

Review

Rethinking Explicit Expectations: Connecting Placebos, Social Cognition, and Contextual Perception

Katharina A. Schwarz,^{1,2,*} Roland Pfister,¹ and Christian Büchel²

Expectancy effects are a widespread phenomenon, and they come with a lasting influence on cognitive operations, from basic stimulus processing to higher cognitive functions. Their impact is often profound and behaviorally significant, as evidenced by an enormous body of literature investigating the characteristics and possible processes underlying expectancy effects. The literature on this topic spans diverse fields, from clinical psychology to cognitive neuroscience, and from social psychology to behavioral biology. We present an emerging perspective on these diverse phenomena and show how this perspective stimulates new toeholds for investigation, provides insight in underlying mechanisms, improves awareness of methodological confounds, and can lead to a deeper understanding of the effects of expectations on a broad spectrum of cognitive processes.

Expectancy Effects on Cognition and Behavior

Expectancy effects are ubiquitous. Be it in clinical contexts [1–5], academia [6,7], or sports [8–10], their impact is investigated, discussed, and debated in diverse scientific fields. Part of their appeal is certainly their profound impact on a wide range of cognitive processes such as perception, motor performance, working memory, and subjective evaluations, among others. However, there is more to it than scientific interest: knowledge about these effects and their consequences also informs applied fields such as modern clinical practice and scientific methodology [1,2,4]. By definition, an **expectation** (see Glossary) is a 'belief that something will happen or is likely to happen' (www.merriam-webster.com/dictionary/expectation). As such, the word 'expectation' entails a variety of concepts, and it is therefore important to clarify which type of expectations will be discussed in this review. Expectations can stem from implicit knowledge about statistical regularities, which is then used incidentally to adapt behavior [11–13], or they can stem from explicit beliefs about, for instance, situations, other agents, oneself, or specific events. Explicitly acquired expectations can be further subdivided into those that are deliberately employed for decision making and those which exert their influence incidentally. It is this latter type of expectations on which we will focus in this review.

A particularly well-studied effect of such expectations on perception and behavior is the **placebo effect**. That is, the expectation of symptom improvement can evoke strong effects on psychological variables and bodily functions, to the point of significant pain alleviation and improved motor performance. However, the impact of expectations is not restricted to treatment

Trends

A lasting impact of expectancy effects has been documented in clinical and non-clinical settings.

Placebo/nocebo effects are major topics for study in clinical research, whereas non-clinical research has focused on phenomena such as stereotype threat and self-efficacy.

Recent studies have begun bridging these fields by investigating different ways of inducing expectations and new types of outcome variables.

Commonalities between superficially dissimilar expectancy effects are beginning to emerge.

¹Institute of Psychology, University of Würzburg, Würzburg, Germany ²Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

*Correspondence: katharina.schwarz@uni-wuerzburg.de (K.A. Schwarz).





outcomes - expectations elicited in social situations can have similar effects on perception and behavior. Moreover, basic perception itself has been studied in relation to influences by expectations. In light of the huge body of literature on such expectancy effects, the impact of expectations on perception and behavior seems to be profound, elicited by a wide range of situational and personal factors, and pertaining to an equally wide range of outcome variables.

However, most of the fields describing and investigating these effects have so far worked in parallel, rather than in conjunction. The goal of this review is to provide a first step into broadening the current view to integrate multiple approaches and instances of expectancy effects into a single framework. This framework specifically considers general expectations pertaining to entire situations, time-periods, or treatments rather than expectations pertaining to specific singular events, which have been studied extensively in domains such as perception and motor control [14,15]. Comparing different instances of expectancy effects reveals startling similarities as well as discrepancies between these effects. However, so far, few studies have attempted to bridge these different fields, and the methodological focus within these fields has been decidedly different, as we will argue in the course of this review. Thus, instead of presenting a full-scale model, which seems premature at this time, we hope to provide strong incentive for future scientific investigations in this vein. To this end, we will present an emerging perspective on the behavioral and physiological effects of such general expectations, and show how this perspective has the potential to provide new insights into the mechanisms involved, stimulate new toeholds for experimental approaches, improve awareness for methodological pitfalls, and ultimately lead to a deeper understanding of the effect of expectations on a broad spectrum of cognitive processes.

Placebo and Nocebo: Treatment Expectations in Clinical Contexts

Expectancy effects in clinical contexts have been reported for centuries (Box 1) [16,17], and recent interest in this topic has led to a surge of investigations concerning the behavioral and neurophysiological underpinnings of these phenomena. The most intensively studied phenomena in this context are placebo and **nocebo effects** on pain [3,18-25], although recent studies have targeted a wide range of additional fields such as psychiatric conditions, respiratory diseases, immune function, and many more [4,5,26-29].

To gain traction in the flood of empirical evidence for placebo and nocebo effects, recent efforts have aimed at providing theoretical frameworks to account for the many aspects associated with treatment expectations. A learning perspective on placebo responses suggests that conditioning cues connected to prior experience with the treatment work in concert with verbal and social

Box 1. Historical Roots of the Study of Expectancy Effects

In 1787 a textbook on empirical psychology written by Ferdinand Ueberwasser dedicated a paragraph to the then current knowledge on the 'impact of the imagination on the body'. In particular, Ueberwasser describes how 'bread crumbs, taken in the shape of pills have, by means of vivid imagination and expectations, yielded the same effects as the medication itself' ([117], p. 141; for a perspective see [16]) and that 'vivid imaginations, confident expectations of recovery or relief, and therefore firm trust in the physician, or in the medication alone, even if the medication is without effect by itself, can sometimes lead to real relief, or even recovery, for the invalid' ([117], p. 146). Ueberwasser does not limit his descriptions to placebo effects, he generalizes that 'these and other observations lead to the general law of the impact of imagination on the body: especially those bodily changes that are caused by external and internal sensations are reinstigated by the awakened feelings of these sensations, though only more or less, and to a weaker degree' ([117], p. 142). Moreover, Ueberwasser emphasizes in his textbook that expectancy effects rely on physiological changes originating in the brain: 'If an image is awakened in the mind, then (as physiology teaches us) specific changes in the brain arise, corresponding to this image and its intensity [...]. Now, because the nerves originate in the brain and because they are the instruments of sensation and movement in the entire body, it ensues that also other, more remote body parts can be affected by imagination' ([117], p. 143).

It has been over 220 years since Ueberwasser described the impact of expectations on body and mind, and we are only now about to fully appreciate the widespread influence of expectations on cognition and behavior.

Glossary

Expectation: a belief that something will happen or is likely to happen (www.merriam-webster.com/ dictionary/expectation). Please note that, in this review, we only focus on explicit expectations (see the main text for a more detailed definition). Hawthorne effect: investigating a specific question may affect outcome measures associated with that question simply as a consequence of the investigation itself. This effect was first reported in a study on worker productivity in the Hawthorne Works of the Western Electrical Company in Chicago during the 1920s and 1930s. It has been controversially discussed since then.

Nocebo effect: a genuine, negative psychological or physiological effect that can be attributed to receiving a substance or undergoing a procedure, but that is not due to the inherent powers of that substance or procedure (adapted from [23], p.326). Nocebo hyperalgesia: nocebo effects in pain perception leading to increased pain sensation.

Placebo effect: a genuine, positive psychological or physiological effect that can be attributed to receiving a substance or undergoing a procedure, but that is not due to the inherent powers of that substance or procedure (adapted from [23], p.326). Placebo hypoalgesia: placebo effects in pain perception leading to decreased pain sensation.

Pygmalion effect: the phenomenon that the expectations of an evaluator regarding the performance of the individual being evaluated affects that performance. This was first reported in a teacher/classroom situation where teachers were led to believe that particular students were particularly likely to improve over time. Although these students were, in fact, picked at random, later analysis revealed that these students improved indeed more than other students who had not been predicted to improve.

Response expectancy theory: at its core, this theory proposes that expectations can directly affect subjective experience without other mediating factors.

Self-efficacy: the belief about one's ability to perform particular actions required by the situation. Social identity threat: the

psychological state that occurs due



cues to generate widespread changes in the central nervous system which, in turn, lead to outcome changes based on treatment expectations [30,31]. Moreover, predictive coding accounts of placebo effects go one step further in postulating that the integration of learning and prior experience during placebo hypoalgesia occurs at multiple levels via recurrent systems in the ascending and descending pathways connected to placebo hypoalgesia [3,32].

These theoretical frameworks are specifically concerned with the role and implementation of both, prior experience and verbal suggestions, in the generation of placebo expectancies. Indeed, this question has occupied researchers for some time [21,23] and, although findings have been somewhat controversial, a lasting consensus in the field assumes roles for both processes in the formation of treatment-affecting expectations. Whereas verbal suggestions alone may or may not lead to changes in pain experience, the combination of conditioning mechanisms with verbal suggestions leads to robust placebo effects (Figure 1) [33,34]. This finding stands in contrast to nocebo hyperalgesia where verbal suggestions alone elicit strong nocebo effects without any further conditioning procedure [35]. Moreover, it seems that lessons from prior experience with the treatment cannot only stem from one's own experience, but also from the observation of the experience of others, lending a strong social component to treatment expectancy effects [34]. This social aspect in placebo hypoalgesia might be modulated by oxytocin and vasopressin, that is, hormones involved in the regulation of social behavior [36,37].

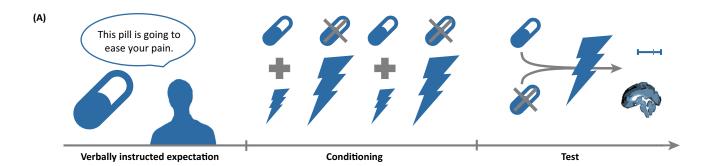
Diverse physiological systems underlie the placebo effect, resulting in the idea of not one single effect, but many (Figure 2) [38]. Endogenous opioids are released during placebo hypoalgesia [39-42] and have effects on the rostral anterior cingulate cortex (rACC), the orbitofrontal cortex (OFC), lateral prefrontal cortex (IPFC), the anterior and posterior insular cortex (alns, plns), the nucleus accumbens (NAcc), the amygdala (Amy), and the periaqueductal grey (PAG) [24,43]. The modulatory descending pain control system further includes the thalamus, the hypothalamus, and the rostral ventromedial medulla (RVM), and descends even further down to the dorsal horn in the spinal cord [41,44-46]. Nocebo hyperalgesia additionally elicited modulated blood oxygen level-dependent (BOLD) activity patterns in the hippocampus [47,48]. Other transmitter systems have also been implicated in placebo effects, such as the endocannabinoid system in placebo hypoalgesia [49] and the release of endogenous dopamine, especially in the NAcc, in Parkinson's disease [26] and in placebo hypoalgesia [43,50]. The dopamine system and the NAcc are both strongly implicated in the processing of reward, leading to the formulation of the placebo-reward hypothesis [51]. This hypothesis states that the expectation of a treatment effect, that is, of clinical benefit, could be considered a reward and therefore rely on similar structures to reward processing [51].

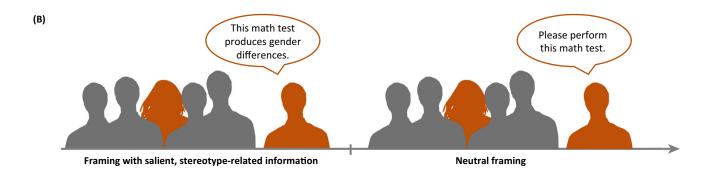
Treatment expectations have been studied almost exclusively in typical clinical outcome measures such as pain experience, motor performance, or scores on diagnostic scales. However, recent efforts have broadened this approach by targeting cognitive functions including working memory and cognitive control [52,53]. Interestingly, placebo instructions did not enhance actual performance in these studies, but significantly influenced the participants' subjective perception of their performance [53] and produced changes in subjective drug effects and in the participants' mood [52,54]. This pattern has also been found for some clinical outcome measures [28]. These findings suggest that the influence of treatment expectations on subjective measures is more widespread and robust than their influence on objective measures. A possible explanation for this difference can be found in response expectancy theory [55,56]. This theory postulates that expectations can directly affect subjective experience; in other words, the effects of expectations on subjective experience are at least partly unmediated [23,55,56]. However, this hypothesis only applies to subjective experience and its direct physiological correlates, whereas other factors are needed to mediate the effects on objective measures.

to awareness that one might be devalued or thought about negatively because of one's membership in a particular social group (cf. [69]). Stereotype threat: the situation in which one is aware of (a) negative stereotype(s) about one's group and one is concerned about confirming this negative stereotype and about being judged because of this stereotype (e.g., [6,62]). This threat potentially leads to performance decrements. Stereotype threat is considered a form of social identity

Winner and loser effects: the winner of a contest between two animals has a higher probability of winning a subsequent encounter, whereas the loser has a higher probability of losing a subsequent encounter, irrespective of opponent identity, size, and other external







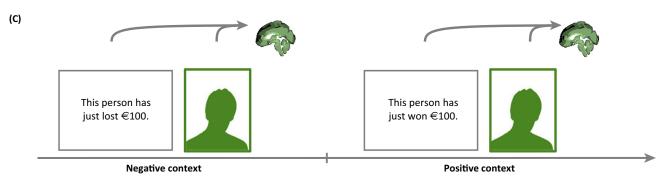


Figure 1. Exemplary Paradigms Targeting Expectancy Effects in Different Fields. Typical study designs employed to investigate treatment expectancies in pain modalities (A), social expectancies such as stereotype threat (B), and contextual modulations of face perception (C). Whereas prior experience with the treatment at hand plays a big role in the study of treatment expectancies (to the point where such prior experience is artificially induced via conditioning paradigms), no such learning component is introduced in typical social expectancy studies, nor in studies targeting basic (visual) perception. Outcome measures include subjective ratings (A,C), performance in tests targeting higher cognitive functioning (B), motor performance (A,B), and (neuro-)physiological recordings (A-C).

The study of treatment expectations has stimulated a spirited debate on how to use the emerging knowledge on placebo and nocebo effects in clinical practice [2,4,38,57-59]. Possible direct applications of the gained knowledge are manifold and form a promising avenue towards improving care and treatment of patients. However, clinical practice is not a faceless operation; it has at its core social processes such as clinician-patient interactions. As it is, these social settings hold a prominent spot in the generation of treatment expectations [31,34], and they even harbor their own types of expectations within and outside of the clinical environment. The next section will focus on such expectations.



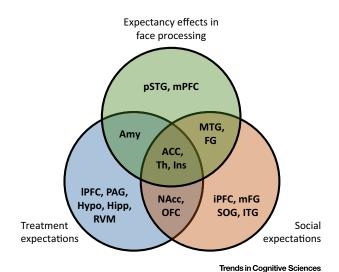


Figure 2. Overlap of Brain Regions Associated with Expectancy Effects in Different Fields. Current knowledge of prominent brain regions associated with treatment expectations, social expectations, and expectancy effects in face processing, and their overlap. Please note that some brain regions listed here are possibly not general modulatory areas but might be associated with the most prominent outcome measures investigated in the different fields, such as pain processing in the case of treatment expectations. Abbreviations: Amy, amygdala; ACC, anterior cingulate cortex; FG, fusiform gyrus; Hipp, hippocampus; Hypo, hypothalamus; Ins, insula; iPFC, inferior prefrontal cortex; ITG, inferior temporal gyrus; IPFC, lateral prefrontal cortex; mFG, medial frontal gyrus; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal grey; pSTG, posterior superior temporal gyrus; RVM, rostroventral medulla; SOG, superior occipital gyrus; Th, thalamus.

Social Expectancies and their Effects

The interactive element of social settings adds another layer to expectancy effects. Not only one's own expectations, but also those of others, are relevant in human interaction - and these latter expectations are particularly relevant for oneself when they relate to oneself. For instance, the expectations of teachers have been shown to affect their students' academic performance (**Pygmalion effect**) [60,61]. Furthermore, even if the expectation is not issued by a specific person, but instead by society as a whole in the form of predominant stereotypes, these expectations can have negative effects on stigmatized individuals (stereotype threat). Stereotype threat describes the phenomenon that the performance of an individual can be severely impaired when that individual is aware of negative cultural stereotypes denying him or her proficiency in the ability in question. For example, when a test was labeled as diagnostic of intellectual ability, African American college students performed worse than their Caucasian counterparts, but this effect did not occur when the test came without such labeling [62]. Even though some seminal observations have been proven difficult to replicate - such as those relating to gender-based stereotypes and math performance (https://replicationindex.wordpress.com/2015/01/06/why-are-stereotypethreat-effects-on-womens-math-performance-difficult-to-replicate/) - many studies have shown $effects \ of \ stereotype \ threat \ in \ various \ stigmatized \ groups \ [6,63-65]. \ Most \ of \ these \ findings \ concern$ outcome measures related to higher cognitive functions such as working memory (Figure 1). Recent evidence further points towards stereotype threat effects on basic processes such as motor performance [8-10,66]. In a broader sense, effects of stereotypes could be construed as nocebo effects because they epitomize the effects of negative expectations on higher cognitive functions and motor performance. This poses the question whether mechanisms behind these two phenomena overlap in parts or whether they are fundamentally different.

An influential model on stereotype threat postulates that such threat diminishes executive function by interfering with working memory in cognitive and social tasks. This effect is mediated by several processes, including the biased appraisal of personal experiences, constant



monitoring processes, and the suppression of unwanted thoughts [65]. Even so, further factors might affect threatened individuals. Such an additional factor seems to be the individuals' selfefficacy because stereotype-vulnerable individuals have been found to show more unstable self-efficacy patterns than non-vulnerable individuals [67].

The exact underlying physiological changes connected to such social expectancy effects remain elusive at present, but initial evidence allows first insights into possible mechanisms mediating this effect. Social identity threats have been found to increase salivary levels of the stress hormone cortisol [68,69]. Cortisol is part of the physiological stress response and its release is stimulated via the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Cardiovascular threat responses and increases in proinflammatory cytokines have also been connected to stereotype threat [70–72]. Moreover, stereotype threat affects neural processing in response to errors and negative feedback [73,74] as well as electroencephalographic (EEG) activity in the default mode network [75]. A possible brain area moderating changes in neural activity is the ACC, which has shown stronger BOLD activity in threatened than in non-threatened individuals [76,77].

However, the focus of studies on social expectancy effects has mainly been directed at characterizing the phenomenon at a behavioral rather than physiological level. This contrasts strongly with research on placebo effects where the focus is on physiological mechanisms and clinical outcome variables. While there seems to be overlap between BOLD activity associated with both expectancy effects (Figure 2), future research will be necessary to systematically compare possible mechanisms at the behavioral and physiological levels in placebo and social expectancy effects. First studies in this direction have targeted social expectations in clinical practice, showing that stereotype threat effects can promote avoidance behavior in patients, impair communication, and lead to poorer adherence to treatment plans [1]. Social expectancies can also influence clinical outcome measures more directly. For instance, common expectations based on traditional gender roles also seem to partly mediate sex differences in pain responsivity [78–82]. Moreover, manipulating gender roles affects the perception, processing, and report of pain [83-86].

Modulations of Perception

Expectancy effects in clinical or social contexts alike, are based on how individuals perceive their environment. However, expectations can also affect how this environment is perceived. Contextual cues and prior notions are analyzed and integrated with the sensory input in question, resulting in a conscious perception of our environment that is colored by expectations. Indeed, prior expectations have been shown to influence stimulus processing already in the visual cortex [87]. This interplay of basic stimulus input and top-down modulation has been extensively investigated in various fields, such as face perception [88–94], language processing [95–97], and the perception of ambiguous figures [98,99], among many others. It would be beyond the scope of this review to account for all findings in this regard (see e.g., [100]). Instead, we have elected to exemplify the impact of expectations on perception by a closer view on contextual effects on face perception and processing, a field that has been well investigated with both, behavioral and physiological measures.

Contextual elements conveying affective or self-referential information have been found to modulate the perception or, at the very least, the judgment of human faces (Figure 1) [93,101,102]. Emotions in facial expressions are categorized depending on an interaction between the facial expression itself and affective contextual information. For example, faces expressing disgust can be perceived as angry or even proud if the context indicates the validity of such a categorization [101]. Participants rated neutral faces as more arousing when they were cued by self-related information as opposed to other-related information, and they perceived



neutral faces cued by negative and positive information as more negative and positive, respectively [93,102]. Facial and contextual information thus seems to be automatically and routinely integrated to form a common perception [88,103]. This modulation of face perception by expectations is accompanied by differential neural processing of these stimuli dependent on context. BOLD activity in the fusiform gyrus (associated with face processing), the Amy (associated with affective processing), the medial prefrontal cortex, and the ACC, among others, proved to be sensitive to additional contextual information (Figure 2) [89,90,93]. Neural processing seems to be affected in its early and its late stages [92,102]. Interestingly, several of the brain areas showing differential BOLD activity in response to different contextual information have also been affected by other types of expectancy effects, as argued above (Figure 2). Moreover, facial expressions are processed differently under social threat, especially in individuals with dispositional social anxiety, that is, in individuals predisposed to expect negative feedback [91,93]. This evidences considerable overlap between social threat effects and modulation of face perception.

The investigation of expectancy effects has primarily focused on humans. We provide short remarks about experience-based expectancy effects in non-human animals in Box 2.

Friend or Foe? Methodological Implications of Expectancy Effects

As outlined in the preceding paragraphs, expectancy effects are found at all levels of cognitive processing from perception to ultimate behavior, with effects on behavioral measures and physiological parameters. It seems reasonable to assume that these effects cannot only be studied experimentally but that these effects also affect our experiments when we actually wish to study something else entirely. Various examples of such inadvertent biases have been reported and, in part controversially, discussed in the past. Awareness of these potential pitfalls during study design is crucial to allow experimenters to improve interpretability of the later results.

While the placebo effect, for instance, is now a popular topic of scientific investigation, it has long been seen (and still is) as a cumbersome confound in clinical research that should be minimized if possible [4]. This is not an easy task because placebo responses to a given treatment vary between individuals [104] and responses to different placebo treatments vary within individuals

Box 2. Expectancy Effects in Non-Human Animals?

It seems particularly difficult to study the influence of expectations in non-human animals, especially the influence of explicit expectations on which we focus in this review. However, interesting comparisons between human and animal research can be drawn if the concept of 'expectations' is viewed more broadly.

An example of introducing the study of traditional expectancy effects to non-human animals is the placebo effect. Placebo effects elicited by conditioning mechanisms have been demonstrated in mice and rats [118–121]. Interestingly. several parallels with findings in humans have emerged: placebo effects seem to be mediated via opioidergic pathways when the conditioning process employs an opioidergic drug; however, if a non-opioid is used for conditioning, placebo effects do not depend on opioidergic pathways [120]. Similar findings have been reported in human studies [39]. These studies suggest that there seem to be, at least partly, comparable processes in humans and rodents regarding placebo effects.

Other taxa have also shown evidence of experience-based expectations, including other mammals, fish, birds, reptiles, crustaceans, arachnids, and insects [122-125]. Winner and loser effects are a prime example of direct effects of experience on subsequent behavior. More precisely, animals that have won a previous fight are more likely to win the next fight, and animals that have lost the previous fight are more likely to lose the next fight, than could be explained by external features such as opponent identity, size, etc. [125]. Interestingly, evidence suggests that there is an adaptive advantage for both, winners and losers, if animals behave according to their social experience [124]. It seems that winner and loser effects are partly based on a re-assessment of one's own fighting ability [123,125,126], which then in turn affects the fight outcome. This finding offers striking resemblance to the self-efficacy phenomenon in humans [127]. Moreover, winner and loser effects seem to primarily affect the subjective perception of the fighting parties, not objective variables of actual fighting ability [123,128] - a phenomenon that also bears resemblance to expectancy effects in humans, as we have discussed in the main text.



[105]. Furthermore, placebo effects might interact with treatment [106,107]. Consequently, this leads to an inability to reliably predict expectancy effects in any given individual. Even when experimenters are careful to minimize placebo effects by choosing active control groups, these active control groups and the treatment group could nevertheless differ in prevalent expectations in the (supposed) treatment, which in turn affects treatment outcome [108]. Indeed, patient and control groups in clinical research might generally differ not only in terms of health but also in terms of performance expectations. For instance, patients after a neurological injury expect cognitive deficits [109] and such differences in expectations potentially affect a variety of outcome measures [85]. That is, the very process of investigating a particular disease might be biased by expectations if the data are only compared to a healthy control group [85].

In addition to expectancy effects in clinical research, potential confounds have been documented in a range of other fields. Pertinent examples include the **Hawthorne effect** [110–112] and the Pygmalion effect [60,61]. Both of these effects claim that outcome measures could be altered through an intervention not because of the effectiveness of the intervention itself but simply because an intervention was performed (Hawthorne effect) or because the experimenter (or teacher in case of traditional Pygmalion effects) expected a change to occur. Avoiding such biases seems vital for data interpretation. Reasonable countermeasures include the use of active control groups which also receive interventions and, if possible, blinding experimenters to the specific experimental condition investigated, especially when experimenters are asked to assess the performance or progress of participants.

Towards a Holistic View of Expectancy Effects

The previous paragraphs constitute a synthesis of expectancy effects in prominent scientific fields. To characterize specific effects of specific expectancies, researchers in these fields have mostly worked within their own disciplines. This approach is excellent when the goal is to delineate the behavioral and physiological details of the expectancy effects in question, and to later use these findings to improve specific situations and procedures in real life. This has been done, for example, in the case of expectancy effects in clinical practice [2,4,38,57-59] as well as in stereotype threat situations in academia [113,114].

However, we suggest here that this approach can be complemented by interconnecting these separate fields. Two main reasons make such efforts appear promising: (i) as outlined throughout this review, there is substantial overlap between different expectancy effects, in their effects on outcome measures in controlled studies as well as in real life situations (e.g., in clinical practice), and (ii) interconnecting these fields into a holistic approach to expectancy effects provides synergies, offers a deeper understanding of expectancy effects on perception and behavior, and provides new directions for theory-driven investigations.

- (i) The previous paragraphs of this review have revealed a substantial overlap between different expectancy effects. For instance, treatment expectations affect clinical outcome measures such as pain, motor performance, or questionnaire scores, and so do social expectations. Moreover, such expectations might also affect a variety of other factors such as the participants' perception of the experimenter or physician. Little is known whether and how such effects interact, and whether these modulations are separate effects or combine to a single modulatory signal.
- (ii) Interconnecting research on different types of expectations appears to be a promising avenue to elaborate the mechanisms underlying their effects. For example, placebo and nocebo studies emphasize the impact of both, situational cues as well as previous experience, on expectancy effects (Figure 1). Such a strong learning component is also likely to play a role in social expectations. Although stereotype threat has been shown to also occur in typically non-threatened individuals when situational cues provoke a threatening environment [115], it is well conceivable that previous experience with performance



decrements under stereotype threat increases the impact of stereotypes. Moreover, different types of expectancy effects come with distinct methodological tools: whereas social expectations have been mostly investigated in behavioral studies with a strong emphasis on forming a conceptual framework, studies on treatment expectations have focused more on the physiological underpinnings mediating the behavioral effects. Because of this discrepancy, it is at this point difficult to ultimately argue for a common physiological mechanism, but it is evident that there is some overlap here as well (Figure 2). Modulatory areas in the brain, such as the ACC, have been found to show differential BOLD activity to treatment and social expectations alike as well as to contextual modulations of perception [24,41,43,76,94]. The dopaminergic system, including the NAcc, also seems to be involved in the mediation of different expectations, as has been found in studies investigating traditional treatment expectations on clinical outcomes as well as treatment expectations regarding cognitive enhancement [26,43,50,51,54]. The NAcc is further involved in the modulation of pain processing by stereotype-related information [85], and specific dopaminergic genes have been associated with susceptibility to external suggestions [116]. The physiological stress response seems a likely candidate to mediate negative expectations because it has been implicated in social identity threat [68,69], in effects of stereotype-related information on pain processing [85], as well as in the nocebo effect [40]. More studies spanning these different fields will be necessary to elaborate on a common framework for different expectations.

A holistic view on expectancy effects thus inspires new toeholds for investigation and can provide new ideas on how to approach a particular subject of study. Questions arising include, for instance, the following: is the mental downward spiral involved in stereotype threat possibly also a factor in nocebo effects? Does the reversibility and longevity of stereotype threat depend on the amount of previous experience with performance decrements under stereotype threat? Several such key questions emerging from a holistic view on expectancy effects are outlined in the Outstanding Questions; they clearly await empirical investigation and may lay the foundation for a comprehensive theoretical model covering expectancy effects in many different fields.

Concluding Remarks

Expectancy effects are a widespread phenomenon, and they come with a lasting influence on cognitive operations, from basic stimulus processing to higher cognitive functions. In this review we have aimed at providing a synthesis of expectancy effects in prominent scientific fields, and at presenting first steps towards a common framework for these diverse phenomena. We demonstrated how such a common framework may stimulate new directions for investigation, may give insights into general physiological underpinnings of modulatory effects, and increase awareness of methodological confounds associated with expectations. There are still many open questions regarding the impact of expectations on cognitive processes. However, with the multitude of findings we already have at hand, and more yet to come, a holistic view on expectancy effects might be within our grasp.

Acknowledgments

C.B. is supported by the European Research Council (ERC-2010-AdG 20100407) and by the Deutsche Forschungsgemeinschaft (Research Group FOR 1328 and SFB 936). The sponsors had no role in the drafting of this manuscript.

References

- 1. Aronson, J. et al. (2013) Unhealthy interactions: the role of 4. Enck, P. et al. (2013) The placebo response in medicine: minimize, stereotype threat in health disparities. Am. J. Public Health 103, 50-56
- 2. Bingel, U. (2014) Avoiding nocebo effects to optimize treatment outcome, JAMA 312, 693-694
- 3. Büchel, C. et al. (2014) Placebo analgesia: a predictive coding 6. perspective. Neuron 81, 1223-1239
- maximize or personalize? Nat. Rev. Drug Discov. 12, 191–204
- Kirsch, I. et al. (2008) Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration, PLoS Med. 5, e45
- Spencer, S.J. et al. (2016) Stereotype threat. Annu. Rev. Psychol.

Outstanding Questions

Questions arising from a holistic view on expectancy effects are manifold: is the mental downward spiral involved in stereotype threat possibly also a factor in nocebo effects? Does the reversibility and longevity of stereotype threat depend on the amount of previous experience with performance decrements under stereotype threat?

Do different methods of inducing expectancy effects stack up in an additive manner or do they interact? Can expectations based on group labeling yield similar or even stronger placebo effects than explicit verbal expectations?

Why are some outcome measures highly susceptible to expectancy effects, whereas others are not? What are the common physiological characteristics of different expectancy effects and which are the specific subsystems?

Research on expectancy effects in nonhuman animals can provide additional clues to how deeply experience-based expectancy effects are anchored in animal behavior and give insights into possible adaptive mechanisms behind

Would it make sense to rethink our current taxonomy of expectancy effects? That is: instead of talking about treatment and social expectations, should we instead talk about positive and negative expectations independently of the precise expectations involved?



- 7. Stoet, G. and Geary, D.C. (2012) Can stereotype threat explain the gender gap in mathematics performance and achievement? Rev. Gen. Psychol. 16, 93-102
- Beilock, S.L. et al. (2006) On the causal mechanisms of stereotype threat: can skills that don't rely heavily on working memory still be threatened? Pers. Soc. Psychol. Bull. 32, 1059-1071
- 9. Laurin, R. (2013) Stereotype threat and lift effects in motor task performance: the mediating role of somatic and cognitive anxiety. J. Soc. Psychol. 153, 687-699
- 10. Stone, J. et al. (1999) Stereotype threat effects on Black and White athletic performance, J. Pers. Soc. Psychol, 77, 1213-1227
- 11. Cleeremans, A. and McClelland, J.L. (1991) Learning the structure of event sequences. J. Exp. Psychol. Gen. 120, 235-253
- 12. Näätänen, R. (1990) The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. Behav. Brain Sci. 13,
- 13. Seidenberg, M.S. (1997) Language acquisition and use: learning and applying probabilistic constraints, Science 275, 1599–1603
- 14. Hommel, B. et al. (2001) The theory of event coding (TEC): a framework for perception and action planning. Behav. Brain Sci.
- 15. Kunde, W. (2001) Response-effect compatibility in manual choice reaction tasks. J. Exp. Psychol. Human 27, 387-394
- 16. Schwarz, K.A. and Pfister, R. (2016) Empirical psychology in the 18th century: a historical rediscovery. Perspect. Psychol. Sci. http://dx.doi.org/10.1177/1745691616635601
- 17. Walach, H. (2011) Placebo controls; historical, methodological and general aspects. Phil. Trans. R. Soc. B 366, 1870-1878
- 18. Atlas, L.Y. and Wager, T.D. (2012) How expectations shape pain. Neurosci, Lett. 520, 140-148
- 19. Colloca, L. and Benedetti, F. (2005) Placebos and painkillers: is 46. Geuter, S. and Büchel, C. (2013) Facilitation of pain in the mind as real as matter? Nat. Rev. Neurosci. 6, 545-552
- 20. Kaptchuk, T.J. et al. (2010) Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS ONE 5,
- 21. Montgomery, G.H. and Kirsch, I. (1997) Classical conditioning and the placebo effect. Pain 72, 107-113
- 22. Price, D.D. et al. (2008) A comprehensive review of the placebo effect: recent advances and current thought. Annu. Rev. Psychol.
- 23. Stewart-Williams, S. and Podd, J. (2004) The placebo effect: dissolving the expectancy versus conditioning debate. Psychol Bull. 130, 324-340
- 24. Tracey, I. (2010) Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat. Med.
- 25. Zubieta, J.K. and Stohler, C.S. (2009) Neurobiological mechanisms of placebo responses. Ann. N. Y. Acad. Sci. 1156,
- 26. de la Fuente-Fernández, R. et al. (2001) Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293, 1164-1166
- 27 Mora M.S. et al. (2011) Lessons learned from placeho groups in antidepressant trials. Phil. Trans. R. Soc. B 366, 1879-1888
- 28. Wechsler, M.E. et al. (2011) Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N. Engl. J. Med. 365, 119-126
- 29. Weimer, K. et al. (2015) Placebo effects in psychiatry: mediators and moderators, Lancet Psychiatry 2, 246-257
- 30. Colagiuri, B. et al. (2015) The placebo effect: from concepts to genes, Neuroscience 307, 171-190
- 31. Colloca, L. and Miller, F.G. (2011) How placebo responses are formed: a learning perspective. Phil. Trans. R. Soc. B 366,
- 32. Anchisi, D. and Zanon, M. (2015) A Bayesian perspective on sensory and cognitive integration in pain perception and placebo analgesia, PLoS ONE 10, e0117270
- 33. Benedetti, F. et al. (2003) Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/ nocebo responses. J. Neurosci. 23, 4315-4323

- 34. Colloca, L. and Benedetti, F. (2009) Placebo analgesia induced by social observational learning. Pain 144, 28-34
- Colloca, L. et al. (2008) The role of learning in nocebo and placebo effects. Pain 136, 211-218
- 36. Colloca, L. et al. (2015) Vasopressin boosts placebo analgesic effects in women: a randomized trial. Biol. Psychiatry http://dx. doi.org/10.1016/i.biopsvch.2015.07.019
- 37. Kessner, S. et al. (2013) Effect of oxytocin on placebo analgesia: a randomized study. JAMA 310, 1733-1735
- Benedetti, F. (2013) Placebo effects: from the neurobiological paradigm to translational implications. Neuron 84, 623-637
- Amanzio, M. and Benedetti, F. (1999) Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J. Neurosci, 19, 484-494
- Benedetti, F. et al. (2006) The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. J. Neurosci. 26, 12014-
- 41. Eippert, F. et al. (2009) Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 63,
- Levine, J.D. et al. (1978) The mechanism of placebo analgesia. Lancet 2, 654-657
- Scott D.J. et al. (2008) Placebo and nocebo effects are defined. by opposite opioid and dopaminergic responses. Arch. Gen. Psychiatry 65, 220-231
- Basbaum, A.I. and Fields, H.I. (1984) Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu. Rev. Neurosci. 7, 309-338
- Eippert, F. et al. (2009) Direct evidence for spinal cord involvement in placebo analgesia, Science 326, 404
- human spinal cord by nocebo treatment. J. Neurosci. 33, 13784-13790
- 47. Bingel, U. et al. (2011) The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil, Sci. Transl. Med. 3, 70ra14
- 48. Kong, J. et al. (2008) A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. J. Neurosci. 28, 13354–13362
- Benedetti, F. et al. (2011) Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. Nat. Med. 17,
- Scott, D.J. et al. (2007) Individual differences in reward responding explain placebo-induced expectations and effects. Neuron 55, 325-336
- 51. de la Fuente-Fernández, R. (2009) The placebo-reward hypothesis: dopamine and the placebo effect. Parkinsonism Relat. Disord, 15S3, S72-S74
- 52. Looby, A. and Earleywine, M. (2011) Expectation to receive methylphenidate enhances subjective arousal but not cognitive performance. Exp Clin. Psychopharmacol. 19, 433-444
- Schwarz, K.A. and Büchel, C. (2015) Cognition and the placebo effect - dissociating subjective perception and actual performance. PLoS ONE 10, e0130492
- Volkow, N.D. et al. (2006) Effects of expectation on the brain metabolic responses to methylphenidate and to its placebo in non-drug abusing subjects. Neuroimage 32, 1782-1792
- Kirsch, I. (1997) Specifying nonspecifics: psychological mechanisms of placebo effects. In The Placebo Effect: An Interdisciplinary Exploration (Harrington, A., ed.), pp. 166-186, Harvard
- 56. Michael, R.B. et al. (2012) Suggestion, cognition and behavior. Curr. Dir. Psychol. Sci. 21, 151-156
- Alfano, M. (2015) Placebo effects and informed consent, Am. J. Bioeth, 15, 3-12
- 58. Colloca, L. and Miller, F.G. (2011) Harnessing the placebo effect: the need for translational research. Phil. Trans. R. Soc. B 366, 1922-1930
- Kaptchuk, T.J. and Miller, F.G. (2015) Placebo effects in medicine, N. Engl. J. Med. 373, 8-9



- 60. Friedrich, A. et al. (2015) Pygmalion effects in the classroom: teacher expectancy effects on students' math achievement. Contemp. Educ. Psychol. 41, 1-12
- 61. Rosenthal, R. and Jacobson, L. (1966) Teachers' expectancies: determinants of pupils' IQ gains. Psychol. Rep. 19, 115-118
- 62. Steele, C.M. and Aronson, J. (1995) Stereotype threat and the intellectual test performance of African Americans, J. Pers. Soc. Psychol. 69, 797-811
- 63. Barber, S.J. and Mather, M. (2013) Stereotype threat can both enhance and impair older adults' memory. Psychol. Sci. 24, 2522-2529
- 64. Lamont, R.A. et al. (2013) A review and meta-analysis of agebased stereotype threat: negative stereotypes, not facts, do the damage. Psychol. Aging 30, 180-193
- 65. Schmader, T. et al. (2008) An integrated process model of stereotype threat effects on performance. Psychol. Rev. 115,
- 66. Huber, M.E. et al. (2015) The effect of stereotype threat on performance of a rhythmic motor skill, J. Exp. Psychol, Human
- 67. Aronson, J. and Inzlicht, M. (2004) The ups and downs of attributional ambiguity: stereotype vulnerability and the academic self-knowledge of African American college students. Psychol.
- 68. Matheson, K. and Cole, B.M. (2004) Coping with a threatened group identity: psychosocial and neuroendocrine responses. J. Exp. Soc. Psychol. 40, 777-786
- 69. Townsend, S.S. et al. (2011) From 'in the air' to 'under the skin': cortisol responses to social identity threat. Pers. Soc. Psychol. Bull. 37, 151-164
- 70. Blascovich, J. et al. (2001) African Americans and high blood pressure: the role of stereotype threat. Psychol. Sci. 12,
- 71. Derks, B. et al. (2011) The threat vs. challenge of car parking for women: how self- and group affirmation affect cardiovascular responses. J. Exp. Soc. Psychol. 47, 178-183
- 72. John-Henderson, N. et al. (2015) Cytokine responses and math performance: the role of stereotype threat and anxiety reappraisals. J. Exp. Soc. Psychol. 56, 203-206
- 73. Forbes, C.F. et al. (2008) The role of devaluing and discounting in performance monitoring: a neurophysiological study of minorities under threat. Soc. Cogn. Affect. Neurosci. 3, 253-261
- 74. Forbes, C.F. and Leitner, J.B. (2014) Stereotype threat engenders neural attentional bias toward negative feedback to undermine performance. Biol. Psychol. 102, 98-107
- 75. Forbes, C.E. et al. (2015) Spontaneous default mode network phase-locking moderates performance perceptions under stereotype threat. Soc. Cogn. Affect. Neurosci. 10, 994-1002
- 76. Krendl, A.C. et al. (2008) The negative consequences of threat: a functional magnetic resonance imaging investigation of the neural mechanisms underlying women's underperformance in math. Psychol. Sci. 19, 168-175
- 77. Wraga, M. et al. (2006) Neural basis of stereotype-induced shifts in women's mental rotation performance. Soc. Cogn. Affect. Neurosci. 2, 12-19
- 78. Alabas, O.A. et al. (2012) Gender role affects experimental pain responses: a systematic review with meta-analysis. Eur. J. Pain 16. 1211-1223
- 79. Racine, M. et al. (2012) A systematic literature review of 10 years of research on sex/gender and pain perception. Part 2. Do biopsychosocial factors alter pain sensitivity differently in women and men? Pain 153, 619-635
- 80. Defrin, R. et al. (2011) Interactions among sex, ethnicity, religion, and gender role expectations of pain. Gend. Med. 8,
- 81. Robinson, M.E. et al. (2001) Gender role expectations of pain: relationship to sex differences in pain. J Pain 2, 251-257
- 82. Sanford, S.D. et al. (2002) Psychosocial mediators of sex differences in pain responsivity. J. Pain 3, 58-64
- 83. Fillingim, R.B. et al. (2002) Sex differences in perceptual and cardiovascular responses to pain: the influence of a perceived ability manipulation. J. Pain 3, 439-445

- 84. Robinson, M.E. et al. (2003) Altering gender role expectations: effects on pain tolerance, pain threshold, and pain ratings. J. Pain 4 284-288
- 85. Schwarz, K. (2015) Between pain and math: how expectations shape cognitive processes from neural activity to behaviour.
- 86. Fowler, S.L. et al. (2011) Concept priming and pain: an experimental approach to understanding gender roles in sex-related pain differences, J. Behav. Med. 34, 139-147
- 87. Kok, P. et al. (2013) Prior expectations bias sensory representations in visual cortex, J. Neurosci, 33, 16275-16284
- Aviezer, H. et al. (2011) The automaticity of emotional facecontext integration. Emotion 11, 1406-1414
- 89. Diekhof, E.K. et al. (2011) The power of imagination how anticipatory mental imagery alters perceptual processing of fearful facial expressions. Neuroimage 54, 1703-1714
- Kim, H. et al. (2004) Contextual modulation of amygdala responsivity to surprised faces. J. Cogn. Neurosci. 16, 1730-1745
- 91. Ofan, R.H. et al. (2014) Situation-based social anxiety enhances the neural processing of faces: evidence from an intergroup context. Soc. Cogn. Affect. Neurosci. 9, 1055-1061
- 92. Righart, R. and de Gelder, B. (2008) Rapid influence of emotional scenes on encoding of facial expressions: an ERP study. Soc. Cogn. Affect. Neurosci. 3, 270-278
- Schwarz, K.A. et al. (2013) Why are you looking like that? How the context influences evaluation and processing of human faces. Soc. Cogn. Affect. Neurosci. 8, 438-445
- 94. Wieser, M.J. and Brosch, T. (2012) Faces in context; a review and systematization of contextual influences on affective face processing. Front. Psychol. 3, 471
- 95. Altmann, G.T. and Kamide, Y. (1999) Incremental interpretation at verbs: restricting the domain of subsequent reference. Cognition 73 247-264
- Del ong, K.A. et al. (2005) Probabilistic word pre-activation during language comprehension inferred from electrical brain activity, Nat. Neurosci, 8, 1117-1121
- 97. Sedivy, J.C. et al. (1999) Achieving incremental semantic interpretation through contextual representation. Cognition 71,
- 98. Bruner, J.S. and Minturn, A.L. (1955) Perceptual identification and perceptual organization, J. Gen. Psychol, 53, 21-28
- Long, G.M. and Toppino, T.C. (2004) Enduring interest in perceptual ambiguity: alternating views of reversible figures. Psychol. Bull. 130, 748-768
- 100. Riccio, M. et al. (2013) Seeing the expected, the desired, and the feared: influences on perceptual interpretation and directed attention. Soc. Pers. Psychol. Comp. 7, 401-414
- 101. Aviezer, H. et al. (2008) Angry, disgusted, or afraid? Studies on the malleability of emotion perception, Psychol, Sci. 19.
- 102. Wieser, M.J. et al. (2014) Not so harmless anymore: how context impacts the perception and electrocortical processing of neutral faces. Neuroimage 92, 74-82
- 103. Barrett, L.F. and Kensinger, E.A. (2010) Context is routinely encoded during emotion perception. Psychol. Sci. 21, 595-599
- 104. Geers, A.L. et al. (2007) Further evidence for individual differences in placebo responding: an interactionist perspective. J. Psychosom. Res. 62, 563-570
- 105. Whalley, B. et al. (2008) Consistency of the placebo effect. J. Psychosom. Res. 64, 537-541
- 106. Kirsch, I. and Rosadino, M.J. (1993) Do double-blind studies with informed consent yield externally valid results? An empirical test. Psychopharmacology 110, 437-442
- 107, Schenk, L.A. et al. (2014) Expectation requires treatment to boost pain relief: an fMRI study. Pain 155, 150-157
- 108. Boot, W.R. et al. (2013) The pervasive problem with placebos in psychology; why active control groups are not sufficient to rule out placebo effects. Perspect. Psychol. Sci. 8, 445-454
- 109. Ferguson, R.J. et al. (1999) Postconcussion syndrome following sports-related head injury: expectation as etiology. Neuropsychology 13, 582-589



- Methods in the Behavioral Sciences (Festinger, L. and Katz, D., eds), pp. 98-135, Holt, Rinehart & Winston
- controlled trial, BMC Med. Res. Methodol, 7, 30
- 112. Wickström, G. and Bendix, T. (2000) The 'Hawthorne effect' what did the original Hawthorne studies actually show? Scand. J. 121. Nolan, T.A. et al. (2012) Placebo-induced analgesia in an operant Work Environ. Health 26, 363-367
- 113. Cohen, G.L. et al. (2006) Reducing the racial achievement gap: a social-psychological intervention. Science 313, 1307-1310
- 114. Cohen, G.L. et al. (2009) Recursive processes in self-affirmation: intervening to close the minority achievement gap. Science 324,
- 115. Aronson, J. et al. (1999) When white men can't do math: necessary and sufficient factors in stereotype threat. J. Exp. Soc. Psychol. 35, 29-46
- 116. Doll, B.B. et al. (2011) Dopaminergic genes predict individual differences in susceptibility to confirmation bias. J. Neurosci. 31,
- 117. Ueberwasser, F. (1787) Anweisungen zum regelmäßigen Studium der Empirischen Psychologie für die Candidaten der Philosophie zu Münster, Friedrich Christian Theißing
- 118. Ader, R. and Cohen, N. (1982) Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. Science 215, 1534-1536

- 110. French, J.R.P. (1953) Experiments in field settings. In Research 119. Ader, R. et al. (1993) Conditioned enhancement of antibody production using antigen as the unconditioned stimulus. Brain. Behav. Immun. 7, 334-343
- 111. McCarney, R. et al. (2007) The Hawthorne effect: a randomised, 120. Guo, J.Y. et al. (2010) Dissection of placebo analgesia in mice: the conditions for activation of opioid and non-opioid systems. J. Psychopharmacol, 24, 1561-1567
 - pain model in rats. Pain 153, 2009-2016
 - 122. Fuxjager, M.J. and Marler, C.A. (2010) How and why the winner effect forms: influences of contest environment and species differences. Behav. Ecol. 21, 37-45
 - 123. Hsu, Y. et al. (2006) Modulation of aggressive behaviour by fighting experience: mechanisms and contest outcomes. Biol. Rev. 81, 33-74
 - 124. Lehner, S.R. et al. (2011) Rats benefit from winner and loser effects. Ethology 117, 1-12
 - 125. Rutte, C. et al. (2006) What sets the odds of winning and losing? Trends Ecol. Evol. 21, 16-21
 - 126. Hsu, Y. et al. (2009) Prior contest information: mechanisms underlying winner and loser effects. Behav. Ecol. Sociobiol. 63, 1247-1257
 - 127. Bandura, A. (1977) Self-efficacy: toward a unifying theory of behavioral change. Psychol. Rev. 84, 191-215
 - 128 Hsu Y and Wolf LT (2001) The winner and loser effect: what fighting behaviours are influenced? Anim. Behav. 61, 777-786