANS may be amenable to top-down modulation via placebo interventions.

The ANS provides via elaborated afferent and efferent fibres a highly specific communication between the organs and the brain [6]. Therefore, the ANS is a likely candidate to mediate the effects of placebo interventions on end-organ functions. As will be shown below, the ANS also possesses a high functional specificity, which would even make it possible that organ-specific placebo effects—according to the suggestion given—can occur.

This review will summarize the available evidence for placebo effects on organ functions that are controlled by the ANS. First, current psychological approaches to explain placebo effects are discussed, and a conceptual framework that can account for placebo effects on organ functions is provided. Second, the organization of the ANS, its afferent and efferent pathways and important relay stations in the brain are summarized. Third, a comprehensive review of studies examining placebo effects on autonomic organ functions will be presented, thereby focusing on the cardiovascular, the gastrointestinal and the pulmonary system.

2. HOW TO EXPLAIN PLACEBO EFFECTS ON AUTONOMIC FUNCTIONS

Let us imagine a laboratory experiment aimed to investigate whether a placebo intervention can lower

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blood pressure, such as recently performed in our laboratory [7]. The participant, a male, healthy volunteer, was informed that he would receive one of three possible interventions: either a homoeopathic remedy to lower blood pressure or an identically looking placebo remedy in a double-blinded fashion or no remedy at all. After filling out some questionnaires, the experimenter asks him to sit in a comfortable chair and places a blood pressure cuff around his arm. The experimenter starts to measure blood pressure every 5 min and does not tell the participant about the results. After 30 min, the experimenter opens the randomization envelope, takes a pill out of a box and tells the participant that he would now receive a remedy that would either be a placebo drug or a homoeopathic drug, which will induce a measurable fall of blood pressure. The participant swallows the pill and the experimenter starts to measure blood pressure every 5 min for another half hour. After the participant has left the laboratory, the experimenter learns that systolic blood pressure levels had decreased from baseline to after treatment by 13 mmHg (from 113 to 100 mmHg), while diastolic blood pressure levels and heart rate remained fairly unchanged. When the code was broken, it was found that the participant had been allocated to the placebo group. Assuming that the fall in blood pressure was owing to a placebo effect, the question arises as to how the effect was mediated. In other words, how do we get from the suggestion of a hypotensive drug effect to a measurable fall in systolic blood pressure? In the following, two classical and one rather new explanation are provided.

A first theoretical explanation would be the lowering of blood pressure by pharmacological conditioning. This means that repeated pairing of a treatment's vehicle with its pharmacological effect will lead to a conditioned effect of the same type, even when the drug is replaced by a pill without pharmacological activity. However, this mechanism does not apply to our participant who had never before taken a hypotensive drug.

A second possible explanation would be to assume that the participant expected a hypotensive drug effect, and that this expectation caused the placebo effect. Kirsch [8] was one of the first to focus on the role of expectancy as a cognitive mediating variable for placebo effects. He assumed that verbal suggestions accompanying drug administration, such as 'this pill will lower your blood pressure', convey information about a non-volitional response. Accordingly, Kirsch termed the occurrence of non-volitional responses as 'response expectancies'. He hypothesized that humans may be 'hard-wired in such a way that expecting a subjective experience produces that experience, in the same way that deciding to emit a voluntary act (e.g. lifting one's arm) produced that act' [8]. Thus, expectancy theory claims that there is a consciously accessible representation of the outcome. That is, the expectation can be activated consciously when attention is directed to it [9]. In the case of our study participant, however, we are confronted with the fact that humans cannot directly experience and usually have no cognitive representation of changes in blood pressure.

An alternative explanation for placebo effects was recently proposed by Frenkel [10]. He refers to the view of the philosopher Maurice Merleau-Ponty that 'the understanding of the world that informs skilful, unreflective actions is not the same as, nor can it be reduced to, the understanding of the world that informs my reflective or cognitive acts'. Frenkel argues that without the prior bodily engagement in an activity, without lived experience, there is no way of representing it. According to this view, a conscious representation of the outcome should not be necessary for inducing a physiological placebo response. All a patient needs is to feel a sense that his response is appropriate to the situation and the verbal suggestions given to him. Thus, the practical significance afforded by a placebo will be determined by the degree of the match between the knowledge and the affordance of the situation [10]. Affordances have been defined as all 'action possibilities' latent in the environment [11].

To be more specific, in the case of our participant, the verbal suggestion of a hypotensive drug effect may have led to an activation of association areas that store memories of bodily and/or mental activities that commonly induce changes in blood pressure. This seems plausible, as most people have some general knowledge about the connection between enhanced bodily and/or mental activity and increased blood pressure. Taking the pill in this situation may then have led to associating the lowering of blood pressure with a state of reduced bodily or mental activity. Thus, without having an explicit understanding of blood pressure regulation or a conscious expectation of how a fall in blood pressure will feel, the participant may have responded in an appropriate bodily way.

According to this view, placebo effects result from the implicit affordance of the treatment situation to respond in a certain way. 'Implicit' refers to the fact that the patient is not directly instructed to lower his blood pressure by cognitive means. In contrast to the conditioning theory that requires prior drug exposure, and the expectancy model that builds upon consciously accessible representations of the outcome, the affordance model can account for physiological placebo effects in a more parsimonious way, namely without the difficulty of bridging the gap between a conscious expectation and a non-volitional response, such as a fall in blood pressure [10].

In addition to providing a conceptual framework to explain placebo effects on autonomic organ functions, we need to know the hardware that might mediate such effects. The following chapter will therefore provide a brief review of the ANS and its control by higher brain centres.

3. CENTRAL CONTROL OF ORGAN FUNCTIONS

All organ functions responsible for maintaining the internal milieu are under the control of the central nervous system. This control is necessary to allow for adjustments to varying internal and external demands, such as motor activities, physiological and mental stress, and emotions [6]. Apart from the hypothalamic neuroendocrine system, efferent control is exerted via the two branches of the ANS, namely the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The afferent feedback is conveyed to the

brain by sympathetic and parasympathetic afferents as well as by endocrine and humoral signals.

(a) *Peripheral organization of the autonomic nervous system*

Most target organs of the ANS are innervated by both the SNS and the PNS. In both systems, axons leave the central nervous system via cranial nerves or ventral roots to synapse upon neurons in specialized ganglia, which innervate all smooth muscles and glands. The cell bodies of the preganglionic sympathetic neurons are situated in the intermediate zone of the spinal cord. The preganglionic parasympathetic neurons are situated in the lower brain stem nuclei, most importantly in the dorsal motor nucleus of the vagus and the nucleus ambiguus, as well as in the sacral spinal cord. They project through cranial nerves (e.g. vagus, glossopharyngeus) and pelvic splanchnic nerves to the parasympathetic ganglia close to the target organs [6,12,13].

Preganglionic sympathetic and parasympathetic neurons are densely interconnected with regions receiving afferent signals from the tissues and organs of the body. Visceral afferents of the SNS are small-diameter (A-delta and C) fibres that terminate in lamina I of the spinal and trigeminal dorsal horns. Parasympathetic afferents are part of the cranial parasympathetic nerves (mainly the vagus nerve) and terminate in the nucleus tractus solitarius (NTS). Neurons in lamina I and the NTS project back to sympathetic and parasympathetic preganglionic neurons in the spinal cord and lower brain stem, respectively, thus enabling autonomic reflexes at the spinal and lower brainstem level [6,14].

(b) *The central autonomic network*

Preganglionic neurons are also under the inhibitory and excitatory control from a series of higher brain centres, which reach over several stations from cortical areas down to the lower brain stem and are summarized as the 'central autonomic network' (CAN; [15]). Importantly, each level of the CAN integrates information from higher order centres with afferent information [16]. These reciprocal interconnections allow for continuous positive and negative feedback interactions and integration of autonomic responses with varying internal and external demands, allowing for contextually appropriate response patterning [17,18].

Afferent signals from the ANS terminating in lamina I and the NTS are conveyed to higher brain centres via two main pathways. The phylogenetically older pathway connects to the parabrachial nucleus (PB), which relays the information to the hypothalamus and, via the thalamus, to limbic cortices, such as the anterior cingulated cortex (ACC) and the insular cortex. The second pathway—that exists only in primates—omits the PB and projects directly to a specific thalamo-cortical relay nucleus in the posterolateral thalamus (VMpo). The VMpo in turn projects to a discrete portion of the dorsal posterior insular cortex, which contains somatotopic and modality-specific representations of all afferent signals from the body and is therefore regarded as a primary sensory cortex for the physiological condition of the body [14,16,19]. Furthermore, the ascending afferent lamina I pathway in primates provides a direct thalamo-cortical connection that activates the dorsal anterior cingulated cortex [16].

There is increasing evidence to believe that interoceptive information in the posterior insula is integrated with homoeostatic, environmental, hedonic, motivational, social and cognitive information, resulting in a representation of 'self awareness' in the anterior insular cortex (AIC). The AIC in turn is densely interconnected with the ACC, presumably via von-Economo neurons that allow for fast communication between the two cortices [14]. The ACC itself has long been recognized to be involved in autonomic motor control [18,20]. Further brain areas, known to modulate the activity of the preganglionic ANS neurons, are located in the rostral ventrolateral and the ventromedial medulla, the periaqueductal grey, the hypothalamus, the amygdala and the prefrontal cortex [15].

One example as to how higher brain centres modulate ANS activity is the phenomenon of 'central command'. In the cardiovascular system, central command refers to changes that occur in anticipation of bodily demands, such as an increase in blood pressure and heart rate before movements are performed. There is ample evidence that such central command signals, initiated in the ACC and AIC, modulate autonomic motor programmes that are involved in the regulation of cardiovascular organs [6,21–24]. Another example is the cephalic phase response, which is stimulated by sight, smell or taste, and even by thoughts of appetizing meals, and leads to specific gastrointestinal changes that prepare the stomach for the ingestion and digestion of food [25].

It is not surprising that the anticipation of specific activities, such as bodily activity or eating, can induce functionally specific changes in the ANS. Animal studies have shown that the vagal afferent pathways from the periphery to limbic cortices are somatotopically organized [26], and neuroimaging studies have revealed equivalent results in humans [27]. Furthermore, SNS and PNS efferents are functionally specific, thereby allowing for a precise organ-specific regulation [6,12]. Indeed, an increase and a decrease of sympathetic and parasympathetic activation of single organs can co-occur in any combination [28]. Specific modulation of ANS functions by higher brain centres is enabled by the distributed organization of the CAN, which allows for multiple avenues to a given autonomic response. The functional specificity of the efferent pathways of the CAN is furthermore illustrated by studies showing different autonomic patterns for discrete emotions (for review, see [29]). Taken together, it is reasonable to suppose that the anticipation of a specific bodily effect during a placebo intervention may likewise induce an anatomically specific response.

4. PLACEBO EFFECTS ON AUTONOMIC FUNCTIONS

(a) *Cardiovascular system*

Parasympathetic efferents from the brainstem alter the force of heart contractions and heart rate via the vagus, while sympathetic efferents innervate blood vessels and

the heart. Heart rate under resting conditions is under tonic inhibitory control by parasympathetic influences [30], while blood pressure is mainly regulated by the SNS [31].

(i) *Blood pressure*

Hypertension is a chronic elevation of the 24 h mean blood pressure that is caused by dysregulations of the ANS, or, less frequently, by primary vascular or renal defects. Blood pressure fluctuates substantially with behaviour, but these changes are not responsible for the long-term regulation of blood pressure, except perhaps in the context of stress-related hypertension [32].

Changes in blood pressure following placebo administration have been observed in the placebo groups of many placebo-controlled studies, but adequate control conditions to separate placebo effects from regression to the mean, spontaneous fluctuations or habituation were usually not included. Moreover, several studies showed that placebo therapy reduced blood pressure when recorded by the physician, but not when recorded by a device in the absence of the physician [33–36]. This so-called 'white-coat' hypertension may be reduced when the patient gets to know the physician better, thereby mimicking a placebo effect [37]. In the following, I will therefore report only studies that include a control condition and thus allow for conclusions about the occurrence of 'true' placebo effects.

In a compelling experiment, aimed to investigate the contribution of subjects' expectation to blood-pressure lowering, 30 hypertensive patients were randomly allocated to two groups that both underwent three sessions of relaxation training. Half of the participants were told that relaxation would produce immediate effects on blood pressure, whereas the other patients were told that effects would be delayed, and that they might even experience a slight increase in blood pressure during the first three relaxation sessions. Credibility tests showed that both interventions were equally plausible. Results indicated a significant decrease in systolic blood pressure in the immediate group, when compared with those receiving the delayed lowering instructions, which showed no change. Diastolic blood pressure did not change in either group. This suggests that verbal suggestions may modulate the effect of medical interventions in hypertensive patients [38].

In another study, which investigated the effects of verbal suggestions more directly, 60 hypertensive and 60 normotensive subjects were assigned to one of four groups, namely blood pressure lowering instructions, no-change instructions, blood pressure increasing instructions or no instructions at all. After a first measurement of blood pressure and heart rate, subjects were given a brief explanation why it was necessary to repeat the measurement and were also told whether the pressure would rise, fall or stay the same. Then a second set of measurements was taken. In both groups, suggestion-specific changes of systolic blood pressure could be observed, while diastolic blood pressure and heart rate remained unaffected [39].

In a third study, the efficacy of continuous biofeedback of systolic blood pressure versus a credible sham-biofeedback was investigated. Subjects (58 hypertensive patients) and the observer were blind to the allocation of treatment. Biofeedback sessions consisted of three 12 min trials with the instructions to ignore blood pressure, to lower systolic blood pressure and to raise it. During the lowering condition, systolic blood pressure could be lowered by 5 or 6 mmHg in the active or placebo biofeedback group, respectively, while diastolic blood pressure and heart rate remained unaffected. In the raising condition, subjects achieved an average rise of systolic blood pressure by 7 or 9 mmHg, respectively, with concomitant increases in diastolic blood pressure and heart rate. These results showed the credible placebo biofeedback intervention to have significant short-time effects on systolic blood pressure, with specific changes in the suggested direction. However, the effects seemed to be restricted to the biofeedback sessions, as arm-cuff blood pressure measurements before and after the sessions as well as 24 h measurements did not change [40].

Interestingly, suggestions to increase systolic blood pressure will also change the heart rate and diastolic blood pressure but, as the above studies show, suggestions to lower systolic blood pressure will do so without affecting the other cardiovascular parameters. The latter finding was confirmed and extended to other autonomic parameters such as heart rate variability, gastric myoelectrical activity and skin conductance in a recent study conducted in our laboratory [7]. In brief, we randomly assigned 45 healthy volunteers to one of three groups: a no treatment group, a placebo group or a homoeopathic treatment group (as in the example above). The administration of placebo and homoeopathic treatment was double-blinded and accompanied by verbal suggestions that the homoeopathic remedy would lower blood pressure. Autonomic parameters were measured for 30 min before and after randomization/intervention. Participants in the placebo group showed a reduction of systolic blood pressure, which differed significantly from a slight increase in the no-treatment group. No effect on diastolic blood pressure or heart rate was found and skin conductance levels, gastric myoelectrical activity and heart rate variability were not affected by the intervention. Thus, the fall of systolic blood pressure induced by verbal suggestions appeared to be mediated specifically by ANS efferents involved in blood pressure regulation. However, how this is achieved, that is, how cortical processing of the placebo suggestion modulates the activity of preganglionic neurons so specifically, is far from clear.

There is to date only one study that has suggested sustained placebo effects in hypertensive patients [41]. It addressed the question whether oral and parenteral placebos would lower blood pressure to a similar extent. After carefully assessing baseline blood pressure, patients received in a double-blinded manner either a drug or placebo parenterally (74 patients) or orally (60 patients) for up to 143 weeks. Results revealed a transient reduction of systolic blood pressure in the parenteral placebo group that lasted upto 59 weeks, and a sustained decrease of diastolic blood pressure. In contrast, those given placebos orally showed no significant changes in either systolic or diastolic blood pressure throughout the study. Besides the interesting finding that invasive

Table 1. Mean duration of 30 contraction periods in the original [53] and the replication study [50]. Values are means ± s.d.

	duration of gastric periods[a] [s]			
	stimulant condition	control condition	relaxant condition	analysis of variance
original study				
post-intervention[a]	18.2 ± 2.2	19.3 ± 1.0	21.4 ± 2.7	$F = 4.40$, $p = 0.040$
replication study[b]				
baseline[c]	20.7 ± 1.0	20.9 ± 1.2	20.6 ± 1.0	$F = 0.55$, $p = 0.543$
post-intervention	20.8 ± 1.1	20.6 ± 1.1	20.2 ± 0.8	$F = 3.53$, $p = 0.040$
change[c]	0.2 ± 0.9	−0.3 ± 0.6	−0.5 ± 0.9	$F = 5.12$, $p = 0.012$

[a] $n = 6$; data extracted from fig.1 in Sternbach [53].
[b] To facilitate comparison with the original study, date are presented as slow-wave periods, which were computed from the average of zero-crossing intervals [54] multiplied by two.
[c] $n = 18$ for both relaxant and control conditions, $n = 17$ for the stimulant condition.

placebos were more efficacious than oral placebos (which actually receives support by other studies [42,43]), results also suggested that the significant reduction of blood pressure in the parenteral placebo group reflected a true placebo effect. However, the results of this early study await replication.

(ii) *Vasovagal syncope*

Vasovagal syncope (fainting) is characterized by a simultaneous enhancement of PNS activity and withdrawal of SNS activity. The resultant bradycardia and drop in blood pressure reduces blood flow to the brain and thus causes fainting. Many potential peripheral and central triggers have been identified. Among the latter are cognitive and emotional stimuli, such as the sight of blood or extreme emotional stress, which are thought to release a vasovagal response by modulating the activity of the NTS.

Despite the lack of adequately controlled studies, evidence for a possible placebo effect on vasovagal syncopes emerged by comparing the outcomes of several clinical trials (cf. [44]). The rationale was: (i) a randomized placebo-controlled trial of beta-blockers for the treatment of recurrent vasovagal syncope revealed no superiority of the drug above placebo [45], and (ii) a study comparing the effects of cardiac pacemakers and beta-blockers showed a significantly better outcome of patients in the pacemaker group [46]. (iii) Further evidence for the efficacy of pacemakers for vasovagal syncope was generated from a study comparing pacemaker implantation to no treatment that showed marked reduction of syncopes by the pacemaker [47]. However, (iv) in a subsequent randomized trial, when all patients were implanted with pacemakers but the device was turned on or off in a double-blinded fashion, the sham pacemaker treatment was as beneficial as the active device in reducing the occurrence of syncopes [48]. Taken together, these results suggested that recurrent vasovagal syncope can be successfully treated by placebo interventions, and that a sham pacemaker may induce a stronger placebo effect than a placebo pill.

(iii) *Coronary blood flow*

We recently investigated the hypothesis that placebo interventions may alter blood flow in the coronary arteries [49]. In a pilot study using 30 chest pain patients undergoing heart catheterization, saline was injected intracoronarily either with or without verbal suggestions of a vasodilatory effect on coronary arteries, and angiograms were performed immediately before and 60 s after the intervention. Remarkably, a significant difference in coronary diameter between groups was found. Contrary to our expectation, however, the verbal suggestion of vasodilation had induced vasoconstriction in the informed group. The possibility that verbal suggestions may modulate the tone of cardiac vessels is intriguing and will be investigated further.

(b) *Gastrointestinal tract*

(i) *Gastric contractions*

Gastric contractions (normally approx. 20 s in duration) are regulated by a pacemaker, which is under the control of the ANS. In particular, moderate vagal stimuli induce a slight increase of the duration of gastric contractions, whereas moderate vagal withdrawal subtly decreases the duration (cf. [50]). Stress and emotions are known to affect gastric pacemaker activity (e.g. [51,52]).

As early as 1964, a study on the effect of placebo interventions on stomach activity was performed [53]. Six subjects, believing to participate in a drug experiment, were given three times an identical placebo capsule with instructions that the expected 'drug' was stimulating, relaxing or not affecting the stomach activity. The capsules contained a magnet, which allowed recording of the stomach activity externally. The duration of gastric contraction periods was analysed and found to have decreased in the stimulant condition and increased in the relaxant condition when compared with the control condition (table 1). However, these results are counterintuitive, as the stimulant condition should have increased parasympathetic activity and thus increased the duration of gastric contractions, and vice versa.

Therefore, we essentially replicated the experiment but used modern electrogastrography (EGG) techniques by recording the myoelectric activity of gastric pacemaker and smooth muscle cells with electrodes placed on the abdomen [50]. Conforming with the original analysis of gastric contraction periods, the duration of gastric slow-wave periods in the EGG was estimated [54] for the first 30 contraction periods. As expected from physiological considerations, we found a significant effect of the placebo interventions, that is, a longer

duration of gastric contraction period during the stimulant condition than during the relaxant condition (table 1). In addition, subjects reported an enhanced or reduced stomach activity in the stimulant and relaxant conditions, respectively.

The fact that significant placebo effects in the opposite direction were found in the original study may have been owing to an anticipation of general changes (accompanying stimulation or relaxation) instead of specific gastric changes. However, this was not the case in the replication study, as changes in gastric slow-wave duration occurred independent of changes in non-gastric autonomic measures, namely heart rate, heart rate variability and skin conductance. Thus, the placebo effect could not be attributed to a generalized stress or relaxation response, but appeared to be organ-specific [50].

(ii) *Nausea*

Nausea is closely associated with the autonomic activity in the gut. When an individual develops nausea, the normal gastric slow-wave frequency of about 3 cpm is disrupted and replaced by a faster rhythm, between 4 and 9 cpm, called 'tachygastria' [55,56]. This induces an interruption of the normal contractile activity of the stomach, which results in a delayed gastric emptying and increased oral–cecal transit times [57].

In the 1950s, a series of elaborate case studies was performed [58] to investigate the influence of pharmacological, cognitive and emotional factors on gastric motility. By administering an emetic drug, a cessation of gastric activity was reliably induced within 10 min, while nausea and retching occurred a further 20 min later. Interestingly and pointing to the power of verbal suggestions, the effect of the drug could be reversed by verbal suggestions: two women, suffering from nausea and vomiting, were told that the drug would abolish nausea. Indeed, after 30 min, nausea subsided and normal contraction waves of the stomach (assessed by a balloon catheter) recurred. The author concluded that the human body reacts not only to direct physical and chemical stimulation but also to words and events which have acquired special meaning for the individual [58].

Confirming these early results, the recent update of the meta-analysis on placebo effects reported a small but consistent placebo effect on nausea [4]. Although this result was based on patient-reported outcomes, the close association between nausea and gastric function strongly suggests that this result cannot be explained by response bias, but is the result of a genuine psychophysiological response.

(iii) *Motion sickness*

Nausea is also a key symptom of motion sickness, which occurs in response to real or apparent motion and is provoked when conflicting inputs arise from the visual and vestibular systems. The ensuing perceptual mismatch results in a cascade of psychological and physiological reactions, including nausea, dizziness, urge to vomit and tachygastria in the EGG [59].

In a study on the effect of expectations on motion sickness symptoms and EGG, 80 patients were randomized in a 2×2 factorial design to either a high or a low expectation group, and to either a nauseating or a non-nauseating condition [60]. The high-expectation groups were made to expect symptoms of motion sickness, whereas the low-expectation groups were told that the procedure would evoke euphoria and excitement. Results revealed that verbal suggestions indeed modulated the development of motion sickness. However, participants in the high-expectation groups showed less motion sickness and tachygastria in the EGG than participants in the low-expectation groups. Thus, the anticipation of motion sickness symptoms had apparently a protective 'placebo' effect [60].

In an extension of this paradigm, placebo pills and verbal suggestions were used to manipulate participants before exposure to an optokinetic drum. Participants were led to believe that the pill would either protect against the development of nausea and motion sickness or that it would increase nausea symptoms. Again, the negative expectation (nocebo condition) had a protective effect on motion sickness severity and the development of tachygastria in the EGG, whereas the positive expectation (placebo condition) had no effect when compared with a control condition [61]. The protective effect of the nocebo conditions in both experiments may have been owing to an anticipatory stress response, as increased sympathetic activity and cortisol are known to reduce motion sickness [57,59].

(iv) *Bowel motility*

The effect of pre-operative suggestions on post-operative gastrointestinal motility was investigated in 40 patients in a randomized controlled trial. Patients who received the assurance that bowel motility would soon return demonstrated a significantly reduced time to the first passage of flatus compared with controls. Although no placebo intervention was involved, results nonetheless indicate that verbal suggestions can influence gastrointestinal motility in a clinically significant manner [62].

(v) *Functional gastrointestinal disorders*

In functional gastrointestinal disorders, symptoms often emerge despite the lack of structural abnormalities, such as inflammatory, infectious or neoplastic changes. According to present knowledge, symptoms can be owing to altered gastrointestinal motility, enhanced visceral sensitivity and/or brain–gut dysregulation. Several clinical trials on treating functional gastrointestinal disorders found in the placebo group a significant decrease in symptom severity [63,64]. However, there is only one study that also assessed gastric motility. Results revealed significant improvement in the motility index during placebo treatment in association with symptomatic improvement [65]. As in most clinical studies, an untreated control group was lacking and thus results await replication under more controlled conditions.

(c) *The pulmonary system*

The ANS plays an essential role also in regulating airway diameter. Both parasympathetic and sympathetic nerves innervate airway smooth muscles. The predominant contractile innervation of airway smooth muscle is parasympathetic and cholinergic in

nature. Sympathetic-adrenergic nerves play little if any role in directly regulating smooth muscle tone in the human airways [66]. Activation of vagal efferents induces bronchoconstriction, whereas sympathetic activation (probably mainly by circulating catecholamines) dilates the airways [6].

Asthma is one of the best studied conditions with regard to nocebo effects. Exacerbation of asthma is triggered by a number of factors, including psychological stressors, infection, inhalation of dry and/or cold air, exercise and exposure to allergens or other airway irritants. Until 1992, a series of at least 23 laboratory studies investigated the effects of verbal suggestions on lung function in asthma (cf. [67]). Subjects typically inhaled a substance they were made to believe to be a potent bronchoconstrictor, but in truth was saline. On average, every third of the asthmatic subjects (35.6%) responded with significant bronchoconstriction. The effect could be distinguished from changes owing to repeated inhalation of saline and did not depend on the kind of bronchial measures used—which may differ in effort and compliance afforded by subjects. Interestingly, non-asthmatic subjects also responded to suggestions of bronchoconstriction. However, these effects were short-lived and not of a magnitude to be classified as pathological.

Other studies showed that suggestions of bronchoconstriction could even antagonize the effects of active bronchodilators [68–70]. These verbally induced bronchoconstrictions appear to be mediated by vagal efferents as anticholinergic agents block the effect [69,71].

However, when the effect of bronchodilatory suggestions on non-constricted airways was tested, no such effects were found [72]. Nevertheless, following the inhalation of saline, an attenuation of bronchoconstriction to a metacholine challenge test was recently demonstrated in asthmatics under double-blinded conditions [73]. Furthermore, a number of studies also demonstrated that bronchoconstriction induced by saline inhalation and concomitant nocebo suggestions could be reversed when preceded by verbal suggestions of bronchodilation [69,71,74–76]. Thus, placebo and nocebo interventions appear to modulate airway diameter by increasing or decreasing bronchoconstriction.

One such study, in which the specificity of the placebo response was investigated by monitoring not only the lung function but also heart rate and skin conductance, deserves further discussion. In this study, the bronchoconstriction of airways was induced by inhalation of saline together with appropriate suggestions (nocebo condition). This could be prevented by a prior inhalation of saline, which now was suggested to be a bronchodilator (combined placebo and nocebo conditions). However, the effects of the nocebo condition on heart rate and skin conductance remained in the combined condition. As the placebo effect on lung function was independent of the nocebo effect on heart rate and skin conductance, it can be concluded that the placebo effect was organ-specific [76].

The question as to whether placebo or nocebo interventions can affect the course of asthma in the long term has not been sufficiently investigated. The marginally significant pooled placebo effect in four asthma trials included in the meta-analysis of Hróbjartsson & Gøtzsche [4] was mainly driven by one trial in asthmatic children that showed a reduction of 30 per cent in clinical visits both in the placebo group and in the active treatment group, when compared with a reduction of only 6 per cent in the no-treatment group [77]. No physiological measures were taken in this study, and the reduction in the placebo group could have been due either to coping with the disease or to improved lung function, or both.

A recent study randomized 601 patients with asthma to a four-week pharmacological treatment, placebo treatment or usual care [78]. In addition, the drug or the placebo was either presented in a neutral or in an enhanced way using positive suggestions and computer animations. The latter only modulated the patient-reported outcomes, such as the score in an asthma-control questionnaire in the placebo group. More importantly, however, the primary physiological outcome (morning peak expiratory flow) improved significantly in the 336 placebo-treated patients when compared with usual care.

(d) *Miscellaneous*

Conditioned immune responses have been demonstrated in several medical conditions, such as psoriasis [79], allergic rhinitis [80] and lupus erythematosus [81]. There is accumulating evidence that afferent and efferent ANS pathways are mandatory for this type of placebo effect [82].

Further studies investigated placebo and/or nocebo responses on pupil size and accommodation [83], urinary function [84–86] and sexual function [87–90]. However, these studies were often small or preliminary, and therefore the effects of placebo interventions on the respective organ systems await further investigation.

5. CONCLUSION AND FUTURE DIRECTIONS

The studies presented in this review clearly indicate that several cardiovascular, gastrointestinal and pulmonary functions can be altered by placebo interventions. Most of the studies were performed under laboratory conditions, but the few clinical trials so far conducted also revealed promising results. Four experimental studies investigated the autonomic pathways involved in placebo responses, and three of these provided first evidence for organ-specific effects, namely on blood pressure, gastric motility and lung function. However, more studies are needed to elucidate brain centres and efferent pathways involved in peripheral placebo effects. Another question that awaits systematic investigation is the modulation of autonomic responses by classical conditioning, which may lead to alternative treatment strategies for asthma, hypertension and gastrointestinal disorders in the future [91].

One of the major handicaps for more research in this area is the lack of a conceptual framework that can explain the (specific) physiological changes induced by verbal suggestions. The model of implicit affordance provided by Frenkel [10] offers a sustainable bridge from mind to body, as placebo effects are no longer believed to be dependent on conscious representations of expected outcomes, but on 'lived experience'. For example, the anticipation of a hypotensive drug effect

may activate specific networks in the brain engaged in blood pressure control, because humans have a general knowledge which allows them to associate blood pressure changes with alterations in (bodily and mental) activity. The practical significance of the affordance model could be tested by investigating placebo effects in children, who should have gained some experience with pain and pain relief, but presumably cannot yet relate blood pressure changes to alterations in activity. Hence, they should be able to show analgesic responses in a placebo pain trial, but not hypotensive effects in a blood pressure placebo trial. Frenkel's affordance model may also be helpful for improving patient care, as it suggests that placebo effects may be maximized when doctors try to formulate verbal suggestions accompanying treatment prescriptions in such a way that they match the personal experience of a patient. Hopefully, this review will stimulate further research in this fascinating, but still widely neglected field of placebo research.

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