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Review article

Uncertainty and stress: Why it causes diseases and how it is mastered by the brain

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ABSTRACT

The term 'stress' – coined in 1936 – has many definitions, but until now has lacked a theoretical foundation. Here we present an information-theoretic approach – based on the 'free energy principle' – defining the essence of stress; namely, uncertainty. We address three questions: What is uncertainty? What does it do to us? What are our resources to master it? Mathematically speaking, uncertainty is entropy or 'expected surprise'. The 'free energy principle' rests upon the fact that self-organizing biological agents resist a tendency to disorder and must therefore minimize the entropy of their sensory states. Applied to our everyday life, this means that we feel uncertain, when we anticipate that outcomes will turn out to be something other than expected – and that we are unable to avoid surprise. As all cognitive systems strive to reduce their uncertainty about future outcomes, they face a critical constraint: Reducing uncertainty requires cerebral energy. The characteristic of the vertebrate brain to prioritize its own high energy is captured by the notion of the 'selfish brain'. Accordingly, in times of uncertainty, the selfish brain demands extra energy from the body. If, despite all this, the brain cannot reduce uncertainty, a persistent cerebral energy crisis may develop, burdening the individual by 'allostatic load' that contributes to systemic and brain malfunction (impaired memory, atherogenesis, diabetes and subsequent cardio- and cerebrovascular events). Based on the basic tenet that stress originates from uncertainty, we discuss the strategies our brain uses to avoid surprise and thereby resolve uncertainty.

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Abbreviations: ACC, anterior cingulate cortex; GABA, γ-aminobutyric acid; GLUT1, glucose transporter 1; GLUT4, glucose transporter 4; GR, glucocorticoid receptors; HPA, hypothalamus pituitary adrenal axis; KL, Kullback Leibler divergence; L1, layer 1; LC, locus coeruleus; LTP, long-term potentiation; LTD, long-term depression; MR, mineralocorticoid receptors; NE, norepinephrine; pre-SMA, pre-supplementary motor area; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SNS, sympathetic nervous system; TrkB, tropomyosin receptor kinase B; vmPFC, ventromedial prefrontal cortex.

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1. Introduction

Individuals, who feel threatened by changes in the external environment or their internal body milieu, may find themselves confronted with the question

'What strategy should I select to safeguard my future physical, mental and social wellbeing? (Question 1)

"Stress" arises in those people who are uncertain about the answer. Thus, stressed individuals lack control. By placing emphasis on the notion of 'uncertainty', we have recently proposed this novel definition of the term 'stress' (Peters and McEwen, 2015).

How does our brain make predictions about the world when it only has access to small fragments of it? Apparently, the brain makes use of sophisticated statistical methods. By operating with probabilities, the brain is able to make predictions of future outcomes even under conditions of *uncertainty*. How exactly these procedures are executed is one of the most fascinating questions in neuroscience (Friston, 2010).

1.1. What is uncertainty?

We begin with a brief summary of how mathematicians deal with the problem of uncertainty. In the 1740's, the Reverend Thomas Bayes had an ingenious idea, which led him to the simple mathematical rule that carries his name – but then puzzlingly he gave it up. Seventy years later, Pierre-Simon Laplace rediscovered it independently and gave it its modern mathematical form. Bayes' rule says: 'By updating our initial beliefs with new evidence we obtain a novel and improved belief'. Bayes' theorem is particularly interesting, because it allows inferring from an *effect* to its probable *cause*. Such causal inference works better as more observational evidence comes available. Current brain research makes use of the very same principle in the so-called Bayesian Brain concept, according to which the brain uses *effects* – that is, the sensory data (or input), which is all the brain has access to – to figure out their probable *causes*. Obviously, this is a fairly brief summary of the application of the Bayesian vernacular to the brain. Underlying it is a more substantial view based on the rather uncontroversial idea that the brain engages with information processing, and that information theory is cast in terms of the probability theory from which Bayes' rule is derived. In 1948, the mathematician, electrical engineer, and cryptographer Claude Shannon founded information theory in his seminal work (Shannon, 1948). It was he who stated that 'information' is 'reduction of uncertainty'.

The Bayesian Brain is essentially a theoretical construct that can be traced back to the students of Plato through to the philosophy of Kant. It inherits much from the writings of people like Helmholtz in the 19th century and people like Richard Gregory in the 20th century. Geoffrey Hinton and colleagues formalized these ideas in the 1980s. One of us has imported these ideas into the biological sciences in the form of a 'free energy principle' (Friston et al., 2006). According to that concept, all cognitive or biological systems are driven to minimize an information-theoretic quantity known as 'free energy'. More precisely, this quantity is 'variational free energy' and differs from 'thermodynamic free energy', though the two are mathematically equivalent. Free energy, defined in the current article as the information-theoretic quantity, bounds surprise, and is conceived as the difference between an organism's predictions about its sensory inputs (embodied in its internal model of the world) and the sensations it actually encounters.

To put it concisely, reducing 'free energy' inevitably reduces 'surprise' – as measured by a violation of predictions. In exactly the same vein, reducing 'expected free energy' inevitably reduces 'expected surprise' – known as entropy or uncertainty. Thus, in the long-term, we are all compelled to avoid surprises and resolve uncertainty. Intriguingly, we found 'variational free energy' (in bits) and 'thermodynamic energy' (in Joules) closely coupled, a finding that emerged first when analyzing their interrelation mathematically (Sengupta et al., 2013, 2016), and second when studying experimentally how the brain responds to stress (Harris et al., 2012; Hitze et al., 2010).

1.2. What are our resources to master uncertainty?

Let us take a quick look at how neuroscientists regard our resources to master uncertainty. In the middle of the 20th century, Hans Selye identified a set of reactions, which he termed the 'general adaptation syndrome' (Selye, 1956). This uniform pattern of responses that he described included the enlargement of the adrenal cortex, atrophy of the thymus, and gastro-intestinal ulcers.

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Selye focused on physical, chemical, and microbiological noxae that caused changes in the external environment and in the internal body milieu: the lack of oxygen, nutrition or water; heat or cold; toxins; microorganisms, etcetera. John W. Mason, however, has criticized that Selye had underestimated the role of psychosocial influences (Mason, 1959). He emphasized that novelty, unpredictability, and uncontrollability of a condition and expectation of adverse sequels are key triggers of a stress reaction (Mason, 1968). Over the past forty years, many researchers have defined stressful situations – from a bio-psychological perspective – as characterized by 'no information, no control, uncertainty with a sense of threat' (Koolhaas et al., 2011; Lyons and Levine, 1994; Monat et al., 1972). More recently, experiments have confirmed that humans are capable of computing environmental uncertainty, and that their beliefs about uncertainty mediate the strength of their stress responses (de Berker et al., 2016). Moreover, the better people tune their beliefs about uncertainty, the better they were able to predict future outcomes – suggesting that the stress response has an adaptive function (de Berker et al., 2016). According to these 'Masonian' notions, family conflicts at home, mobbing at work, or highly disordered neighborhoods also indicate an inhospitable environment. In any case, as suggested above, the uncertainty about how to deal with such changes in the internal body milieu or the external environment causes 'stress'.

The approach to stress proposed here entails a well-defined question (i.e., Question 1), where we have in mind a set of answers without necessarily knowing which is correct. This means that we can treat Mason's aspects of stress – novelty, unpredictability and uncontrollability – more precisely and formally by using Shannon's uncertainty (entropy). A second aspect of this novel stress definition is that a 'sense of threat' is required. A third feature is the inclusion of optional behavioral responses.

To resolve uncertainty, three processes play a crucial role: attention, learning and habituation. When persons feel uncertain and threatened, because of a changing internal or external environment, their brains enter a hypervigilant status to decrease uncertainty (about strategy selection) as fast as possible. To garner the required information, extra cerebral energy is needed. From the physical point of view, the following applies: Obtaining any information costs energy, erasing information produces energy (Berut et al., 2012; Brillouin, 1953; Toyabe et al., 2014; Tribus and McIrvine, 1972). With respect to the brain, this means: Reducing uncertainty and providing the brain with the necessary energy entails neuroendocrine and neuroenergetic responses that constitute the stress response (Fig. 1). The Selfish Brain theory – founded by one of us in 1998 – describes this characteristic of the vertebrate brain to cover its own, relatively high, energy requirements with the highest priority when controlling energy fluxes within the organism (Peters et al., 2004). In this respect, the brain behaves 'selfishly' – as has been confirmed experimentally (Hitze et al., 2010; Kubera et al., 2012b; Oltmanns et al., 2008; Peters et al., 2011). Such a prioritization of brain energy metabolism is an inherent feature in vertebrates – a feature that is evident on short and long time-scales for preserving cerebral function, energy and mass during stress or food deprivation (Gong et al., 1998; Kind et al., 2005; Miller et al., 2002; Muhlau et al., 2007).

The key mechanisms of the acute stress response – that have been disclosed so far – are as follows: The anterior cingulate cortex (ACC) assesses the degree of uncertainty about whether future outcomes are uncertain (Fig. 2) (Behrens et al., 2007; Feinstein et al., 2006; Karlsson et al., 2012; Liljeholm et al., 2013; Paulus et al., 2002; Sarinopoulos et al., 2010). The amygdala (by exchanging information with the orbitofrontal cortex) may play a key role in responding to threats to wellbeing (Schulkin et al., 1994). People who are not certain about their future wellbeing exhibit correlated activity in the ACC and amygdala (Sarinopoulos et al., 2010). The

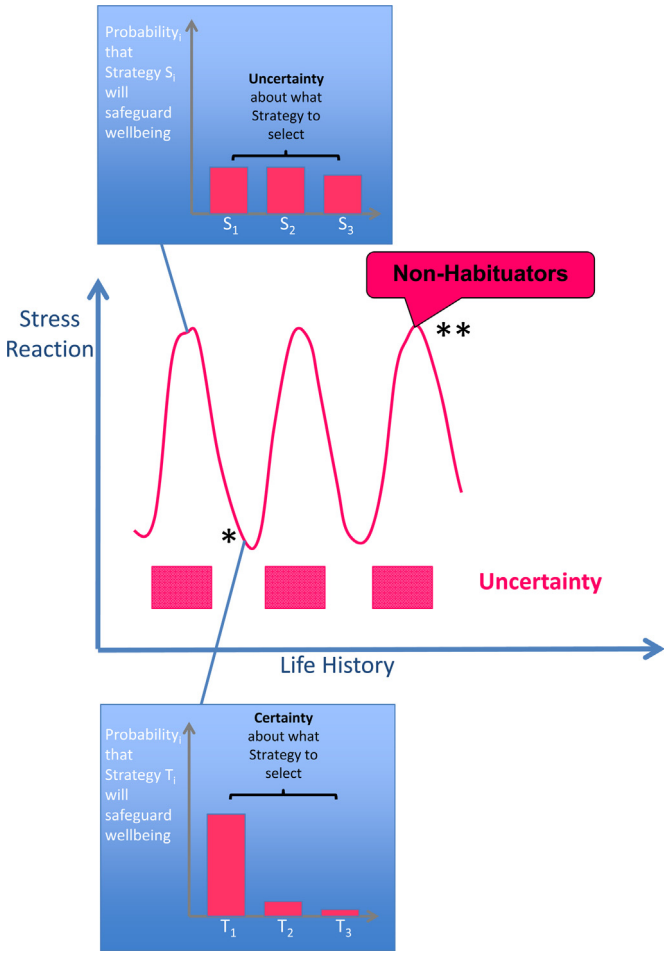

Fig. 1. Repeated stress responses in times of uncertainty. Stress responses are elicited, when the environment changes and the individual becomes uncertain about which strategy to select in order to safeguard his/her future wellbeing. In this situation, the brain computes the probabilities for each available strategy (S_1, S_2, S_3) that it will safeguard future wellbeing (upper insert). If all available strategies display equal probabilities, then uncertainty (entropy) is maximal. Novel information is needed to resolve uncertainty. To get novel information energy is required. Thus, the stress responses contain a key component, namely, the procurement of additional energy for the brain. With the help of the extra cerebral energy, information processing is enhanced. If uncertainty is resolved, the individual may certainly select a suitable strategy from a repertoire (T_1, T_2, T_3) (lower insert). In this case, the certainty has been regained, and stress reactions have subsided (*). Non-habituators are people who show full neuroenergetic, neuroendocrine, emotional and cardiovascular responses when repeatedly exposed to an inhospitable environment. Chronically activated stress responses also exert adverse effects that lead to damage of the body and the brain-referred to as allostatic load (**).

descending pathways from the ACC are numerous and include the amygdala, as well as midbrain (e.g., periaqueductal grey) and brainstem nuclei, which contribute to multiple elements of the 'stress' response (Barrett and Simmons, 2015). The ACC-amygdala complex can stimulate two important descending projections: first, the pathway to the locus coeruleus (LC); this activation causes a hypervigilant state (Hermans et al., 2011; Reyes et al., 2011; Valentino and Van Bockstaele, 2008), which has been linked to an augmented brain energy consumption (Hitze et al., 2010; Kubera et al., 2012b); second, the pathway to the ventromedial hypothalamus and the paraventricular nucleus, thereby stimulating the sympathetic nervous system (SNS) and the hypothalamus pituitary adrenal (HPA) axis, which in turn provide the additional energy required for the brain (Fig. 3) (Hitze et al., 2010; Kubera et al., 2012b; Peters et al., 2004).

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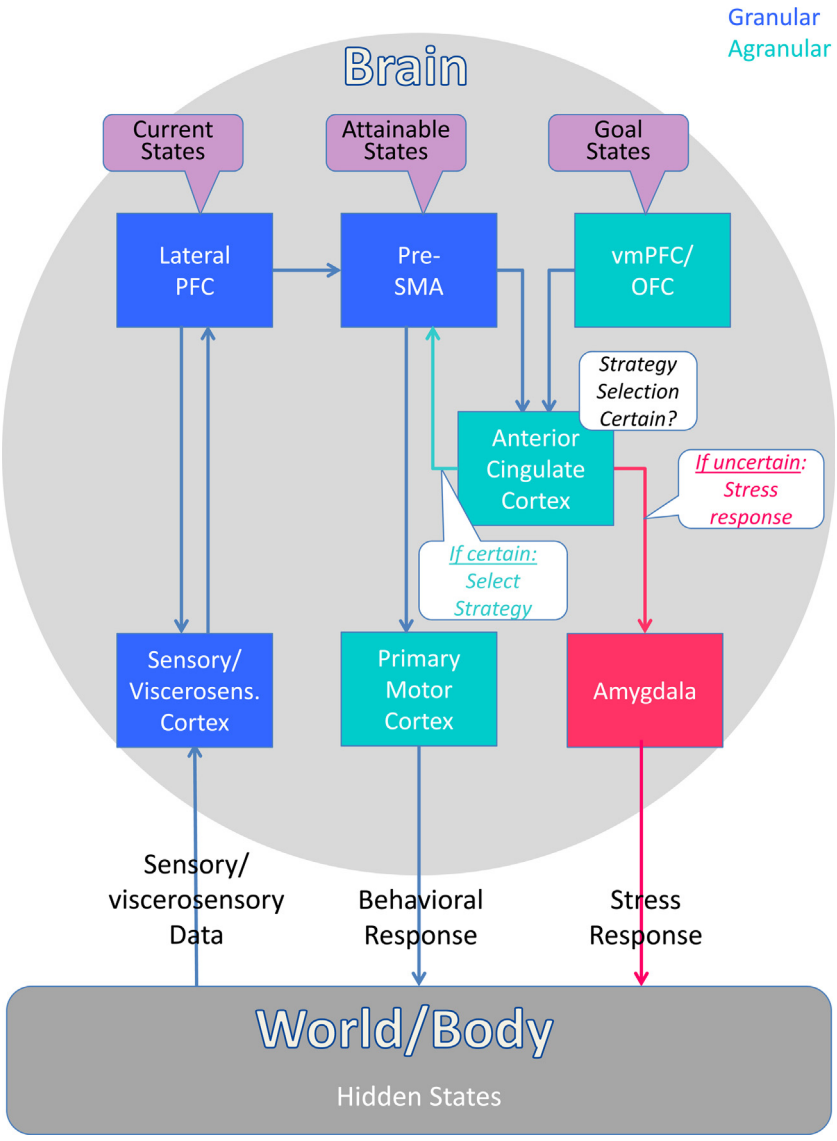

Fig. 2. Generating a stress response. The brain receives sensory and viscerosensory data about the hidden states of the world and the body. In turn, the brain acts on the world and the body through its behavioral responses and stress responses. Both perception and action aim at minimizing prediction errors (free energy). Beliefs about the current states of the world/body, about the attainable states, and about the goal states are proposed to be represented in the lateral PFC, the pre-SMA and the vmPFC/OFC, respectively. The anterior cingulate cortex (ACC) compares attainable states with goal states. From that comparison, the risks for alternative strategies can be assessed. Based on the risk assessment the ACC may select the best strategy for safeguarding future wellbeing: If strategy selection is certain, the pre-SMA and the primary motor cortex initiate the respective behavioral response. If action selection is uncertain and threatening, the amygdala initiates a stress response.

Activated by the first path, the LC in the brain stem feeds back to the cerebral hemispheres, where norepinephrine (NE) acts at cortical synapses (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003). In this way, norepinephrine increases *attention* and enhances information transmission at neuronal synapses. Crucially, enhanced information transmission at synapses is itself particularly expensive in terms of energy (Harris et al., 2012). Activated by the second path, the HPA-axis releases cortisol into the general circulation. Cortisol passes the blood-brain-barrier easily and binds to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) located in and on neurons of the hippocampus, the amygdala, and the cerebral cortex (Arriza et al., 1988; McEwen et al., 1968; Patel et al., 2000; Sanchez et al., 2000). Here, cortisol regulates synaptic plasticity (long-term potentiation and long-term depression) and in this way gates learning (Maggio and Segal, 2007, 2009; Pavlides et al., 1995). *Learning* after stress can be interpreted as updating flawed beliefs about the world, thereby furnishing better predictions of future outcomes (Fig. 3).

Some people – but not all – adapt to chronic stress by habituating. Stress *habituation* can be regarded as a form of adaptation when living under uncertainty. We define 'habituators' as those who display attenuated autonomic, endocrine and metabolic reactions, when being repeatedly exposed to the same hostile environment. As we shall see later on, stress habituation reduces the uncertainty about what strategy to select.

1.3. What happens when uncertainty cannot be resolved?

Next, we look at how neuroscientists and physicians are concerned with the health effects that arise from the failure to resolve uncertainty. When the acute stress responses turn out to be insufficient for resolving uncertainty, the critical situation may become chronic, and the organism is burdened by 'allostatic load'. According to the concept of *'allostatic load'* – developed by one of us (McEwen and Stellar, 1993) – the neuroendocrine, cardiovascular, neuroenergetic, and emotional responses become persistently

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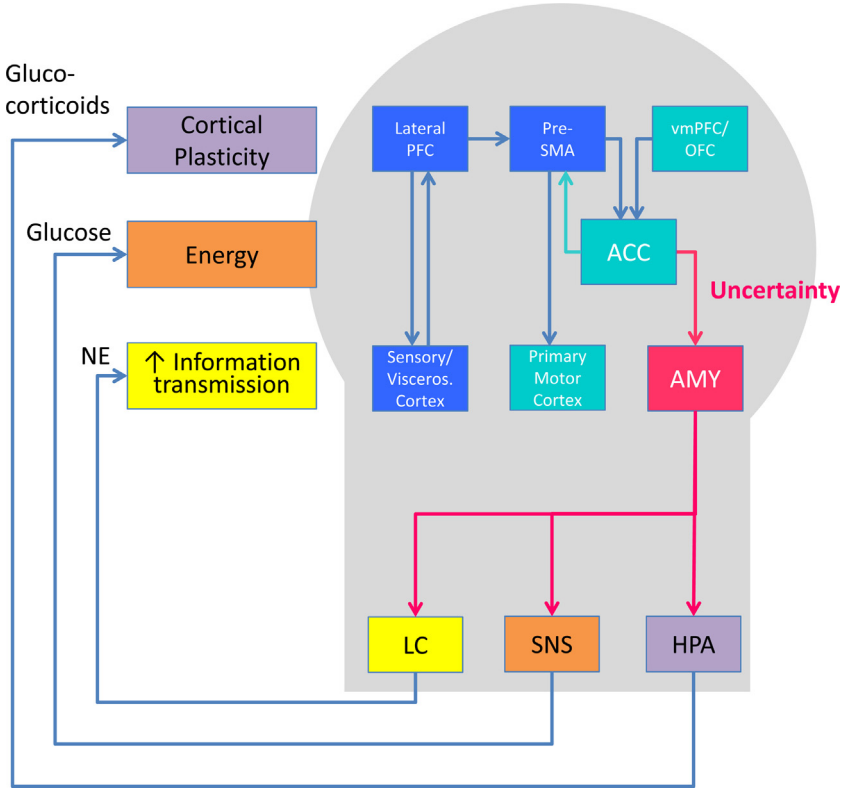

Fig. 3. Three stress responses for reducing uncertainty. During uncertainty about what to do next, the ACC-amygdala complex activates three subsystems that feed back to the brain: the LC, SNS and HPA-axis. First, LC-drive leads to cortical NE release, which enhances cortical information transmission. Second, the SNS allocates the required extra energy to the brain that is necessary to support enhanced and more precise neuronal message passing. Third, the HPA-axis releases glucocorticoids, which suspend cortical plasticity.

activated so that blood flow turbulences in the coronary and cerebral arteries, high blood pressure, atherogenesis, cognitive dysfunction and depressed mood accelerate disease progression. All of these long-lasting effects of persistently activated stress reactions are called 'allostatic load' (McEwen, 1998). When serious damage manifests, the effects are referred to as 'allostatic overload' (McEwen and Wingfield, 2003). Uncertainty can lead to a vicious cycle of altered brain architecture and systemic pathophysiology, which further damages the capability of the subject to cope with uncertainty. People living in a volatile and insecure environment (e.g., an insecure job, unhappy relationship, poverty, etc) have a high risk of depression, cognitive impairment, myocardial infarction, and stroke (McEwen, 1998; Peters and McEwen, 2015).

In the current paper, the mathematical, neurobiological and medical aspects of uncertainty are combined. On this background, stress is regarded as a form of uncertainty: We often make false predictions about the world, and our prediction errors are therefore large. When stressed, we find ourselves unable to avoid prediction errors or resolve uncertainty. In short, brains in distress do not work at their minimum of 'free energy'. Again and again there are surprises. Although relating the Bayesian Brain concept to 'stress' appears plausible, the underlying neuroendocrine mechanisms of such a link have yet to be established. The aim of the current paper is to disclose those neuroendocrine mechanisms that could fulfill Bayesian functions in regulating attention, learning, and habituation. In brief, we will consider the resources the Bayesian brain has at its disposal to master uncertainty – but also what happens when uncertainty cannot be resolved.

2. The Bayesian brain

The Bayesian brain casts neuronal processing as the process of inferring the causes of sensations (e.g., this pattern of visual input is caused by someone smiling at me). This inference conforms to Bayes rule, which says that (sensory) evidence is used to update 'prior beliefs' into more informed, evidence-based 'posterior beliefs'. Accordingly, the Bayesian Brain iteratively updates its prior beliefs based on emerging evidence. All past experiences over the life course have ultimately formed the current prior beliefs, which form the basis for how the Bayesian Brain makes predictions or decisions. Thus, early life adversity and failed attachment to parental, but also any strong positive or negative experience in school, work and personal life influence the way the Bayesian Brain selects its strategy for securing the future wellbeing.

To understand the Bayesian Brain, two key processes have to be considered in relation to each other: perceptual and active inference. We begin with the first process, which focuses on how we perceive. This perceptual aspect of the Bayesian Brain is often referred to as 'predictive coding'.

2.1. Perceptual inference

Our senses are bombarded with information about objects in the world. On the basis of that sensory input, we perceive what is out there. The problem that will concern us is how the brain accomplishes this feat of perception – turning sensations into percepts.

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A basic and useful formulation of the problem of perceptual inference is in terms of cause and effect. States of affairs in the world have effects on the brain – objects and processes in the world are the causes of the sensory input. The problem of perception is the problem of using the effects – that is the sensory data that the brain has access to – to figure out the causes. This represents a problem of causal inference for the brain, analogous in many respects to our everyday reasoning about cause and effect, and to scientific methods of causal inference (Hohwy, 2013). The problem of perception is a problem because it is not easy to reason from only the known effects back to their hidden causes. This is because the same effect can arise from many different causes. In other words, in many situations we face an ill posed problem that can only be solved using prior expectations. Inferring the causes of sensations – and making that inference easier by resolving uncertainty – is essential for navigating our world and, on some views, a necessary prequel for action.

2.1.1. Two modalities of Bayesian updating

We will illustrate Bayesian inference using the example of a medical doctor, who infers the diagnosis (cause) of the unconsciousness (effect) seen in a young patient (Box 1): the doctor has to choose between three possible diagnoses. Although a current textbook of medicine could extend the list of possible diagnoses, it is typical for humans to consider a limited number of options (Ortega and Braun, 2015). The examples used in Box 1 and Box 2 describe two distinct formulations of Bayesian inference in easily understandable terms. The first is *exact Bayesian inference* (Box 1), using the explicit formula of the Bayes theorem, in which a prior belief is directly updated into a posterior belief. The second is *approximate Bayesian inference* (Box 2), which is typically used in 'predictive coding' and has been extensively studied in the field of machine learning. The latter approach describes how a 'generative model' is used to infer from an effect to its probable cause. The generative model consists of a 'prior' belief and the 'likelihood' (for details see Box 2). With the help of the generative model one can predict an effect given the cause that one considers as most likely. In other words, one can generate an effect from a cause. Accordingly, generative models in the brain are capable of predicting sensory data. The predicted effect is then compared to the observed effect, and the difference between the two constitutes the so called 'prediction error'. The prediction error is used in turn to update the prior belief to transform it into an approximate posterior belief. Unlike the mathematical procedure in exact Bayesian updating, the procedure used in predictive coding prescribes a particular process that gets the same results.

Furthermore, both forms of Bayesian inference can be cast as a process that minimizes variational free energy, where free energy is, effectively, the overall amount of prediction error. It has been shown that both perceptual inference and learning can be described as a minimization of free energy or the suppression of prediction errors (Friston, 2005; Rao and Ballard, 1999). The concept of free energy originates from statistical mechanics; it is often used to convert difficult integration problems – inherent in the direct application of Bayes rules – into an easier optimization problem (e.g., the minimization of prediction error). 'Free energy' can be regarded as the information a person is lacking, and which he/she could use to make his/her internal model as close as possible to reality. Thus, free energy minimization corresponds to prediction error minimization in predictive coding. By minimizing

Box 1. Exact Bayesian approach to medical diagnosis

Here, we give an example of how a clinician could use the Bayesian approach to estimate the probability of an underlying disease. In this first example, the doctor is mathematically talented and makes use the explicit formula of Bayes (Eq. (1)). As an emergency physician, she has been called because an occasional passer-by found a 17-year-old comatose patient at the roadside. When seeing the young patient lying unconscious (what the doctor sees is an effect), she is uncertain about the probable cause, i.e. the underlying disease. Three possible diagnoses come to her mind: intoxication (e.g. alcohol or drugs), neuroglycopenic coma (i.e. brain energy deficiency) or cerebral bleeding. Based on her previous experience she assigns so-called 'prior probabilities' to each of her three potential diagnoses (see table). By the way, the brief version of the term 'prior probability' is 'prior'. Note, that these three prior probabilities add up to 1.0. First of all, the doctor leaves other possible diagnoses out of consideration. At this time point, 'intoxication' is her favorite diagnosis, because it has highest prior probability P(X) = 0.5. However, she still remains uncertain. The physical examination is followed by a blood glucose check, which indicates 25 mg/dl (normal 70–110 mg/dl). The measurement can also be regarded as an effect (Y) of the underlying disease (X). *After the blood glucose value is obtained*, the doctor considers 'how likely it is that the disease (cause) fits the blood glucose measurement (effect)'. This is the 'likelihood' P(Y|X): the probability that the cause described in the diagnosis would actually cause that particular effect. If 'neuroglycopenic coma' is the underlying cause in that patient, then the probability is high that a life-threatening blood glucose measurement of 25 mg/dl is obtained. The likelihood for the diagnosis 'neuroglycopenic coma' is 0.9. The other two diagnoses display a particularly small likelihood (0.1 in both cases). In Bayesian belief updating, the 'prior probability' is multiplied by the 'likelihood', and the result is proportional to the so-called 'posterior probability' P(X|Y).

$$\text{Bayesian belief updating}: P(X|Y) = P(X)\cdot\left[\frac{P(Y|X)}{P(Y)}\right] \quad (1)$$

We call the factor in brackets 'update factor', since the prior multiplied with this update factor equals the posterior. Bayes' inference leads to a new favorite diagnosis, which is 'neuroglycopenic coma' with a posterior probability P(X|Y) = 0.857. The other two diagnoses become less likely. Of note, the posterior probabilities for all diagnoses again add up to 1.0 (see table). After all, the posterior becomes the new prior, which can be used in the next diagnostic step that involves further diagnostic evidence.

17-year old patient in coma

Cause X	Effect Y	Prior P(X)	Likelihood P(Y|X)	Posterior P(X|Y)
Intoxication	Blood glucose measurement shows 25 mg/dl	0.5	0.1	0.119
Neuroglycopenic coma		0.4	0.9	0.857
Cerebral Bleeding		0.1	0.1	0.024

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Box 2. Approximate Bayesian approach to medical diagnosis

'Perceptual inference' – as it is believed to be implemented in the brain – differs from a methodological point of view from the explicit ('exact') Bayesian updating described in Box 1. To illustrate the way 'perceptual inference' works, we give a second example: A different doctor is also confronted with a comatose 17-year old patient. In contrast to the doctor in the first example (Box 1), he does not use the explicit Bayes formula, but in his case the process of Bayesian inference is rather based on subconscious intuition. In fact, 'perceptual inference' works in such an unconscious way. The second doctor also has his favorite diagnosis, which is 'intoxication', i.e., the diagnosis with the highest prior probability. The prior probabilities are again as shown in the table (Box 1). *Before the blood glucose measurement is obtained*, the doctor would use his favorite diagnosis together with the likelihood P(Y|X) to predict, which blood glucose measurement is most likely to be observed (given his favorite diagnosis is true). This means, generally speaking, that the 'prior distribution over the causes' together with the 'likelihood of the effect given the causes' is used for predicting observable data values. In probability theory and statistics, such a model used for predicting observable data values is referred to as a 'generative model'. In case the favorite diagnosis 'intoxication' is true, the doctor would predict a blood glucose value of Y = 90 mg/dl. When the doctor sees the actually obtained blood glucose value of Y* = 25 mg/dl, it is different from what he had expected. He is surprised. The difference between the predicted 90 mg/dl (Y) and the actually observed 25 mg/dl (Y*) is called 'prediction error'. Thereon, the doctor uses the prediction error to estimate a new posterior probability. The technical problem is that the precise calculation of the new posterior cannot be performed easily. Instead, he may use an approximation of the true posterior Q(X), which can still be very useful. Put simply, he successively adjusts his values of Q(X) to minimize (blood glucose and prior) prediction errors. In perceptual inference, the 'approximate true posterior' lies close to 0.857 for the diagnosis of a 'neuroglycopenic coma', indicating that this is now the best choice. It should be mentioned that the process of 'predictive coding' is a little more complex than illustrated here, since it deals with continuous states while the example with the doctor deals with discrete states. Although different in mathematical terms, 'exact Bayesian inference' and 'approximate Bayesian inference' (used in predictive coding) follow the same line of thought: inferring from the effect to its probable cause. The key utility of predictive coding is that it prescribes a process theory for doing Bayesian inference (by suppressing prediction errors or variational free energy) that could be implemented in the brain.

prediction error, the internal model is improved step-by-step updating posterior beliefs, given the prior beliefs and the likelihood of sensory observations.

In conclusion, Bayesian inference, as used in perception, reduces our uncertainty about the states of affairs in the world that have caused our sensations.

2.1.2. Precision and attention

A key concept – that we will develop later – is the notion of 'precision' in predictive coding. In brief, the predictive coding formulation of the Bayesian Brain says that prediction errors represent the newsworthy information that has yet to be explained. Clearly, the brain also has to select the 'news' channels it should attend to. This process of selection corresponds to increasing the volume or 'gain' of precise or reliable prediction errors. 'Gain modulation' is a phenomenon commonly observed in neuroscience that alters the amplitude of a neuronal response, but not its selectivity. Computationally, the increase in the gain of neurons encoding prediction errors ensures that precise information is used to revise internal models. Psychologically, it provides a nice metaphor for attentional selection. Finally, from a physiological perspective it places neuromodulation and cortical gain control in a key position to influence perceptual synthesis. This follows from the fact that increasing the influence of prediction errors rests on increasing the responsivity of the neuronal populations, which report them.

Put simply, the higher the precision of prediction errors, the greater their influence on belief updating. During stress, neuromodulation amplifies the precision of sensory prediction errors, endowing sensory information with greater weight, in relation to prior expectations.

2.1.3. The anatomical correlates of hierarchical predictive coding

The brain's architecture is hierarchically organized (Felleman and Van, 1991). This organization has been intensively investigated in the visual system: the lower cortical areas are located closer to primary sensory input, while the higher areas play an associational role. The hierarchical architecture enables the brain to learn its own priors as well as the intrinsic causal structure of the world that creates the sensory input. In hierarchical Bayesian inference (or predictive coding) the priors at intermediate levels now become 'empirical priors'. This follows because they become accountable to empirical (sensory) data and can therefore be optimized to minimize prediction errors at each hierarchal level.

Neuroanatomically, the notion of a hierarchy is based on the distinction between bottom-up and top-down connections (Salin and Bullier, 1995). The notion of top-down connections provided a better explanation of experimental data than the idea that only bottom-up connections are necessary (Garrido et al., 2007). Top-down connections arise largely from layer-5-pyramidal cells and target layer-2-pyramidal cells of lower cortical areas (Fig. 4). Conversely, bottom-up connections arise largely in layer-2-pyramidal cells and project to the spiny layer-4-neurons of a higher cortical area.

Fig. 4 illustrates our simplified model of the hierarchical organization of the brain. In agreement with neuroanatomical studies (Feldmeyer et al., 2005; Harris and Shepherd, 2015; Lubke et al., 2000; Ramaswamy and Markram, 2015; Thomson and Lamy, 2007) and neurocomputational analyses (Bastos et al., 2012; Haeusler and Maass, 2007; Shipp, 2016; Shipp et al., 2013), we propose the following assignment of empirical prior beliefs, the likelihood, the sensory data, and the prediction errors to their anatomical substrates. Accordingly, empirical prior beliefs are located in layer 3 of the cortex, and the likelihoods or predictions are represented in layer 5. The empirical prior expectation encodes the most likely cause of sensory inputs. The combination of empirical prior and likelihood furnishes a prediction that is conveyed to layer-2-pyramidal cells at the level below. Here, the prediction is compared to the sensory data, and in this way, a prediction error is calculated. In return, this prediction error is conveyed upwards, through layer-4-stellate cells to layer-3-pyramidal cells, where it can update the empirical priors. This brief description has been simplified for clarity; for a more detailed account, see legend of Fig. 4. The computational architecture depicted in Fig. 4 enables continuous updating of prior beliefs in a hierarchical fashion, in response to fluctuating sensory input at the lowest level.

In perceptual inference, the brain makes use of an internal hierarchical model where top-down predictions are continuously

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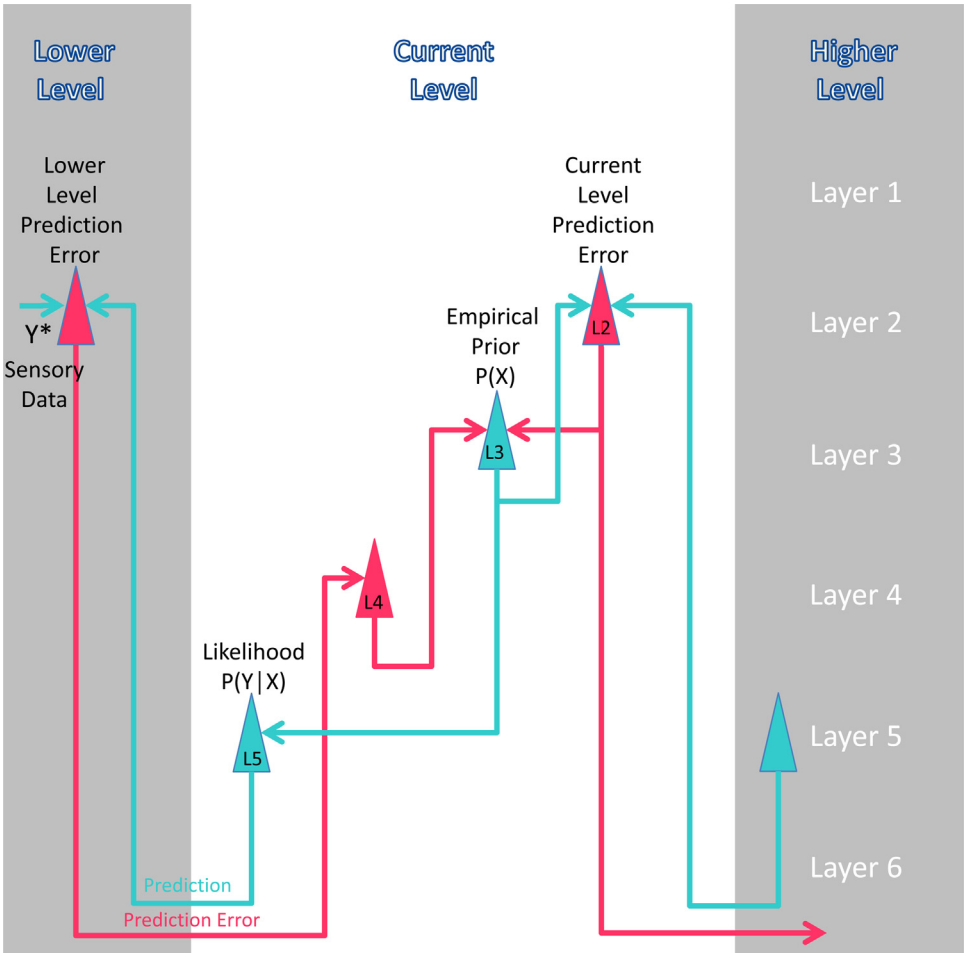

Fig. 4. Simplified model of the hierarchical organization of the brain. Here, posterior or empirical prior beliefs P(X), likelihoods P(Y|X), sensory data (Y*), and prediction errors are associated with anatomical structures. Superficial L3-pyramidal cells encode the sufficient statistics (i.e., the mean) of the empirical prior probability distribution; deep L5-pyranidal cells encode the sufficient statistics of the likelihood probability distribution. The updating of the empirical prior involves two processes: First, the empirical prior (L3) and the likelihood (L5) generate a top-down prediction. This prediction is compared to the sensory data (Y*), thereby generating a first prediction error in L2-pyramidal cell of the lower level (Y*-Y). This lower-level prediction error is conveyed further upwards via L4-stellate cells to L3-pyramidal cells. It contributes to the update of the empirical prior. Second, a current-level-prediction error is calculated in layer-2-pyramidal cells. This second prediction error results from the comparison between the higher-level predictions and the current-level-empirical prior. The relative influence of the first and second prediction error on empirical priors is determined by their precision or reliability. Technically speaking, the precision of a prediction error corresponds to its inverse variability. Physiologically, precision is thought to be encoded by the responsiveness or gain of cells encoding prediction error while, psychologically, it can be associated with attentional gain that selects precise sources of prediction error; namely, reliable information that is yet to be explained. The ultimate aim of the belief propagation or neuronal message passing it implied by this circuitry is to minimize (precision weighted) prediction error or free energy, and thereby optimizing the generative model. For simplicity, we have only shown the lowest sensory level and the first level of the hierarchy. A similar architecture can be imagined for subsequent levels, where the data become empirical priors at the lower level.

updated by bottom-up prediction errors (Friston et al., 2006). The reciprocal top-down/bottom-up-message passing in this hierarchy seems able to accommodate the context sensitive and invariant aspects of perception, while at the same time explaining many neuroanatomical and neurophysiological facts about cortical hierarchies (Hohwy, 2013).

In summary, perceptual inference reduces our uncertainty about what caused our sensory observations. Next, we consider the important fact that we can choose which sensations to sample.

2.2. Active inference

The second process that is important for understanding the Bayesian Brain is 'active inference'. 'Perceptual inference' and 'active inference' represent the two ways in which we can minimize prediction errors. In perceptual inference, individuals strive to update their internal model of the world, while in active inference individuals change their environment (or their sampling of the environment) with the aim of better informing their beliefs about the world (Adams et al., 2013; Friston et al., 2006). Put simply, one can either change empirical prior beliefs (through perception) to make predictions more like sensations or one can change sensations (through action) to make them more like predictions. The second is 'active inference'. Experimental evidence supports the notion that the principles of active inference underlie the functioning of the visual and auditory systems (Chennu et al., 2013; Kok and de Lange, 2014). In the here and now, minimizing certain forms of prediction errors (e.g., proprioceptive prediction errors) through action can be very simple. For example, motor reflexes can be described as quenching proprioceptive prediction errors (Adams et al., 2013). Another example concerns the allostatic (predictive) regulation of the internal body milieu (Sterling, 2012), where viscerosensory prediction errors are reduced (Barrett and Simmons, 2015).

There appears to be a dialectic regarding action and uncertainty. Both exploratory behavior and avoidance behavior show biphasic effects on uncertainty. Exploratory behavior is costly because it involves a variety of risks, leading to 'short-term uncertainty' (e.g.,

the voyages of Christopher Columbus); but the possible (epistemic) benefit of exploratory behavior is the reduction of 'long-term uncertainty' (filling in the white areas on the maps). In contrast, avoidance behavior can reduce 'short-term uncertainty' (retreat may indeed have a relaxing, uncertainty reducing effect); but people who have suspended appropriate belief-updating during an avoidance episode might be very surprised by a world that has changed profoundly in the meantime. As avoidance behavior impairs epistemic foraging, it can promote adherence to outdated beliefs, thereby causing 'long-term uncertainty'. In short, there is an optimum balance between approach and avoidance behavior that rests upon environmental volatility and, more importantly, the ability of an agent to estimate volatility and use it to minimize long-term uncertainty (Friston, 2009). By analogy, the exploration for energy faces the same dialectic: Although foraging behavior itself is an energy-consuming process, it serves to access energy resources (Peters et al., 2007b).

The same notion of minimizing expected prediction errors in the future (i.e., uncertainty) underlies extension of active inference into the domain of goal-directed-decision making and planning (Friston et al., 2015). The implicit action selection is the endpoint of active inference and has particular relevance to our treatment of stress. We now take a closer look at how the brain infers the best strategy.

2.2.1. Goal-directed-decision making

Recently, goal-directed-decision making has been considered in terms of active inference (Friston et al., 2013, 2014). In other words, the problem of selecting behavioral strategies can be treated as an inference problem. For such a decision-making process three kinds of probability distributions are relevant: Probability distributions over the

- current states of the world/body,
- states that can be reached, i.e., attainable states,
- states that the agent believes he/she should occupy, i.e., goal states.

Strategy selection occurs under the prior belief that it will minimize the difference between the probability distribution over 'attainable states' (given beliefs about the current state) and the probability distribution over 'goal states'. Or, put another way, choices are based upon beliefs about alternative strategies, where the most likely strategy minimizes the difference between attainable and desired outcomes (repertoire versus goal) (Friston et al., 2013, 2014).

The beliefs about the 'current states of the world' are continuously updated during perceptual inference. The lateral prefrontal cortex (PFC) is a key brain region where current environmental states are thought to be encoded (Panagiotaropoulos et al., 2012). Thus, this brain region represents updated empirical priors or posterior beliefs about the 'current states of the world'. The lateral PFC occupies a high hierarchical position in the brain. It sends *predictions* to the sensory cortex, which is located at a lower level, and in turn the lateral PFC receives *prediction errors* from the sensory cortex. The viscerosensory cortex evaluates interoceptive signals (e.g. pain, cutaneous light 'sensual' touch and thermal sensations) that result from changes in the internal body milieu (viscera, muscles and skin) (Barrett and Simmons, 2015; Chanes and Barrett, 2016).

The beliefs about the 'states that can be reached' may be represented in the pre-supplementary motor area (pre-SMA) (Fig. 2) (Nguyen et al., 2014; Rushworth et al., 2004). On this view, the pre-SMA comprises a generative model that predicts outcomes that can be reached by the use of alternative strategies ($strategy_1$, $strategy_{2,\ldots,}$ $strategy_n$) taken from a given repertoire (Friston et al., 2013). Past experiences – such as early life adversity and failed attachment to parental – have a strong impact on what future events are foreseen when considering the respective strategy. In a long-lasting iterative process, the amygdala- and hippocampus-dependent emotional and declarative memories shape the generative model, which allows the prediction of the attainable states. In this regard, no person or animal is free from such biographical biases towards the prediction of new events. Technically speaking, the beliefs about the 'states that can be reached' are represented by a probability distribution over – or expectations about – (counterfactual) states (Fig. 6A; blue).

The 'states that agents believe they should occupy' are represented in regions like the ventromedial prefrontal cortex prefrontal cortex (vmPFC) and the orbitofrontal cortex (OFC) (Barron et al., 2015; Bechara et al., 2000; Gottfried et al., 2003; O'Doherty et al., 2003; Roesch and Olson, 2004). These regions occupy the highest hierarchical position in the Bayesian Brain. They play a key role in defining the expected value (i.e. free energy) of future states. These goal or prior preferences provide a point of reference for goal directed behavior but can also be updated. The beliefs about the goal states are also represented as a probability distribution over states of the world (Fig. 6A; red).

The ACC is a central region that is in a position to integrate beliefs about attainable states and goal states (Lee et al., 2007; Nguyen et al., 2014). From a theoretical perspective, the difference between attainable states and goal states can be formalized by the so-called 'Kullback Leibler (KL) divergence' (Kullback and Leibler, 1951). In information theory, the KL divergence measures the difference between two probability distributions. Although it is often intuited as a way of measuring the distance between probability distributions, the KL divergence is not a true metric. It is often used as a measure of the information gained when one revises one's beliefs from a prior to a posterior probability distribution. In the case of the ACC, the KL divergence can be considered as a measure of how much the attainable states differ from the goal states (Fig. 6A and B). In engineering and optimal control theory, the process of minimizing the divergence between predicted and preferred states is called KL control. In economics, the KL divergence is known as *risk*; leading to a formal description of risk sensitive behavior.

In summary, an important aspect of resolving uncertainty is the selection of actions or strategies that reduce expected surprise, in relation to prior preferences or goals.

2.2.2. The degree of uncertainty about what to do next

The principle of how the brain resolves uncertainty about which action or strategy to select is also found in the most basic forms of life. In the chemotaxis, for example, a bacterium changes its strategy (i.e., the direction of swimming) until it reaches a nutrient-rich environment (goal state). This itinerant strategy is based on the prior expectation that the agent will only change its direction of movement if it is facing unexpected states (Friston, 2011). Likewise, the (ideal) Bayesian Brain entertains alternative strategies when it cannot reach goal states. Figuratively speaking, the nutrient-deprived bacterium shows the same restless behavior – which is an indication of 'uncertainty' where it should go – as many stressed humans who are uncertain about what to do next.

Among the various brain regions, the ACC is in a prime position to integrate information from the pre-SMA and the vmPFC/OFC and evaluate the relative risk (KL divergence) (Fig. 2). Action selection is based upon these divergence measures, where the most likely strategy minimizes the KL divergence or relative risk (Fig. 6C). In this way, the ACC plays a central role in selecting a strategy.

If an individual feels *certain* about the answer to question 1 ('What strategy should be selected to safeguard future wellbeing?'), strategies are available for achieving the desired goals (i.e.,

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strategies with small KL divergences), and the strategy that produces best approximates the desired outcome (smallest KL divergence) can be selected and conveyed from the pre-SMA to the primary motor cortex. In turn, the primary motor cortex generates proprioceptive 'predictions', which are fulfilled by transforming peripheral proprioceptive 'prediction errors' into movement (Adams et al., 2013; Shipp et al., 2013). In this way, the selected behavior is instantiated (Fig. 2). The certainty about what to do next manifests itself through a strong sense of control.

Clearly, it is possible that none of the strategies in the game will achieve the desired goal with a sufficiently high probability (i.e., no strategies in play are likely to reach the desired goal). We suggest that in such a risky and *uncertain* state of affairs, the ACC initiates an emergency program comprising a set of coordinated stress responses (Fig. 2). Accordingly, the ACC issues visceromotor 'predictions' to the brainstem and spinal cord via connections that cascade through the amygdala. Such visceromotor 'predictions' are fulfilled by converting visceromotor 'prediction errors' into neuromodulatory, autonomic and hormonal action (Barrett and Simmons, 2015). In this way, the allostatic network is activated. The 'visceromotor regions' controlling the allostatic processes (the amygdala, ventral striatum, insula, orbitofrontal cortex, anterior cingulate cortex, medial prefrontal cortex) are commonly regarded as the 'circuits for emotions' (Barrett, 2017). With such an emergency activation of the ACC-amygdala complex, the individual experiences feelings of threat, uncertainty and lack of control. As has been shown experimentally, persons who display the largest stress responses exhibit lowest levels of self-esteem and locus of control, i.e. self-concept of own competence (Kirschbaum et al., 1995; Pruessner et al., 2005, 1999). In extreme cases, however, when it appears precluded that any of the available strategies can achieve the goal state (i.e., every strategy exhibits an extremely large KL divergence), the individual may despair and abandon his/her goal.

In the following, we will focus on the risky state of affairs – in which the individual experiences feelings of threat, uncertainty, and loss of control. The associated risk is twofold: first, there is the risk of surprising outcomes (e.g., physical injury, loss of social position, financial loss, separation from life partner, etc.). Secondly, there is a risk that the lack control associated with 'toxic stress' and allostatic overload might progress to disease. Once exposed to threatening changes in the external or internal environment, the individual is confronted with three possible outcomes: The first outcome indicates 'good stress'; it represents a satisfying result; certainty could be regained and the individual experiences a sense of mastery and good self-esteem; wellbeing is restored completely (Fig. 1; asterisk) (McEwen and Gianaros, 2010). The second outcome specifies 'tolerable stress'; in this case, the individual could not undo the changes in the inhospitable environment; however, uncertainty could be reduced through buffering mechanisms such as habituation. These people show only low stress responses and intermediate levels of self-esteem and locus of control (Kirschbaum et al., 1995; Pruessner et al., 2005, 1999). This second outcome is discussed later on in the chapter 'Habituation – updating of goal states'. The third outcome characterizes 'toxic stress'; in this case, the buffering mechanisms failed, and the individuals remain trapped in the inhospitable environment; their stress responses are maximal whereas their levels of self-esteem and locus of control are minimal (Kirschbaum et al., 1995; Pruessner et al., 2005, 1999); these persons are at high risk for physical and mental morbidity and mortality (Fig. 1; two asterisks) (McEwen, 2012).

In conclusion, if we feel confident that we can reach our goal states (i.e., one course of action has a particularly low risk), the ACC informs the motor system about the best action. However, if we feel uncertain about what to do next (all strategies are equally risky) then the ACC initiates an emergency program to ensure inferences about the state of the world are properly informed.

To prevent all these short- and long-term risks associated with uncertainty, the brain starts its emergency program as soon as a person gets into such a precarious situation. Pivotal to this formulation is the activation of the amygdalae. These brain regions – located within the temporal lobes – organize the stress responses that are ultimately aimed at resolving the risk and uncertainty portended by the ACC. The reduction of uncertainty in such states of emergency involves the beneficial actions of the stress hormones. Both cortisol and catecholamines are important in determining memory of significant things to avoid danger in the future. Stress hormones are necessary to update our beliefs about the world (and our plans), which are no longer fit for purpose.

3. Mastering uncertainty

As mentioned, the brain uses of three processes to master uncertainty: attention, learning, and habituation. Crucially, this repertoire of uncertainty resolving processes is closely intertwined with cerebral and systemic energy metabolism.

3.1. Attention – the procurement of more precise sensory information for Bayesian updating

The first and immediate response to a stressful challenge is arousal. Arousal includes an increase of attention and vigilance. In an uncertain situation, the brain switches from the normal vigilant state during wakefulness into a hypervigilant state. Here, we review evidence that speaks to how the neuroendocrine mechanisms that lead to hypervigilance procure more precise sensory information. As mentioned above, information is required to reduce uncertainty (Shannon, 1948). To get the more precise information, extra cerebral energy is needed. The relation between information and thermodynamic cost follows from the fact that energy is required to change the information encoded in any system. From a neuronal perspective, the increase in the gain of neurons encoding prediction errors is metabolically costly. From the point of view of predictive coding, an increase in precision or attentional gain necessarily entails an increase in neuronal energy supply.

During a psychosocial challenge (e.g., oral examination, dispute), the amygdala and the bed nucleus of the stria terminalis provide input to the LC, the SNS and the HPA axis (Fig. 3) (Swanson, 2000). As a result, corticotrophin-releasing factor is released from nerve terminals targeting LC neurons, thereby regulating their firing patterns (Valentino and Van Bockstaele, 2008). This neuropeptide leads to an increase in tonic and a decrease in phasic discharge of LC neurons. Phasic discharge involves only a limited number of LC neurons and characterizes the mode of 'focused attention'. In this mode, LC projections to cortical areas lead to enhancement of only the few parts of the cortex involved in a specific task (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003). In contrast, tonic discharges of locus coeruleus neurons involve large number of these neurons. This mode leads to widespread activation of cortical areas (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003). The tonic mode is activated during acute stress and facilitates the interaction of many cortical areas (i.e., by increasing the influence of ascending prediction errors), which – in concert – aim at revising beliefs in order to reduce uncertainty.

In the following, we will look at how attention optimizes the processing of precise sensory information. Specifically, we consider how norepinephrine increases cortical synaptic information transmission, how particular information flows are augmented, what energy costs arise, and how the extra energy required is provided.

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3.1.1. Noradrenergic regulation of presynaptic glutamate release

LC projections target cortical synapses, where they release norepinephrine in a paracrine manner (Fig. 3) (Berridge and Waterhouse, 2003). Here, norepinephrine modulates the release probability of glutamate and GABA from presynaptic nerve terminals. We focus on the modulation of inputs arriving at the basal dendrites of layer-2-error-units-pyramidal cells (Fig. 5). Mara Mather and coworkers have described a positive feedback loop and have coined the term 'hot spot', describing the coincidence of a 'high-frequency-arriving-spike train' with a 'high LC-drive' (Mather et al., 2015). Upon such a coincidence, a 'hot spot' can be observed where glutamate release probability is enhanced (for details see Box 3).

The concept of NE hot spots (Mather et al., 2015) nicely explains two experimental observations: First, increasing the frequency of LC stimulation either leads to facilitation or suppression of sensory evoked neuronal responses (Devilbiss and Waterhouse, 2004). For, according to Mather's concept, a NE hot spot facilitates synaptic transmission of a high-frequency-spike train, while it suppresses synaptic transmission of a low-frequency-spike train. Second, high LC activation increases the likelihood that an action potential results in the release of glutamate, while low LC activation decreases that likelihood (Chiu et al., 2011; Kobayashi et al., 2009).

These neuromodulatory hotspots appear to offer the perfect mechanism for the gain control implicit in predictive coding accounts of perceptual inference. In other words, selecting certain streams of ascending prediction errors (arising in hotspots) affords precision and influence to those prediction errors – so that they exert a greater effect higher in the cortical hierarchy. In this way, NE-mediated presynaptic gain control is in a prime position to selectively procure unexplained or newsworthy sensory information that is necessary to revise empirical prior beliefs about the world.

In summary, stress ignites multiple NE hotspots, thereby selectively enhancing the transmission of precise sensory information.

3.1.2. Energetic constrains on information transmission

Neural information transfer incurs an exceptional amount of energy (Harris et al., 2012). The brain uses 20% of the total energy that is available in the human organism, although its mass contributes only 2% to the total body mass (Peters et al., 2004). Thus, the brain occupies a privileged metabolic position. Its primary fuel is glucose. It takes up more than 60% of the circulating glucose at rest (Reinmuth et al., 1965). Remarkably, an experimental mental or psychosocial challenge increases whole-brain-glucose uptake by more than 10% (Hitze et al., 2010; Madsen et al., 1995). So-called 'brain pull mechanisms' – a term which originates from logistics – allow such a rapid systemic (re-) allocation of energy resources within the human organism (Peters and Langemann, 2009). Even on the cell-to-cell level, it has been

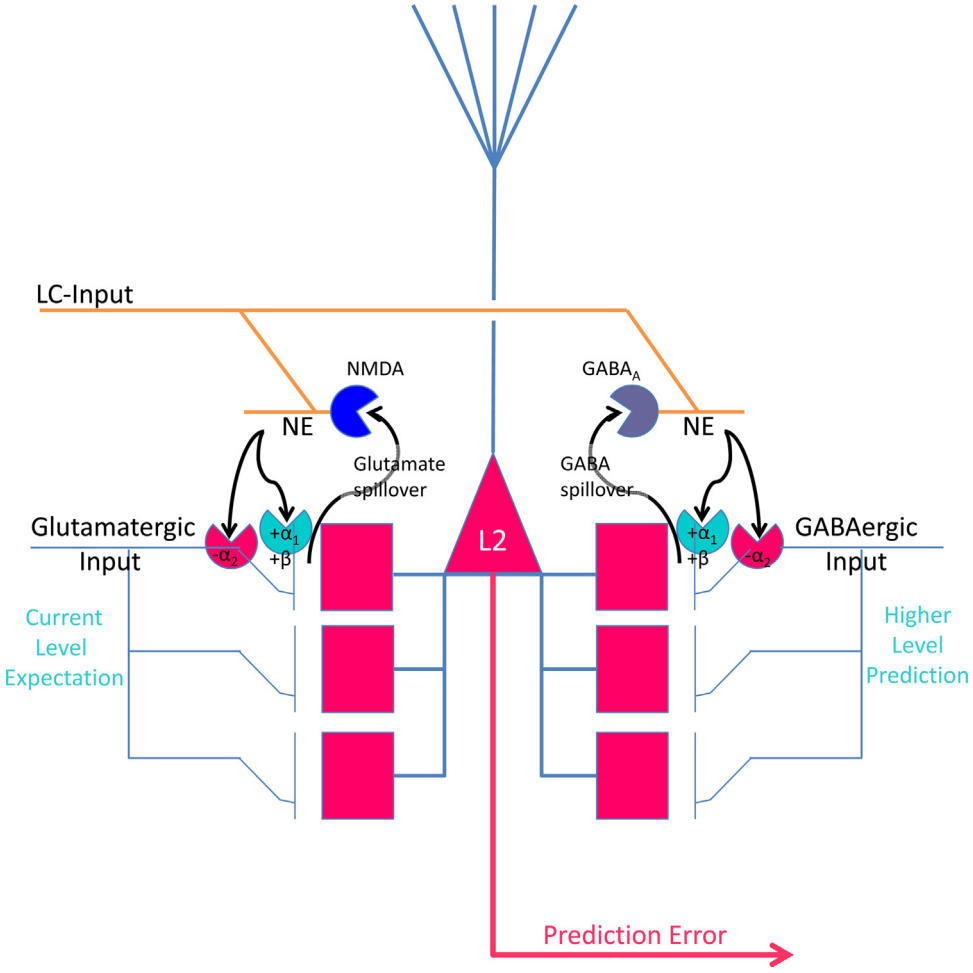

Fig. 5. LC activity enhances synaptic information transmission at multiple release sites. Upon high LC activity, hotspots are ignited both at glutamatergic and GABAergic synapses. In the case of multiple release sites from one axon onto a postsynaptic cell, the energetically optimal release probability of neurotransmitters is 25%–50%. By igniting hotspots at multiple release sites, NE increases the share of action potentials that release neurotransmitter vesicles (glutamate or GABA). Hotspots decrease energy efficiency of synaptic transmission, and increase total synaptic energy consumption. By expending extra energy, hotspots allow for a selection or boosting of specific prediction errors; thereby endowing them with greater precision.

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Box 3. Norepinephrine ignites local 'hot spots' of neuronal excitation

If a high LC activity leads to NE-release at a glutamatergic synapse, NE binds to adrenergic receptors located on the presynaptic glutamatergic neuron: it binds to the high-affine α_2-adrenoreceptors and the low-affine α_1- and β-adrenoreceptors (Fig. 5)(Ramos and Arnsten, 2007). At the presynaptic site of cortical neurons, high-affinity and low-affinity adrenoreceptors have been shown to exert opposing actions. While low-affine α_1- and β-adrenoreceptors increase the glutamate release probability (Ferrero et al., 2013; Kobayashi et al., 2009), high-affine α_2-adrenoreceptors receptors decrease it (Chiu et al., 2011). Furthermore, at low NE concentrations the actions of high-affine α_2-adrenoreceptors prevail, while at high NE concentrations the actions of low-affine α_1- and β-adrenoreceptors prevail (Nai et al., 2009, 2010). These findings are in line with the biphasic NE-dose-response curves on patch clamp recordings (Linster et al., 2011).

Once glutamate has been released from the presynaptic site into the synaptic cleft, it binds on the one hand to postsynaptic AMPA and NMDA receptors and on the other hand – as glutamate spillover – to NMDA-receptors located on the norepinephrine release sites. In this way, we find a modulatory loop with NE regulating glutamate release probability, and glutamate spillover regulating NE release (Mather et al., 2015). This modulatory loop acts in a positive feedback manner, and has been termed 'hot spot' (Mather et al., 2015).

Thus, high LC-drive leads to high concentrations of NE at the presynaptic site, which lead to an increase of glutamate release probability. If coincidently there is a high-frequency-spike train arriving at the presynaptic site, a particularly high amount of glutamate is released into the synaptic cleft. A high glutamate spillover in turn amplifies further NE release, resulting in maximal glutamate release probabilities. In contrast, in case of a low LC-drive and spontaneous glutamate release, the low concentrations of the glutamate spillover are insufficient to promote further release of NE – the glutamate release probability is even more reduced. High LC activity also ignites hotspots at GABAergic release sites. NE enhances GABA-release probabilities by low-affine α_1-adrenoreceptors, whereas NE suppresses GABA-release probabilities by high-affine α_2-adrenoreceptors (Hirono and Obata, 2006; Salgado et al., 2012). In summary, from among the action potentials arriving at the synapse, only a few actually elicit the release of the neurotransmitter vesicles (glutamate or GABA). Only in the case of high LC activity do hotspots occur, where most of the incoming action potentials of a high-frequency train actually produce a neurotransmitter release (glutamate or GABA).

Noteworthy, NE also affects postsynaptic excitability of cortical neurons (by suppressing excitatory and inhibitory postsynaptic potentials) (Kobayashi et al., 2009; Salgado et al., 2011), but the facilitatory NE effects on presynaptic neurotransmitter release (glutamate and GABA) have been shown to override the less effective NE-effects on postsynaptic excitability (Salgado et al., 2011). In summary, NE ignites hotspots at neurotransmitter release sites, thus increasing the transmitted information (bits per second).

demonstrated that neurons take up energy 'on demand' (Magistretti et al., 1999; Pellerin and Magistretti, 1994). This demand process is caused by other 'brain pull mechanisms', which allow a rapid local (re)allocation of energy resources within the brain itself (Peters and Langemann, 2009). Most brain energy is spent on synaptic transmission (Harris et al., 2012).

Not every action potential arriving at the synapse leads to the release of a glutamate vesicle. Levy and Baxter used an information-theoretical approach to show that the brain optimizes the quotient of 'information transmitted to energy expended', rather than optimizing its 'coding capacity' (Levy and Baxter, 1996). In other words, the brain is, in principle, able to transmit information at a much higher rate than it actually does, because operating at a lower transmission capacity is more economical; i.e. energy efficient (for details see Box 4).

Under non-stress conditions, LC-activation is low and the brain operates in an economic energy-efficient mode, abstaining from the [mis]use of its potentially higher information processing capacity. Under stress conditions, however, LC-activation is high and the brain operates in an energetically expensive mode, exploiting its full information processing capacity, while forsaking optimal energy efficiency.

In short, the use of the energetically expensive mode is restricted to times of stress and uncertainty.

3.1.3. Prediction errors are encoded with higher precision during stress

Now the question arises, for which task is extra energy actually needed. On the predictive coding view, uncertainty or loss of confidence about the top-down predictions calls for an increase in the precision of sensory prediction errors – that induce Bayesian belief updating. Prediction error units assess how much bottom-up information about sensory evidence differs from top-down information on expectations (Fig. 5). But what neurobiological mechanisms help layer-2-error-unit-pyramidal cells to evaluate a mismatch between descending predictions and the expected state of affairs at the current level?

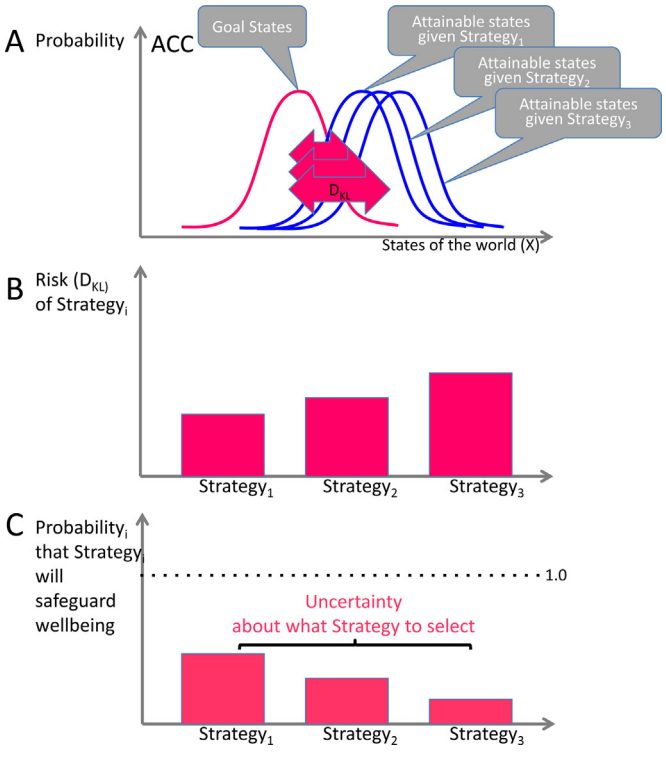

Fig. 6. Selecting the best strategy. Panel A. During stress, the ACC monitors the divergence between the probability distribution over 'attainable states' and 'goal states' for plausible strategies that constitute a repertoire. Such divergences are called Kullback-Leibler divergence (D_{KL}). The greater the divergences or relative risk, the greater the uncertainty about which strategy to select – and the stronger is the activation of amygdala. Panel B. Each strategy displays a different relative risk (D_{KL}). Panel C. Based upon the risk distribution, the ACC assesses for each strategy$_i$ ($i = 1,2, \ldots ,n$) the probability that it will ensure wellbeing. In the example depicted here, none of these probabilities is high. Thus, the individual remains uncertain about the answer to question 1. Because of the high degree of uncertainty or entropy, a stress response is initiated.

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Box 4. Energetic costs limit presynaptic release probabilities

In neurons with a maximal firing rate of 400 Hz, transmission capacity is maximal, if they fire at half of their maximum rate; i.e. 200 Hz. Yet in practice, the mean firing rates of neurons *in vivo* is much lower – around 4 Hz (Harris et al., 2012). Against this background, it seems plausible that such a low basal glutamate release probability could be enhanced on demand. An action potential is much more likely to result in the release of glutamate, if locus coeruleus output is high. According to the calculations of Levy and Baxter, such a high glutamate release probability – that is induced by high LC activation – is energetically much more expensive than synaptic transmission occurring with low LC activation, which constitutes the economically optimal mode (Levy and Baxter, 1996).
With respect to energetic constrains, the number of release sites from an axon onto a postsynaptic cell is also important. This number is larger than 6 for cortical pyramidal to interneuron synapses, larger than 4 for pyramidal cell to pyramidal cell synapses in cortex, and 6 for excitatory synapses onto pyramidal cells in hippocampal area CA1 (Deuchars and Thomson, 1995; Larkman et al., 1997; Markram et al., 1997). Julia Harris and David Attwell showed that in case of multiple release sites – from one axon onto a postsynaptic cell – the optimal release probability is 25%–50%; optimal with respect to the quotient of information transmitted to energy expended (in bits per joule) (Harris et al., 2012).

It has long been recognized that cortical neurons collectively exhibit synchronous activity patterns (Salinas and Sejnowski, 2001). Correlated (i.e., coherent) fluctuations play a crucial role in many cortical processes. If one neuron fires, and the other one is more (or less) likely to fire, we call their activity 'temporarily correlated'. Many neurons are able to sense temporarily correlated input patterns. A neuron can detect coincident firing patterns, if spikes from two inputs arrive within a short time interval. But neurons can also can sum up their inputs to elicit an action potential (Konig et al., 1996; Shadlen and Newsome, 1994). A neuron is called 'balanced', if both excitatory and inhibitory inputs are strong and cancel each other out. In this way, the mean input current approximates zero, and the average steady-state voltage is insufficient to generate an action potential. Yet, such a balanced neuron might still generate an action potential, since stochastic voltage fluctuations always occur that are large enough to cross the necessary threshold. Balanced neurons are more sensitive to coherent (i.e. correlated) presynaptic input than unbalanced neurons (Salinas and Sejnowski, 2001).

A few years ago, it was shown that if the input from an *excitatory* neuron A and the input from an *inhibitory* neuron B are correlated, then the fluctuations of the postsynaptic neuron decrease (Salinas and Sejnowski, 2001). Let us assume that L2-error-unit-pyramidal cells receive inhibitory input (conveying predictions from the level above) and excitatory input (encoding the empirical priors from the current level). If predictions from the level above and priors from the current level are highly correlated, then fluctuations of L2-error units will be attenuated. Conversely, if there is a mismatch, then synaptic fluctuations will ensue, and the L2-error unit will start firing. In this way, the L2-error units are capable of encoding and conveying prediction errors.

The mechanisms described here for the detection of non-correlated inputs can explain how superficial pyramidal cells extract newsworthy prediction errors for broadcasting deeper into the brains hierarchy. However, the precision of these prediction errors depends upon how L2-error units respond to their opposing presynaptic inputs (Brown and Friston, 2012). It is here that NE (and other neuromodulators) comes into play in a very special way.

3.1.4. NE increases the precision with which prediction errors induce Bayesian updating

If the brain is in the business of inferring what its body should do next, it has to encode – at some level – probability distributions (Richmond and Wiener, 2007). Several probabilistic neuronal codes are mathematically possible, but most of the available evidence points to predictive coding, in which the activity of single units or populations encodes the mean of a Gaussian probability distribution (Friston, 2009). When assuming that neurons encode a Gaussian posterior distribution (the so-called 'Laplace approximation'), their firing rate is taken to represent the posterior mean or expectation. However, if neuronal firing encodes a mean what encodes the standard deviation; i.e. uncertainty? The premise of predictive coding is that precision is encoded by the response amplitude or gain of the neurons encoding prediction errors. The key point here is that the noradrenergic modulation affects presynaptic gain control – and therefore contributes encoding of precision: NE increases the probability of *presynaptic* neurotransmitter release onto L2-neurons, and in so doing renders the *postsynaptic* L2-neuron more responsive to non-correlated inputs. Thus, NE increases the number of action potentials that the L2-error unit generates when it receives non-correlated input signals. Such an increase in the number of action potentials of the L2 error unit forwards more weight to the ascending prediction error; i.e., to the bottom-up sensory information flow.

In summary, NE enhances information transmission at the synapses, and in so doing enables the L2-error-unit-pyramidal populations to endow prediction errors with higher precision. In this way, NE acting on the sensory cortex – that occurs in situations of uncertainty – adds value and weight to the bottom-up-information flow. Therefore, during stress, the sensory evidence becomes more influential than (relatively imprecise) prior expectations. Such selective increases in precision are key for updating beliefs about the world that engender uncertainty and stress.

3.1.5. The 'selfish brain' provides the energy for increasing precision

Where does the extra brain energy needed during uncertainty and stress come from? In many people – but not in habituators (see below) – the brain demands supplementary cerebral energy from the body stores (Peters and McEwen, 2015). The ACC-amygdala complex not only stimulates LC neurons, but in parallel stimulates the SNS and the HPA-axis (Fig. 3). SNS and HPA-axis activations immediately suppress insulin secretion from the pancreatic β-cells (Ahren, 2000; Chan et al., 2007; Frühwald-Schultes et al., 2000; Tong et al., 2007). Consequently, insulin-dependent GLUT4-mediated glucose uptake in muscle and fat is prevented, rebalancing energy consumption in favor of the insulin-independent GLUT1-mediated glucose uptake at the blood-brain barrier (Hasselbalch et al., 1999). In this way, the brain foreshadows its own increased cerebral energy need induced by stress.

In conclusion: During arousal, noradrenergic regulation of presynaptic neurotransmitter release probabilities leads to precise, high gain transmission of sensory evidence required to update deep, hierarchical beliefs about changes in the external and internal milieu. At the same time, the selfish brain supplies itself with the extra energy required for precision-engineered belief updating.

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3.2. Learning – updating during and after stress

The second key process for mastering uncertainty is learning. Glucocorticoids control functional and structural plasticity in many brain regions (Fig. 3).

3.2.1. Glucocorticoids gate the time window for cortical plasticity

In the case of uncertainty about what to do next (i.e., large divergences between the beliefs about 'attainable states' and 'goal states' under all available strategies), the ACC-amygdala complex stimulates the HPA-axis and – in so doing – increases the concentration of glucocorticoids in both blood and brain (Fig. 7A). In the hippocampus, amygdala, and cerebral cortex, glucocorticoids bind to MR and GR receptors that are located both within neurons (cytosol, nucleus) and on neuronal surfaces (membranes) (Arriza et al., 1988; Patel et al., 2000; Sanchez et al., 2000).

Here, we focus on intracellular MRs and GRs. These two intracellular receptors differ in their affinity for cortisol: MR binds cortisol with high affinity, GR with low affinity (Arriza et al., 1988). Once cortisol has activated these receptors in the cytosol, MR and GR enter the cell nucleus where they exert differential effects on gene expression (de Kloet et al., 1998). Fig. 7B shows the MR and GR binding characteristics of glucocorticoids in a pyramidal cell. With respect to synaptic plasticity; i.e., long-term potentiation (LTP) and long-term depression (LTD), MR and GR have been shown to act in an opposing manner on gene expression (Diamond et al., 1992; Pavlides et al., 1994, 1996). Here, we focus on how declarative memories are formed under stress, which is distinct from the way emotional memories are conserved (Maggio and Segal, 2012; Quirarte et al., 1997; Zhou et al., 2010).

At low cortisol concentrations, the facilitatory effect of MRs on plasticity prevails, while at high cortisol concentrations, the inhibitory effect of GRs prevails. Due to the opposing actions of MR and GR, the *difference* in effects on gene expression becomes paramount (Datson et al., 2001). The MR-GR difference depends on the glucocorticoid concentration and shows a 'bell-shaped' (or 'inverted U-shaped') dependency (Fig. 7C) (de Kloet et al., 1998; Joels, 2006). A bell-shaped dependence on glucocorticoids is evident, for example, for the probability occurrence of LTP (Fig. 7C) (Diamond et al., 1992; Joels, 2006; Pavlides et al., 1994, 1996). Consolidation of declarative memories is most likely when glucocorticoid concentrations are low in the normal range (where the bell-shaped curve has its peak). In contrast, consolidation is unlikely when glucocorticoids are absent (left-hand side of the bell-shaped curve) (Wagner et al., 2005) or when glucocorticoid concentrations are high (right-hand side of the bell-shaped curve) (Plihal et al., 1999). Likewise, retrieval of memories also shows a bell-shaped dependency on glucocorticoids, i.e. retrieval is optimal at low (normal range) glucocorticoid concentrations, but impaired at very low and very high glucocorticoid concentrations (Rimmele et al., 2013).

For an inclusive understanding of the role of glucocorticoids in updating the 'internal model of the world', we have to consider learning in the context of predictive coding. Previously, we have talked about *inferring* states of the world in terms of neuronal *activity* and how this depends on the precision of prediction errors encoded by *activity* dependent changes synaptic efficacy mediated, in this setting, by NE. However, this inference depends upon having a good model of the world encoded in the hierarchical connections that convey descending predictions. This model is learned over long timescales through *experience* dependent plasticity; such as LTP and LTD. On this view, the MR-GR difference is therefore in a prime position to control the *rate of learning* – in the same way that NE controls the *rate of inference* and evidence accumulation by boosting the precision of prediction errors. This learning rate has

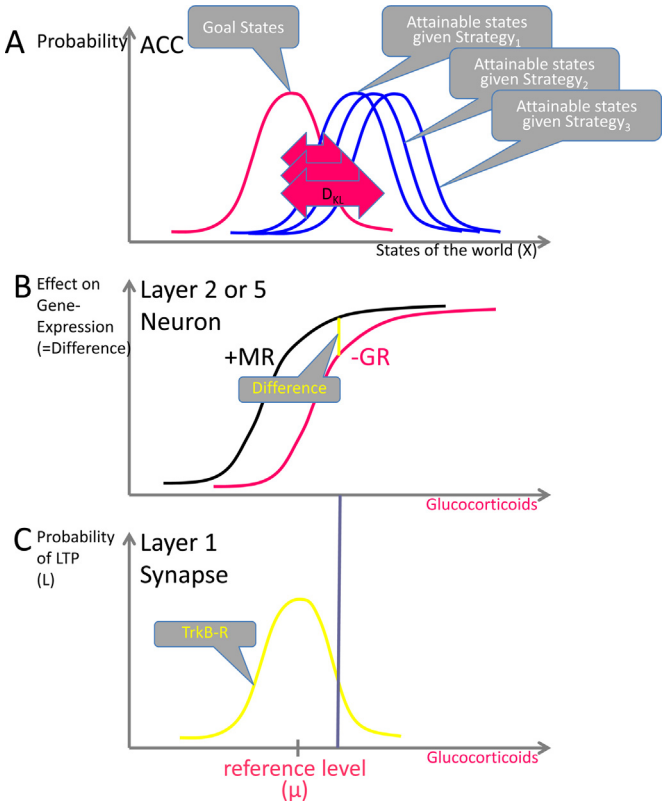

Fig. 7. Glucocorticoids enable or preclude cortical plasticity. Panel A. In case the ACC fails to select among plausible strategies, uncertainty arises about which strategy to pursue, leading to amygdala activation, which results in the increase of glucocorticoid concentrations in blood and brain. Panel B. Glucocorticoids bind with high affinity to intracellular MR and with a low affinity to intracellular GR. Intracellular MR and GR exert opposing actions on the expressions of a subset of genes involved in long-term plasticity, e.g. the gene encoding the TrkB receptor (Schaaf et al., 1997). Thus, the combined effect of MR and GR on gene expression corresponds to the difference between the MR-dose-response curve and the GR-dose-response curve. Panel C. The combined effect of MR and GR is represented by a 'bell-shaped' curve. For instance, the production rate of TrkB receptors follows such a bell-shaped function. Since protein production is necessary for maintaining long-term plasticity, the dependency of LTP-probability on glucocorticoid concentrations also shows a bell-shaped form. Of note, the bell-shaped curve depicted here can be interpreted as a probability over consolidation of experience dependent plasticity. The mode μ indicates the glucocorticoid concentration, where probability of LTP has its peak.

itself to be optimized to produce the best generative models. Clearly, if we experience the world as uncertain or ambiguous, we want to suspend learning. Conversely, if we experience it as predictable and lucid, we want to consolidate what we have learned. Given that LTP is selectively enabled over a carefully controlled window of MR-GR difference (Fig. 7), glucocorticoids open and close the time windows for 'learning' (Joels, 2006; McEwen, 2015). They are therefore in a key strategic position to selectively consolidate when and what we learn.

In conclusion: High glucocorticoid concentrations create a 'phase of change', revising the current model of the world (including its strategies). Low glucocorticoid concentrations create a 'phase of conservation', stabilizing the current model of the world.

As mentioned, LTP shows a bell-shaped dependency on glucocorticoids. The crucial insight now lies in the fact that TrkB signaling is required for the production of proteins that maintain LTP (Langemann et al., 2008; Minichiello et al., 1999; Zhang and Poo, 2002), and that TrkB receptor production rate displays a bell-shaped-dose-response dependency on glucocorticoids (Schaaf et al., 1997; Shi and Mocchetti, 2000). Consequently, TrkB constitutes a link that mediates the bell-shaped-dose-response

dependency of LTP probability on glucocorticoids – and determines when changes to our internal models should or can be consolidated.

Many other biological functions also show a bell-shaped dependency on glucocorticoids (de Kloet et al., 1998). In the current paper, we regard this bell-shaped dependency on glucocorticoids as embodying a reference point for the optimal level of experience-dependent plasticity. As uncertainty or stress is, by definition, a sign that our generative models are not fit for purpose (i.e., have a high free energy), we should not endorse anything learned under these models by consolidating associative plasticity. This is consistent with a suspension of (maintenance of) LTP during high glucocorticoid and stress levels. Turning this argument on its head, the minimum free energy state must be associated with low glucocorticoid levels that permit learning. These optimal levels therefore reflect a reference signal or setpoint to which our bodies (and brains) must aspire. In short, glucocorticoid levels can be interpreted as a correlate of uncertainty over the timescales of experience-dependent plasticity.

Heuristically, this means that we strive to achieve states that go along with low (i.e., normal) glucocorticoid concentrations (i.e., the reference level μ in Fig. 7C). A special and interesting case presents itself, where the glucocorticoid-dependent biological function is the 'glucocorticoid release into the blood circulation'. In this case, the glucocorticoid concentration *itself* depends on the glucocorticoid-dependent bell-shaped relationship. Thus, a setpoint is generated that depends primarily on the functioning of the MR in coordination with GR (de Kloet et al., 1998; Peters et al., 2007a). As a result, the HPA-axis always strives to retain a low blood concentration of cortisol. Therefore, those states with low (normal) glucocorticoid concentration are the most probable states that we find ourselves in. It works like this: Decreased glucocorticoid concentrations stimulate the HPA-axis, while increased glucocorticoid concentrations (circadian or stress-induced) inhibit it (Akana et al., 1988; Fehm et al., 1977; Jacobson et al., 1988; Peters

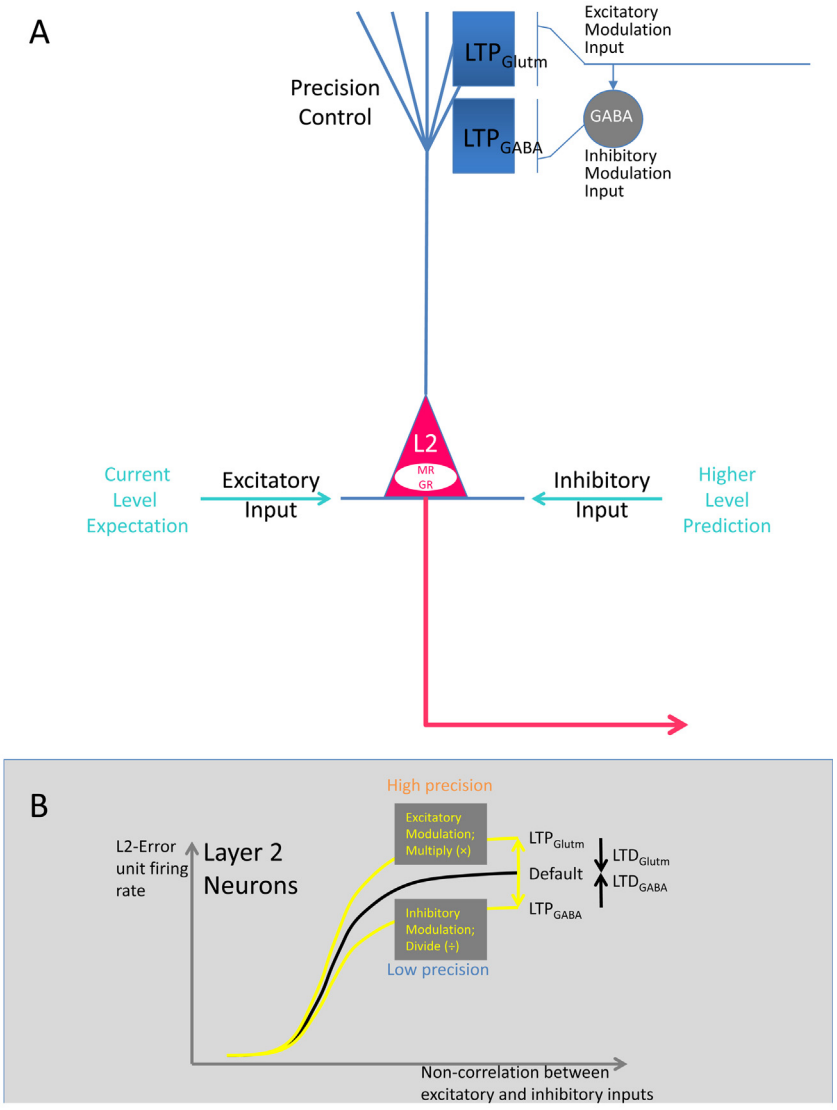

Fig. 8. Learning the prediction error precision. Panel A. The apical tuft of an L2-pyramidal neuron is involved in precision control. The apical tuft receives excitatory and inhibitory input from layer 1 that modulates the postsynaptic gain of the pyramidal neuron. Excitatory modulation input increases the postsynaptic gain, while inhibitory modulation input decreases it. Panel B. The output of the L2-neuron, which is the precision weighted prediction error, depends on the difference between excitatory and inhibitory inputs. Modulatory input onto the apical tuft increases or decreases the slope of the input-output function; therefore, controlling the gain of postsynaptic responses encoding prediction error. LTP occurring at glutamatergic input synapses of the apical tuft fixes an increased slope of the input-output function. In this case, the prediction error is encoded with a high precision, i.e. it gets more weight as compared to the corresponding higher-level prediction error. LTP occurring at GABAergic input synapses of the apical tuft fixes a decreased slope of the input output function. In this case, the prediction error is endowed with low precision, i.e., is weighted lower.

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et al., 2007a). In this way, an equilibrium cortisol concentration is reached (typically during deep sleep) that represents the mode of the reference distribution shown in Fig. 7C. In contrast, states with high glucocorticoid concentrations are to be avoided (e.g., when learning to drive a car).

In addition to the self-stabilizing MR/GR feedback, the HPA-axis receives input from the cerebral cortex. A substantial input derives from the ACC, which is in a position to convey messages about rising uncertainty (i.e., expected free energy), and in so doing stimulates the HPA-axis. Under the assumption that our choices are informed by biological and prosocial goals (e.g., satiety, affiliative touch, pleasant temperature, etc.), then glucocorticoid concentrations will remain low if these goal states are attainable. Conversely, if these goals are deemed unattainable, then the glucocorticoid concentrations rise. In short, glucocorticoid concentration is a direct reflection of whether the world is unfolding according to expectations or not.

In conclusion, the probability that a synapse undergoes LTP shows a bell-shaped dependency on the glucocorticoid concentration. There is an optimal glucocorticoid concentration that favors LTP. This optimum reflects the absence of prediction errors, or in other words, the free energy minimum.

3.2.2. Stress and surprisal

In information theory, the term 'surprisal' – coined by Myron Tribus – is used to describe the deviation from one's expectations (Tribus, 1961). For a given probability distribution over outcomes Y, surprisal is defined as the negative logarithm of P(Y): i.e., $-\log(P(Y))$. Thus, surprisal represents the improbability or 'surprise' of observing an outcome; for example, reaching into your pocket for your phone and finding it is not there. Crucially, the 'expected surprisal' is 'entropy'. Entropy is the mathematical measure of uncertainty, which is approximated by expected free energy. This means that glucocorticoid levels may not only underwrite the

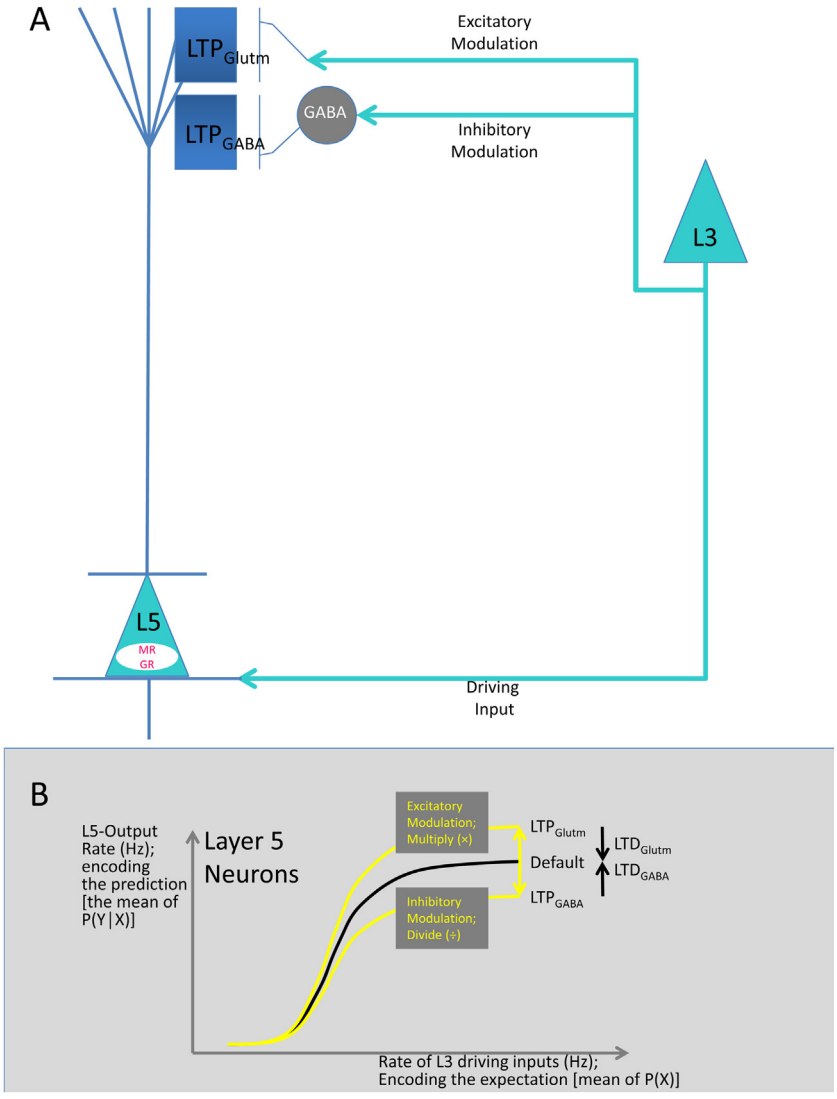

Fig. 9. Learning the generative model. Panel A. Triple pathways control the updating of the generative model. The prior-L3 neuron sends three pathways to the likelihood-L5 neuron: the driving-input path, the excitatory-modulation-input path, and the inhibitory-modulation-input path (which includes an inhibitory interneuron). As long as glucocorticoid concentrations are high (during stress), LTP at glutamatergic and GABAergic synapses is prevented. LTP occurs at the L5 neuron's tuft only if glucocorticoid concentrations fall (after stress) and can ensue either in the excitatory or in the inhibitory path. Panel B. The generative model consists of the prior and the likelihood. The slope of the input-output function of the layer-5 neuron represents functional gain between expectation and prediction. Excitatory modulatory input increases the postsynaptic gain, while inhibitory modulatory input decreases it. Once the generative model is updated it can be conserved through LTP. In contrast, LTD would reset the slope of the input-output function into a neutral 'default slope'.

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expected metabolic free energy associated with stressful (e.g., flight or fight) responses, it may also reflect changes in informational or variational free energy. The above analysis also suggests that levels of high free energy preclude a consolidation of experience dependent plasticity – until the world becomes more predictable and glucocorticoid levels return to their equilibrium levels.

In uncertain and threatening situations, descending predictions of stress-related responses are broadcast by the ACC to the anterior insular and onto autonomic centers to elicit autonomic reflexes (Barrett and Simmons, 2015; Behrens et al., 2007; Feinstein et al., 2006; Karlsson et al., 2012; Liljeholm et al., 2013; Paulus et al., 2002; Sarinopoulos et al., 2010). The ACC-amygdala complex activates the HPA-axis, cortisol concentrations increase, cortisol binds primarily to cerebral GRs. Only if the glucocorticoid concentrations return to low concentrations, which bind primarily to cerebral MRs, will long-term plasticity in cortical neurons (e.g. layer-5-pyramidal cells) be induced and maintained. Thus, learning of our internal model of the world can only occur at a low glucocorticoid concentration, when our models are fit for purpose – according to our ACC.

In conclusion, if the internal model of the world makes false predictions, high glucocorticoid values indicate a high free energy (i.e., uncertainty); the model is changed and functional plasticity is precluded. Once the updated model succeeds in making correct predictions, low glucocorticoid values indicate a low free energy (i.e., predictability); the model is consolidated and functional plasticity re-emerges.

3.2.3. Functional plasticity at the apical tuft

In the preceding treatment, we distinguished between inference and learning; where the former entails optimizing expectations about states of the world through synaptic *activity* and the latter entails optimizing expectations about parameters of the model through synaptic *plasticity*. In the following, we will focus on the specific mechanisms that the glucocorticoids use to optimize long-term synaptic efficacy.

Glucocorticoids act, among other things, on synapses that are located in the apical tuft of pyramidal cells. A layer-1-input axon excites either the dendrites of apical tuft or inhibits them using axonal collaterals with an interposed GABA interneuron (Figs. 8 A and 9 A) (Jiang et al., 2013). Glucocorticoids control the maintenance of LTP or LTD at these glutamatergic and GABAergic synapses. The excitatory and inhibitory inputs arriving at the apical tuft play an important role in regulating the postsynaptic gain of the pyramidal neurons. Thus, glucocorticoids are in an ideal position to modulate the synaptic gain of pyramidal neurons in the long term.

By controlling the postsynaptic gain of pyramidal neurons, the glucocorticoids may play a key role in learning the 'precision of prediction errors' (encoded by L2 neurons) and the 'generative model' (encoded by L5 neurons) (Figs. 8 A and 9 A). Dendritic gain modulation at the apical tuft has been shown to increase the gain of layer-5-pyramidal neurons (Larkum et al., 2004, 1999). The combination of input to basal dendrites or soma with distal input into the apical tuft increases the slope of the input-output function of the neuron. This increase in gain is due to the fact that the back-propagating Na^{+} action potentials interact with the weak distal synaptic input; such an interaction generates forward propagated Ca^{++} action potentials that in turn elicit a burst of multiple action potentials originating from the axonal spike initiation zone (Larkum, 2013; Larkum et al., 2004). Excitatory input to the apical tuft increases the postsynaptic gain of the pyramidal neuron, while inhibitory input to the apical tuft reduces it (Figs. 8 B and 9 B).

Whether LTP or LTD occurs at a synapse depends on two factors: first, correlated activity between the pre- and postsynaptic neuron and the glucocorticoid concentrations. LTP is consolidated if there is highly correlated activity between the pre- and postsynaptic neuron *and* the glucocorticoid concentrations remain in the low (normal) range (Maggio and Segal, 2007, 2009). In all other cases, LTP is attenuated or even LTD occurs (Maggio and Segal, 2007, 2009).

The consolidation of a generative model through LTP or LTD occurring at the apical tuft of pyramidal neurons is selectively enabled when the world is learnable; i.e. when expected surprise, uncertainty and glucocorticoid levels are low. In what follows, we consider this learning in more detail.

3.2.4. Glucocorticoids gate learning of prediction-error precision

Why would the brain learn the precision of prediction errors? It is often difficult to decide whether one should rely on sensory input or prior expectations. At dusk, for example, it is better to rely on prior expectations than on sensory input (the latter provides imprecise information due to the low levels of illumination). However, in bright daylight, it may be better to trust reliable and precise sensory input than prior expectations. Thus, the precision of prediction errors encoded at lower and higher levels of the cortical hierarchy allow the optimal weighting of the bottom-up and top-down information flow. Depending on what is more precise, either the sensory input or the prior expectation is afforded greater weight. The key point here is that precision can be learned on the basis of past experiences that enable the brain to predict when sensory input will be precise or imprecise.

As mentioned above, NE increases the probability of presynaptic neurotransmitter release at basal dendrites, making the L2 neuron more sensitive to non-correlated presynaptic inputs. In this way, NE effectively increases the precision of the reported prediction error, which manifests itself as increased attention. In contrast, glucocorticoids alter the efficacy of synapses located on the apical tuft of pyramidal neurons, resulting in long-term changes in the way that prediction error is evaluated – and the way that it is weighted according its precision. LTP at glutamatergic synapses of layer-1 inputs increases the precision of the prediction error (Fig. 8B). LTP at GABAergic synapses of layer-1 inputs decreases the prediction-error precision. However, if LTD is involved in glutamatergic or GABAergic synapses on the apical tuft, such a long-term depression returns the input-output function to a default mode with a 'neutral default slope' (Fig. 8B). Therefore, high glucocorticoid concentrations may lead to 'unlearning' of the precision of prediction errors, while low concentrations of glucocorticoids may facilitate the learning of precision weighting (Liston et al., 2013; Liston and Gan, 2011). This may sound complicated; however, the brain has to (i) optimize the precision of ascending prediction errors (e.g., through creating NE hotspots), it has to (ii) learn the right predictions (e.g., through synaptic plasticity that is selectively consolidated during low (normal) levels of glucocorticoid) and, finally, it has to (iii) learn how to optimize the precision of prediction errors (e.g., through the interaction between NE and glucocorticoid levels described above).

In conclusion, glucocorticoids govern how the brain learns the precision of prediction errors. Such a learning process allows us to discriminate between trustworthy and imprecise sources of information.

3.2.5. Glucocorticoids gate learning of the generative model

We can also optimize and learn the way we translate an expectation into a prediction. As noted above an empirical prior is encoded by an *expectation* (i.e., the firing rates in layer-3-pyramidal cells), and the likelihood by a *prediction* (represented in layer-5-pyramidal cells). The L3-'empirical prior' neuron provides the input to the L5-'likelihood' neuron, which in turn responds with

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the prediction. It has been shown experimentally that three input paths can influence the output of the pyramidal cell: driving input, excitatory modulation input and inhibitory modulation input (Mehaffey et al., 2005; Silver, 2010). The driving input targets the basal dendrites or the soma of the pyramidal cell. The excitatory modulation input targets the apical tuft of the pyramidal cells that is located in layer 1. The inhibitory modulation input – which consists of an interposed GABAergic elongated neuroglia form cell (Jiang et al., 2013) – also targets the apical tuft. These modulation input pathways allow modifying the slope of the input-output function or postsynaptic gain of the pyramidal cell (Mehaffey et al., 2005; Silver, 2010).

Here, we apply this triple input concept to the connections between L3 empirical prior neurons and L5 prediction neurons (Fig. 9) (Jiang et al., 2013; Thomson and Lamy, 2007). The excitatory and inhibitory modulation paths increase or decrease the slope of the L5-input-output function. Low (normal) glucocorticoid concentrations facilitate LTP at glutamatergic and GABAergic synapses on the apical tuft, thereby fixing an increased or decreased slope of the input-output function (Fig. 9B). An increase in the slope means that a given expectation (encoded by the L3-driving input) results in a larger value of the prediction (encoded by the L5-output rate). Thus, the functional relationship between expectation and prediction can be learned. In contrast, LTD, which occurs at high glucocorticoid concentrations, resets the slope of the input-output function to a default mode. Such a long-term depression may correspond to an 'unlearning' of the functional relationship between expectation and prediction (Bennett et al., 1964).

In summary, glucocorticoids also govern expectations generating predictions. A beneficial effect of glucocorticoids is that they enable us to learn how to make optimal predictions in a particular situation.

3.2.6. Structural plasticity at the apical tuft

In pyramid cells, the glucocorticoids also influence how the structure of the dendritic tree is shaped. Brain circuitry can be remodeled by experience (Bennett et al., 1964), and stressful experiences have functionally relevant effects on synapse number, dendritic spine formation, and dendritic arbor shaping in many brain regions, including the hippocampus, amygdala, and the PFC (Liston et al., 2013; McEwen and Gianaros, 2011). Plasticity and remodeling are processes that consume a considerable amount of energy (Placais and Preat, 2013).

In dendritic spine remodeling, learning leads to the induction of spine formation, and successively, a portion of novel spines is stabilized and a portion of existing spines is pruned (Hubener and Bonhoeffer, 2010; Yang et al., 2009). Spine stabilization shows a bell-shaped dependency on glucocorticoids. High glucocorticoid concentrations have been shown to favor postsynaptic dendritic spine formation (GRs exert trophic effects via TrkB signaling) (Ikeda et al., 2015; Jeanneteau et al., 2008), whereas low glucocorticoid concentrations are required for the stabilization of freshly formed spines, the latter process being essential for memory consolidation (Liston et al., 2013).

Dendritic arbor shaping also depends on stress exposure. In the PFC of young animals, chronic stress leads to shrinkage of the distal apical dendrites; after cessation of chronic stress, dendritic trees regrow (McEwen and Morrison, 2013). When animals recovered from stress, distal dendrites were not fully rebuilt, but proximal dendrites showed hyperextension and spine growth, and deficits in synaptic plasticity were complete restored (Goldwater et al., 2009). Such recovery after stress cessation is blunted by middle age and disappears in aged animals (McEwen and Morrison, 2013). Long-term glucocorticoid treatment mimics the effects of chronic stress; it leads to retraction of apical dendrites in the PFC (Cerqueira et al., 2005). If uncertainty and stress persist, diverse processes like LTD, suspended spine stabilization, and the shrinkage of the apical dendrites prevent dendritic gain modulation (Liston and Gan, 2011; McEwen and Gianaros, 2011). In this way, the specification of both the generative model and the precision of prediction errors are suspended. Thus, chronic stress results in functional and structural alterations, which can be regarded as the deconstruction of the 'internal representation of the world' – that was no longer appropriate. Such a deconstruction seems to be a prerequisite for rebuilding a new model of a world that is more fit for purpose.

In summary, both functional and structural plasticity of pyramidal neurons show a bell-shaped dependency on glucocorticoids. Thus, the high concentrations of glucocorticoids during stress and uncertainty allow the synaptic efficacy of apical tuft inputs to change over time. Moreover, stress and uncertainty lead to the shrinkage of the distal apical dendrites. In this way, both the generative model and the synaptic mechanisms of precision or gain control are disassembled. When stress is resolved and the situation is eased, the glucocorticoid concentrations fall: Then the (synaptic efficacy) parameters that learn the precision of prediction errors and the generative model are consolidated – enabling the learning of an internal model when, and only when, they are capable of resolving uncertainty and stress.

3.3. Habituation – updating of goal states

3.3.1. Habituation

The third process for coping with uncertainty is stress habituation. How individuals react during stressful episodes may change during the life course. When exposed to threatening changes in the external environment or the body milieu, people show two distinct genetically predisposed response patterns (Kirschbaum et al., 1995). Non-habituators maintain their high stress responses when the stressful episodes recur. In contrast, habituators show attenuation of their autonomic and endocrine responses over time. Stress habituation can be viewed as a special form of learning, in which not only the glucocorticoids, but also the endocannabinoids play a central role (Hill et al., 2010; Patel and Hillard, 2008). Crucially, habituation enables us to better discriminate between conditions that should be avoided and conditions that could be tolerated. Habituation not only occurs in the stress system but also in many other biological processes at the cellular and systemic level. With respect to habituation, the question arises whether the typical repetition-induced attenuation is caused by inhibitory mechanisms or by more sophisticated (central) processes like 'predictive coding'. In fact, there is experimental evidence supporting the view that habituation has all the hallmarks of predictive coding (Ramaswami, 2014; Wacongne et al., 2012).

3.3.2. Habituators can tolerate stress

Problems occur, if we cannot appropriately update of our beliefs about *current states* and *attainable states* of the world. As a final resort, we can alleviate uncertainty by updating the beliefs about our *goal states*. This option can be regarded as a last option, because it entails revising our primary preferences or goals (that are usually held with high confidence or precision).

If habituators revise their prior preferences by broadening the probability distribution over goal states (i.e., attenuating their precision), KL divergences will decrease. As the goal state probability distribution is broadened, beliefs about the attainable states and the goal states start to overlap more. As can be seen from Fig. 10, a less precise prior preference enables a greater overlap between the beliefs about 'attainable states' and 'goal states' (compare Fig. 10A and B). Thus, habituation reduces the relative risk (KL divergence) of one or more strategies (Fig. 10C). These changes in relative risk also ensure that one or more strategy can secure future wellbeing; thereby reducing uncertainty about

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future outcomes (Fig. 10D). Through these adaptive changes in the probability distribution over strategies, the habituated individual becomes more confident about which strategy to select (Fig. 11). Because a broadening of the beliefs about goal states reduces uncertainty in many situations, habituators exhibit smaller glucocorticoid and cardiovascular responses than non-habituators. Accordingly, the glucocorticoid and cardiovascular responses are lower in habituators as compared to non-habituators (Fig. 11; three asterisk) (Kirschbaum et al., 1995). In parallel, stress habituation improves the levels of self-esteem and locus of control; i.e. the self-concept of own competence (Pruessner et al., 2005, 1999). In the context of habituators there is another tangible long-term benefit; namely, escape from the tyranny of allostatic load.

In short, allostatic load can be averted – at a subpersonal level – by reducing the precision of one's prior preferences; heuristically, adopting more realistic expectations about what can be achieved.

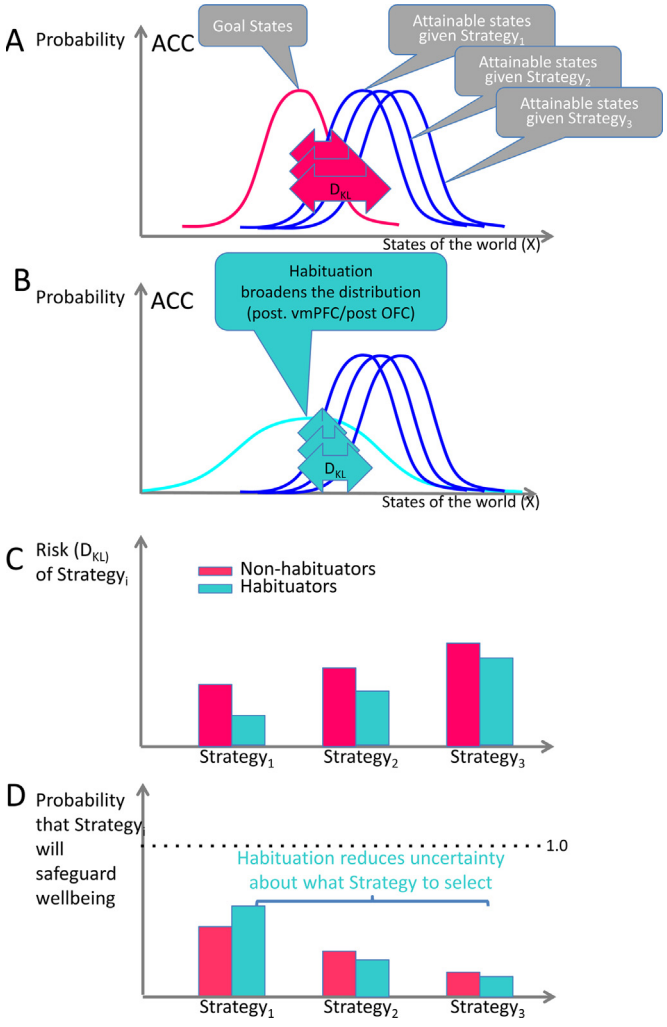

Fig. 10. Habituation as 'updating of goal states'. Panel A. In non-habituators the goal states are fixed and remain unchanged. Panel B. In habituators the precision of goal states is relaxed. Even though, for a given strategy, the habituators' beliefs about attainable states and the beliefs about goal states do not completely overlap, they still exhibit more overlap than non-habituators. Panel C. The KL divergences for each strategy are is smaller in habituators than in non-habituators. Thus, habituation decreases the risk. Panel D. Because a broadening of the beliefs about 'goal states' reduces KL divergences, it changes the probability of each strategy that it may secure wellbeing. These changes in the probability distribution over strategies mean that habituators become more confident about what strategy to select. This explains why habituators exhibit smaller glucocorticoid responses than non-habituators.

4. Allostatic load

4.1. The plasticity and vulnerability of the brain

Uncertainty about our responses to situations can be resolved by updating our beliefs about current states, attainable states, and goal states. A major problem arises if Bayesian belief updating fails to resolve uncertainty, leading to surprising or aversive outcomes. A successful update would require a reorganization of the brain architecture and neuronal circuits that includes synaptic plasticity (LTP) and structural plasticity (spine remodeling; rebuilding of the dendritic trees) (McEwen et al., 2016). However, when updates cannot avoid surprise, learning processes on different levels are suspended. Evidence accumulated that learning is suspended when glucocorticoids are persistently secreted during chronic stress (Bangasser and Shors, 2007; De Quervain et al., 1998; Lupien et al., 1998). With high glucocorticoid concentrations, postsynaptic dendritic spines are lost and dendritic branches shrink in various parts of the cortex and the hippocampus (Dias-Ferreira et al., 2009; Liston and Gan, 2011; Liston et al., 2006; Radley et al., 2006; Watanabe et al., 1992; Wellman, 2001). Fluctuating concentrations of glucocorticoids support a fine-tuned interplay between spine formation, pruning and maintenance, whereas states of prolonged glucocorticoid exposure interrupt this interplay (Liston et al., 2013).

Thus, inappropriate updates of our internal model lead to high glucocorticoid concentrations, and high glucocorticoid concentrations in turn prevent the conservation of such inappropriate updates. Likewise, inappropriate updates can lead to disturbed sleep or bad dreams (Antonijevic, 2008; Rodenbeck and Hajak, 2001). While sleep normally serves to optimize and conserve our generative models (Hobson and Friston, 2012), poor sleep is likely to preclude the revision of inappropriate models (Wagner and Born, 2008). Similarly, if someone is on therapeutic or recreational drugs that interfere with the cerebral mechanisms for mastering

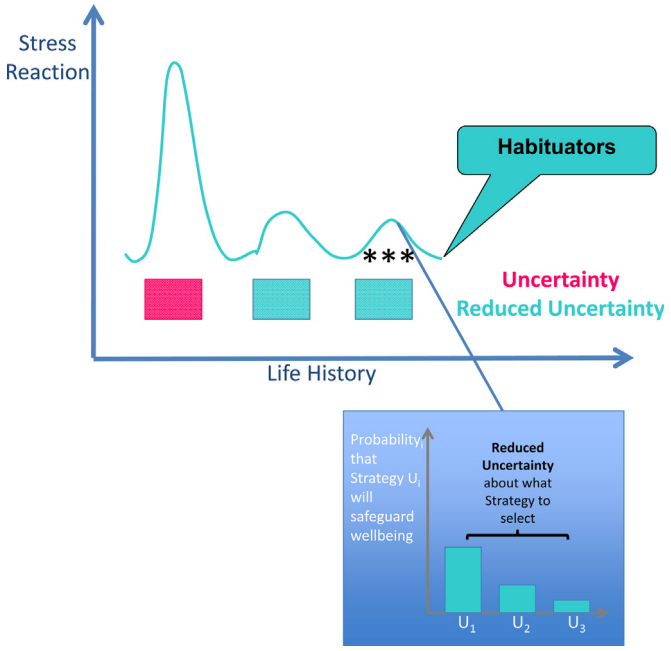

Fig. 11. Stress habituation. We define habituators as those who show repetition-induced-response attenuation (neuroenergetic, neuroendocrine, emotional and cardiovascular), when being chronically exposed to an inhospitable environment. When habituators are repeatedly exposed to the same homotypic stressor, they can reduce their uncertainty about which strategy they should select by redefining their goal states (***).

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uncertainty, a temporary well-being may be achieved by relieving the allostatic network, but a successful Bayesian updating of his/her internal model is suspended.

As mentioned above, high glucocorticoid concentrations create a 'phase of change' revising the current model of the world (including its strategies). If no appropriate update can be found, the ACC continues to report high uncertainty (or entropy) about which strategy to select. We suggest that the ACC-amygdala complex then sustains a hypervigilant state and hyperactivity of the allostatic network; in particular, the key components SNS and the HPA axis – the latter maintaining high glucocorticoid concentrations. The recurrent or persistent activation of the allostatic network then leads to damaging adverse effects that lead to systemic and brain pathology. This is allostatic load (McEwen and Stellar, 1993).

The healthy brain is resilient in the face of stressors and epigenetic cellular and molecular mechanisms produce continuous changes in gene expression. Thus, one cannot 'roll back the clock' after stress is over, so that we must speak of 'resilience' and 'recovery' rather than 'reversal' even though the alterations in neuronal structure and function may appear to have been 'reversed'; yet they are not the same as before (McEwen et al., 2015a,b; McEwen and Morrison, 2013). Acute and chronic stress interferes with cognition, decision making, anxiety and mood, and in so doing affects systemic physiology through neuroendocrine, autonomic, immune and metabolic mediators and multi-morbidity of disorders frequently occurs (McEwen, 2007; McEwen et al., 2015b; Rasgon and McEwen, 2016). In the short run, increased vigilance or anxiety in a hostile environment may be adaptive; however, when the danger passes and the behavioral state and the changes in neural circuitry become chronic, which get 'stuck', such maladaptation may require an external intervention to get it 'unstuck', as is the case for chronic anxiety or depressive disorders (McEwen, 2007; McEwen et al., 2015b).

Structural and functional allostatic plasticity is particularly evident in the hippocampus, a key structure for episodic and spatial memory and mood regulation (McEwen, 2007; McEwen et al., 2015a). The hippocampus was the first brain structure outside of the hypothalamus found to possess stress and sex hormone receptors and it provided a gateway into the hormone sensitivity of the rest of the brain (McEwen et al., 2015b).

The amygdala involved in fear, anxiety and aggression and the prefrontal cortex, important for working memory and executive function, both show functional and structural allostatic plasticity. In the amygdala, overlapping waves of excessively high concentrations of glucocorticoids and norepinephrine cause an extended window of excitability (Karst and Joels, 2016). Such a prolonged window of excitability is thought to contribute to the development of pathological conditions; e.g., posttraumatic stress disorder (Karst and Joels, 2016). Basolateral amygdala neurons expand dendrites from chronic stress (Chattarji et al., 2015) while, as noted earlier, medial PFC neurons, as well as hippocampal neurons, show dendritic shrinkage from the same stress (McEwen and Morrison, 2013).

4.2. Non-habituators are fully exposed to toxic stress

Because of continued uncertainty, the brain is constantly demanding for extra energy. Such an energy crisis with lack of habituation leads to allostatic load contributing to systemic and brain pathology. This energy crisis has two consequences: first, SNS/HPA-axis hyperactivity and second, metabolic alterations and stress-related health damaging behaviors (tobacco smoking, drinking alcohol, sleep deprivation). SNS/HPA-axis hyperactivity increases the risk of arterial blood flow turbulences, leading to atherosclerosis, thereby causing systemic and brain pathology (Peters and McEwen, 2015). Metabolic alterations and poor health behaviors lead to inefficient mitochondrial metabolism, resulting in reactive oxygen species (ROS) and inflammation and worsen systemic and brain pathology (Picard et al., 2014). These pathologies include memory impairment, depression, myocardial infarction, stroke, visceral fat accumulation, type 2 diabetes, muscle loss, osteoporosis, disturbed growth and reproduction (McEwen, 1998).

On the one hand, a long-lasting energy crisis of the brain damages the vascular system. To safeguard its high-energy demand, the brain (via the amygdalae) sends a sympathetic message to the heart, thereby increasing heart rate, and in so doing increases cardiac output in order to procure extra energy for itself. As stress-induced tachycardia increases flow velocity in the arterial vascular system, high flow speed in turn increases the risk of arterial turbulences (Falsetti et al., 1983) – particularly at branching sites of the blood vessel system (Malek et al., 1999). 'Adaptive vascular remodeling' describes processes in the vasculature that ameliorate such turbulences (Chatzizisis et al., 2007). However, if the capacity of 'adaptive vascular remodeling' is overwhelmed, turbulences are likely to persist. In this case, there is an increased risk that turbulences occur at predilection sites, thereby leading to atherosclerosis (Stone et al., 2012). Atherosclerosis in turn often causes myocardial infarction or stroke – and thus leads to an increased cardiovascular mortality. Just recently, a team of cardiologists, psychiatrists and psychologists showed that resting amygdala activity independently and robustly predicted cardiovascular disease events (Tawakol et al., 2017).

On the other hand, a long-lasting energy crisis of the brain may damage the mitochondria, and in this way toxic products may accumulate, which can lead to systemic inflammation and accelerated cellular ageing (Du et al., 2009; Picard et al., 2014). Mitochondrial allostatic load can be brought about by elevated glucocorticoid levels, even though low (i.e., normal) levels cause translocation of glucocorticoid receptors into mitochondria to promote Ca++ sequestration and maintain low levels of free radicals (Du et al., 2009).

4.3. Comparison of mortality among habituators and non-habituators

Randomized controlled trials have shown that psychosocial stress is a factor that causes cardiovascular mortality, and that decreasing allostatic load through stress-relief programs reduces cortisol responses and cardiovascular mortality (Gaab et al., 2003; Gulliksson et al., 2011; Hammerfald et al., 2006; Orth-Gomer et al., 2009; Storch et al., 2007). The special feature of these stress-relief programs is that participants can learn, among other things, to update their outdated models of the world in a cognitive manner, while the Bayesian Brain often updates its beliefs at a subpersonal level. There are also observational studies supporting the notion that people who respond strongly to stressful challenges display a high risk of atherosclerosis and cardiovascular mortality (Carroll et al., 2012; Everson et al., 1997; Hamer et al., 2010; Lynch et al., 1998; Seldenrijk et al., 2012). Conversely, people who respond weakly to stressful challenges exhibit a lower cardiovascular mortality, even if they stay in an inhospitable environment. In this way, habituators can alleviate their allostatic load when repeatedly exposed to the same stressor. As a consequence of an alleviated allostatic load, habituators can tolerate an inhospitable environment and are sheltered against cerebro- and cardiovascular events (Carroll et al., 2012; Everson et al., 1997; Hamer et al., 2010; Lynch et al., 1998; Seldenrijk et al., 2012). Such a tolerance leads to side effects on the systemic energy metabolism of the individual, which we will report elsewhere. Non-habituators, however, are fully exposed to toxic stress and thus are at increased risk of cardiovascular death.

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Box 5. Open Questions

There are still gaps in our knowledge of the neurobiological underpinnings of the Bayesian Brain concept. Future research may address the following open questions:

- What is the functional role of fast-acting membrane MR and GR in the Bayesian Brain concept?
- How does the Bayesian Brain control the encoding and retrieval of emotional memories?
- What happens in the Bayesian Brain when posttraumatic stress disorder develops?
- How do alterations/adaptations of the Bayesian Brain affect systemic energy metabolism, i.e. promote the development of anorexia or obesity?

*In summary, habituators can update their 'goal states'; as a consequence, they show attenuated responses when recurrently challenged, and in this way – although they continue to live in the inhospitable environment – they show a barely limited life expectancy. In contrast, non-habituators display a drastically shortened life expectancy; but they are the individuals who would benefit most from stress-relief programs that include cognitive restructuring, social skills development, and mindfulness (*Gulliksson et al., 2011; Orth-Gomer et al., 2009).

5. Updating the 'stress definition'

As suggested in the current paper, stress occurs, if we are surprised by our sensations and we are uncertain about what to do to safeguard our physical, mental or social wellbeing. Surprises can be manifold and can concern our internal body milieu (lack of energy, lack of oxygen, loss of blood, infection, toxins, trauma, myocardial infarction, etc.) or our external environment (social conflicts, overload/underload, disordered neighborhood, mobbing, discrimination, social defeat, etc.). Activation of the SNS or the HPA axis is typical in all these situations, but is not considered here to be a sufficient criterion for 'stress'.

Two examples illustrate the principle how we react upon changes in the internal and external environment: fasting and marital dispute. Fasting – as referred to as the metabolic state achieved after complete digestion and absorption of a meal – goes along with the activation of the SNS and HPA-axis. Such SNS- and HPA-axis activations serve to adequately supply the brain with energy (glucose, ketones, or lactate) (Kubera et al., 2012a, 2014). Since the brain-energy concentrations are tightly regulated (Oltmanns et al., 2008), such increases in SNS and HPA-axis activity are common in everyday life (Peters and Langemann, 2009). The Selfish Brain procures itself with energy (Peters et al., 2007b). After a few hours of fasting, we feel hunger and perceive SNS-induced interoceptive signals like nervousness, weakness, tremor, tachycardia, dizziness, and sweating. The (Selfish) Bayesian Brain uses perceptual inference to infer the cause (lack of thermodynamic energy) from the effect (the interoceptive signals). Then it uses active inference (food seeking behavior) to minimize variational free energy; i.e., to eliminate the prediction errors (hunger, autonomic symptoms). If we are certain that food would be available soon, the appropriate action is selected and 'no stress' occurs. However, if we are uncertain about whether we might get food at all, stress occurs – as is the case in 'food insecurity' (Bhattacharya et al., 2004). In such a case, uncertainty (entropy) monitored by the ACC stimulates the amygdala, and in so doing increases LC, SNS and HPA-axis activity; in this way, stress facilitates the search for a novel strategy (Figs. 2 and 3).

In a marital dispute, surprising external sensations may immediately evoke a state of uncertainty, in which one does not know how to resolve the situation. This is also 'stress'. The uncertainty monitored by the ACC stimulates the amygdala, and consequently the LC, SNS and HPA-axis; also in this case, stress facilitates a shift in strategy (Figs. 2 and 3). The Selfish Bayesian Brain procures itself with extra thermodynamic energy (enhanced glucose allocation to the brain) in order to minimize variational free energy (prediction errors) by searching for a novel strategy.

In light of the foregoing, we define 'stress' as the individual state of uncertainty about what needs to be done to safeguard physical, mental or social well-being.

6. Conclusions

We have introduced an information-theoretic account of stress and allostatic load based upon recent developments in theoretical neurobiology. In particular, we have established the link between the Bayesian Brain and the Selfish Brain in terms of minimizing variational and metabolic free energy respectively. When unpacked, the theoretical considerations provide a remarkable level of explanatory detail; particularly in relation to the role of norepinephrine in nuancing perceptual inference (and action) through its effects on presynaptic gain control – and implicit effects on the ability of sensory evidence to revise beliefs about hidden causes in the world or the body. Having established the close relationship between the roles of synaptic activity and efficacy (i.e., precision) in optimizing perceptual inference in situations of uncertainty, we then went on to look at the permissive role of glucocorticoids in learning. This analysis suggests that there is an optimum glucocorticoid level that enables the consolidation of activity-dependent plasticity (where the 'bell-shaped' glucocorticoid-dependency curve has its peak) (Joels, 2006) that mediates experience-dependent learning – when and only when, our generative models are sufficient to resolve uncertainty, stress and elevated glucocorticoid levels.

Finally, we considered long-term processes that could minimize variational free energy and stress by looking at the ultimate cause; namely, the discrepancy between states that we can attain by acting on the world and the states we *a priori* expect to occupy (i.e., interoceptive, proprioceptive, emotional and prosocial goals). Our key observation is that exposure to chronic stress – and the allostatic load that this entails – can be remediated by revising our highest-level prior beliefs; namely, prior expectations about the states we aspire to. This provides a nice metaphor that distinguishes between habituators and non-habituators in response to chronic stress.

Functional and structural remodeling of the neural architecture often makes it possible to avoid or master states of uncertainty, anxiety, and hypervigilance. 'Good Stress' denotes an episode of uncertainty in which the beneficial effects of stress responses support a successful Bayesian updating and learning of the internal model of the world. As a result, uncertainty is resolved. 'Tolerable stress' characterizes a situation in which habituation leads to a partial reduction in uncertainty; this reduction is achieved by the adjustment of the primary goals. In this case, the damaging effects

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of persistent stress reactions can be kept at bay. Of note, individuals cannot always resolve uncertainty by reconstructing their internal model of the world. The inhospitable environment may also limit such a resolution, e.g. when the individuals live in poverty, in war-afflicted areas, are long-term unemployed or victims of discrimination (Kubera et al., 2016; Ludwig et al., 2012; Puhl and Heuer, 2009). If the resolution of uncertainty is achieved too late or is not possible at all, the adverse effects of the futile and brain-energy-consuming efforts for the resolution come to the fore, and the ongoing brain-energy crisis leads to allostatic load that contributes to systemic and brain pathology. 'Toxic stress' refers to such a chronic condition in which the damaging effects of the stress responses prevail and the uncertainty can neither be resolved by a successful Bayesian update nor reduced by habituation. If, in such a situation, the brain 'gets stuck' and does not recover, external intervention is required.

The potential utility of formulating stress and allostatic load in terms of a Selfish Bayesian Brain is that one might use the principles afforded by theoretical neurobiology to organize existing and future empirical results (Box 5; 'Open questions'). Furthermore, the interrelationships brain function and physiology are laid bare in the sense that everything appears to be the game of reducing uncertainty, variational free energy, surprise, or more simply stress. Conceptual principles of this sort may be useful, not just from a scientific perspective, but as organizing frameworks for cognitive behavioral therapy in stress disorders.

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