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Review

The Bayesian brain: Phantom percepts resolve sensory uncertainty

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ABSTRACT

Phantom perceptions arise almost universally in people who sustain sensory deafferentation, and in multiple sensory domains. The question arises 'why' the brain creates these false percepts in the absence of an external stimulus? The model proposed answers this question by stating that our brain works in a Bayesian way, and that its main function is to reduce environmental uncertainty, based on the free-energy principle, which has been proposed as a universal principle governing adaptive brain function and structure. The Bayesian brain can be conceptualized as a probability machine that constantly makes predictions about the world and then updates them based on what it receives from the senses. The free-energy principle states that the brain must minimize its Shannonian free-energy, i.e. must reduce by the process of perception its uncertainty (its prediction errors) about its environment. As completely predictable stimuli do not reduce uncertainty, they are not worthwhile of conscious processing. Unpredictable things on the other hand are not to be ignored, because it is crucial to experience them to update our understanding of the environment. Deafferentation leads to topographically restricted prediction errors based on temporal or spatial incongruity. This leads to an increase in topographically restricted uncertainty, which should be adaptively addressed by plastic repair mechanisms in the respective sensory cortex or via (para)hippocampal involvement. Neuroanatomically, filling in as a compensation for missing information also activates the anterior cingulate and insula, areas also involved in salience, stress and essential for stimulus detection. Associated with sensory cortex hyperactivity and decreased inhibition or map plasticity this will result in the perception of the false information created by the deafferented sensory areas, as a way to reduce increased topographically restricted uncertainty associated with the deafferentation. In conclusion, the Bayesian updating of knowledge via active sensory exploration of the environment, driven by the Shannonian free-energy principle, provides an explanation for the generation of phantom percepts, as a way to reduce uncertainty, to make sense of the world.

Contents

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1. Introduction

In 1551, exactly 300 years before Herman Melville described phantom pain in Captain Ahab's missing leg in the book Moby Dick (1851), Ambroise Paré, a French military surgeon described the first phantom pain, and he believed it to be originating in the brain (Bittar et al., 2005).

Somatosensory deprivation leads to phantom perception in 90–98% of limb amputees (Ramachandran and Hirstein, 1998): immediately after the amputation in 75% of the patients and in a delayed fashion, after two to three weeks, in the remaining 25% (Ramachandran and Hirstein, 1998). Phantom pain, a specific kind of phantom perception, is present in 70% of limb amputees (Sherman et al., 1984). Even though in 14% the pain decreases in time (Sherman et al., 1984) it is generally accepted that once the pain continues for more than 6 months it becomes difficult to treat (Ramachandran and Hirstein, 1998).

Similarly, deprivation of auditory input can result in an auditory phantom phenomenon, also known as tinnitus. In sudden deafness 67% of patients present with tinnitus (Graham et al., 1978). In patients presenting with a vestibular schwannoma 70–80% of patients have tinnitus referred to the ipsilateral ear to the schwannoma (Moffat et al., 1998) and between 8.5% (Kameda et al., 2010) and 39.8% (Levo et al., 2000) of those who have no tinnitus develop it after tumor and cochlear nerve resection.

Both phantom perceptions occur in the deafferented area. For phantom sound the frequency spectrum of the tinnitus reflects the individual's hearing loss (Norena et al., 2002). Neuropathic pain is felt as coming from the area that was initially innervated by the injured neural structure (Flor et al., 2006) and phantom pain is perceived in the missing body part (Flor et al., 2006; Ramachandran and Hirstein, 1998). Phantom pain has to be differentiated from residual limb (or stump) pain in the still-present body part, adjacent to the amputation or deafferentation line (Flor et al., 2006).

Tinnitus and phantom pain can thus be defined as an involuntary simple auditory or somatosensory conscious percept in the absence of an external stimulus. In this sense it can be regarded as a simple form of hallucinations. The involuntary aspect differentiates it from imagery, and the absence of an external stimulus excludes it to be considered as an illusion, a distorted percept of a sensory stimulus. It is a symptom that can develop in virtually all diseases and disorders associated with a lesion in any part of the auditory or somatosensory pathway leading to partial or complete sensory deafferentation. Furthermore it is not limited to the auditory and somatosensory domain. Some cases of phantom percepts have also been described for the visual (Ffytche et al., 1998), olfactory and gustatory systems (Henkin et al., 2000). So, the question is why does this almost universally occur? Why does the brain, as Ambroise Paré already suggested 500 years ago, generate phantoms for missing sensory input? The answer to this question might be simple: this is the way brains operate normally on sensory input, constructing orderly perceptions from chaotic sensations. Why do brains do this? It is to reduce uncertainty and why phantom phenomena?

2. Two models of perception

Perception is different from sensation. Whereas sensation can be defined as the detection and processing of sensory information, perception is the act of interpreting and organizing this sensory information to produce a meaningful experience of the world and of oneself (De Ridder et al., 2011a; Freeman, 1999).

Historically two different models of perception have been developed (see Fig. 1), one which assumes that the brain passively absorbs sensory input, processes this information, and reacts with a motor and autonomic response to these passively obtained sensory stimuli (Freeman, 2003). This concept is based on Plato, later Christianized via Saint Augustine and has become mainstream thinking in sensory neuroscience through Descartes' influence (Freeman, 2003). However, a second model of perception posits that the brain actively looks for the information it predicts to be present in the environment, based on an intention or goal. This goal or intention can drive action which will influence perception. According to David Hume the motivation for action is desire, with reason being a slave, steering emotionally motivated action in a certain direction (Hume, 1740). This active form of perception is based on Aristotle, Christianized via Thomas Aquinas (Aquinas, 1268; Freeman, 2003) and evolved in constructivist or representational perception (Norman, 2002). Aristotle used Plato's concept of 'forms', which were abstract ideals and made it into something practical. According to Aristotle, in his book 'On the Soul' the 'form' is the sum of essential properties of a thing, which is stored in the soul, and used as a reference to look for as a recognizable pattern in the environment (Aristotle, 1986). In-form-ation is then imposing a 'form' on something (von Baeyer, 2003).

Constructivist perception is a top down indirect information creation, depending on what is expected in the sensory environment, relying on what is stored in memory ('form'). This goes back to the philosophy of Hume (1740) and Merleau-Ponty (1945), according to whom perception is always directed 'towards something': "to move one's body is to aim at things through it" (Merleau-Ponty, 1945).

Active touch perception has the advantage of being a better discriminator of the sensory environment than passive perception (Gibson, 1962). Active touch is an exploratory rather than a merely receptive sense. In fact, active touch can be termed tactile scanning, by analogy with ocular scanning (Gibson, 1962). When people are given six different equally large forms (cookie cutters) such as a triangle, a star, and teardrop, the accuracy of recognition can be compared when the form is pressed into the palm of the hand (passive touch) and when it is held above the palm and explored by the fingertips (active touch). A chance level of judgments would be 1/6 or 16.7%. For passive touch the mean frequency of correct matches was 49%. For active touch the mean frequency was 95%, significantly different (Gibson, 1962). This is similar to the visual system. During natural, active vision, we move our eyes to gather task-relevant information from the visual scene: objects and subjects are actively scanned (Yarbus, 1967). Thus seeing is similar to exploratory touch.

The major difference between passive perception and active constructive perception is that active perception critically depends on predictions of what is likely to occur in the environment, based on intentions or goals arising from experience, in contrast to passive perception.

3. The Bayesian brain

Humans and other animals operate in a changing environment (Knill and Pouget, 2004). In phenomenological terms, uncertainty

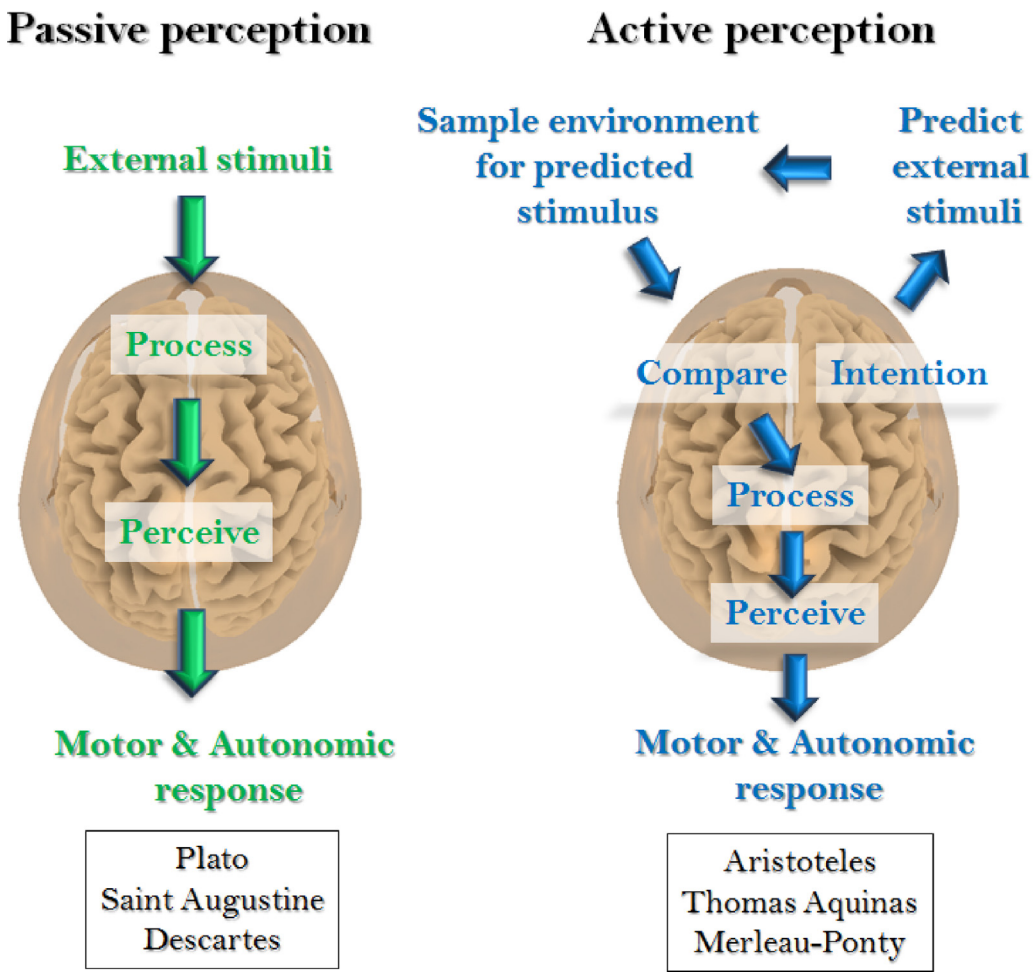

Fig. 1. Passive versus active perception. In passive perception it is assumed the brain passively absorbs sensory input, processes this information, and reacts with a motor and autonomic response to these passively obtained sensory stimuli. Active perception posits that the brain actively looks for the information it predicts to be present in the environment, based on an intention or goal.

is a state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing (Harris et al., 2008). As animals move around, resulting in a changing environment, this change implies an inherent uncertainty of what is going to present next in this changing environment (Quartz and Sejnowski, 2002). Key to survival is our ability to rapidly attend to, identify, and learn from unexpected events, to decide on present and future courses of action (Ranganath and Rainer, 2003). The sea squirt has been used as an example of this concept (Llinas, 2002): the sea squirt, in its larval stadium swims around in the sea and has a notochord and central ganglion, a simple nervous system. At a certain moment the sea squirt attaches to a rock from which it will never move. At that time the notochord and central ganglion degenerates, supposedly because to change from a moving to a sedentary creature permits it to survive equally well without a nervous system (Llinas, 2002). However, even when moving around, a brain is useless in a random world, as this does not permit predictions to be made. But the environment is not random, there are recurring patterns in the environment that can be predicted (Quartz and Sejnowski, 2002), suggesting that the inherent uncertainty of the environment is not complete but partially predictable based on previous or genetically stored experience. Brains must thus effectively process the resulting uncertainty to generate perceptual representations of the world and to guide our actions (Knill and Pouget, 2004). Hence, processing of sensory information may have evolved to adapt to, to predict, and to process the expected statistical regularities, i.e. recurring patterns of the world (Dragoi et al., 2002; Muller et al., 1999; Olshausen and Field, 1996), focusing instead on events that are unpredictable or surprising (Rao and Ballard, 1999). This leads to the idea that perception is a process of probabilistic inference (Knill and Pouget, 2004). The underlying idea is that the brain has a model of the world that it functions by optimizing using sensory inputs (Friston, 2010). It does so by applying a probabilistic model that can generate predictions, against which sensory samples are tested to update beliefs about their causes (Friston, 2010). The probabilistic model the brain uses is Bayesian. Bayes' theorem permits one to compute an updated probability something is true, based on the old probability of something being true with added new information. Twelve-month-old preverbal children can already predict moving objects based on Bayesian inference (Teglas et al., 2011).

Thus the Bayesian brain can be conceptualized as a probability machine that constantly makes predictions about the world and then updates them based on what it senses (Friston, 2010). In this way brains can be considered prediction machines that use information from previous experiences (memory) to predict future events (intelligence) in order to reduce uncertainty, which is important for survival (Quartz and Sejnowski, 2002). This is compatible with the concept of activist constructivist perception.

4. The importance of predictability

One of the most striking features of schizophrenia is hallucinations, false or distorted perceptions, such as people hearing other

people talking about them or hearing their thoughts spoken aloud (Fletcher and Frith, 2009) without an external sound source, without the person speaking to them really being present.

A fundamental problem underlying hallucinations is the loss of the distinction between relevant and irrelevant perceptions (Fletcher and Frith, 2009). The person persistently attends to stimuli that should be ignored, and this failure to ignore irrelevant stimuli might be due to a failure to tag these stimuli as self-generated (Fletcher and Frith, 2009). A significant difference between self-generated actions and something that occurs outside one's control is that in self-generated actions one can predict what will happen. If something is predictable it is easy to ignore and its sensory consequences can be dampened, because they are unsurprising (Fletcher and Frith, 2009). Physiologically this has been explained by the efference copy model: any motor action is accompanied by an efference copy of the action that produces a corollary discharge in the sensory cortex (Fletcher and Frith, 2009; Ramnani, 2006). Thus the preparation for the motor act entails a prediction of its ideal consequences, and efferent information is sent to the sensory cortex to suppress or fine-tune its perception. Mechanistically, motor commands generated in the motor cortex are sent to lower motor control centers in the brainstem and spinal cord. The cortico-ponto-cerebellar fibres on their way to the spinal cord collateralize, and the collateral projections synapse onto neurons in the pontine nuclei and are relayed to the cerebellar cortex (Ramnani, 2006). Outputs from the motor modules of the cerebellum project back via the cerebellar nuclei to the motor cortex via the thalamus to influence motor control at a relatively high level, perhaps directly influencing motor commands. The thalamus also relays the information as a corollary discharge to the sensory cortices (Ramnani, 2006). A comparator identifies discrepancies between the actual and predicted sensory consequences, and signals errors in the accuracy of the forward models. This error signal is used to alter input–output mappings in forward models so that subsequent predictions for the same situation can be made more accurately (Ramnani, 2006). The inferior olive has been proposed to perform this comparator function (Ramnani, 2006). A reafference mechanism sends the predicted motor consequences and corollary discharge of the predicted sensory consequences to the inferior olive which after comparing the actual and predicted consequences sends an error signal back updating the plastic cerebellar modules (Ramnani, 2006).

By contrast, a sensory experience that derives from an external stimulus is not predicted and hence not suppressed or adapted to the outside world. Unpredictable things are difficult to ignore, because it is crucial to experience them to update our understanding of the environment (Fletcher and Frith, 2009). From an information theory point of view information consists of the information content plus redundancy (Shannon, 1948). The information content is that what surprises, the change, reducing the prior uncertainty. The redundancy is what is already known, and serves as a protection and errors in information transmission. For completely predictable stimuli there is no information content that can further reduce the uncertainty of the environment, whereas information content that can reduce the uncertainty is present in changes occurring in the environment, thus worthwhile of conscious processing.

5. Free-energy principle

Biological systems maintain their internal states (milieu intérieur) and form in a constantly changing environment, also known as homeostasis (Bernard, 1865; Cannon, 1929). From the point of view of the brain, the environment includes both the external and the internal milieu, and it must maintain its state within certain physiological limits. The second law of thermodynamics posits that in a closed or isolated system, without external intervention, entropy remains constant or increases, but never increases. Entropy can be described as the degree of disorder or uncertainty in a system. Thus, in an isolated system, the system will gradually become more and more disordered, until it reaches maximum entropy. The phenomenon of entropy was developed to explain why hot items become colder, never hotter, and was investigated in thermodynamic systems such as heat baths. As it loses heat over time, its entropy increases, until finally it reaches its maximum. However Prigogine described that in open systems, that operate far from thermodynamic equilibrium, a supply and dissipation of energy can override the maximization of entropy rule imposed by the second law of thermodynamics, and order can be created from chaos (Prigogine and Stengers, 1984). Living matter evades the decay to thermodynamical equilibrium, as posited by the second law of thermodynamics, by homeostatically maintaining negative entropy in an open system (Schrödinger, 1944). Negative entropy (i.e. negentropy) is the available energy, also known as Gibbs' free energy, that a body imports and stores (Fig. 2). It is mobilisable stored energy (Mahulikar and Herwig, 2009). The human brain is a substantially isothermal, isobaric system which is supplied with a constant source of thermodynamic free energy (Kirkaldy, 1965). The source of this free energy is provided by the chemical nourishment of the blood and by the information-gathering channels of the body (Kirkaldy, 1965). Brains burn glucose to store energy in the form of glycogen, ATP and transmembrane ionic gradients that support the resting potentials (Freeman, 2008). This metabolic free energy is dissipated by dendritic and axonal ionic currents (Freeman, 2008). In other words, the thermodynamic free energy supports the capacity for the brain to transiently create order (network structure) from chaos, but due to the second law of thermodynamics this order will dissolve spontaneously to maximize entropy by dissipating energy as heat through the venous circulation in processing information (Fig. 2). The repertoire of physiological and sensory states in which an organism can exist is limited, which means that the probability of these (interoceptive and exteroceptive) sensory states must have low entropy (Friston, 2009).

Uncertainty (lack of information) and Gibbs' free energy are generally considered by information theorists as equivalent quantities (Kirkaldy, 1965), one physical, the other conceptual. This was already suggested by Boltzmann, who stated that entropy measures the missing information of a system. In information theory, entropy is a measure of disorder or unpredictability, or in other words of uncertainty (Friston, 2010; Shannon, 1948), whereas information serves as a source and in some circumstances as a measure of negentropy.

The free energy principle states that any adaptive self-organizing system, such as the brain, that is in a non-equilibrium relationship with its environment must minimize its Shannonian free energy (Friston, 2010) in order to continue to exist. The brain thus taps thermodynamic free energy to generate Aristotlian information, i.e. patterns, in order to reduce uncertainty, i.e. to minimize Shannonian free-energy. It does so by avoidance of surprise or uncertainty. Free energy can also be defined as the amount of prediction error in the context of Shannonian information theory (Friston, 2009). Thus there is a distinction between information-theoretic free-energy (Shannonian) and thermodynamic free energy (Gibbs). Shannonian free-energy (uncertainty) is minimized by perception; thermodynamic free energy is reduced during the act of perception, and is thereafter re-optimized by the metabolic restoration of the ionic gradients that were depleted during the intentional action – revealed by the classic after-potentials. In summary, the brain, as a dissipative system uses thermodynamic free energy to reduce uncertainty by looking for information that can update prior knowledge in a Bayesian way, decreasing Shannonian free-energy. This increases thermodynamic entropy which is removed as heat, while negentropy is

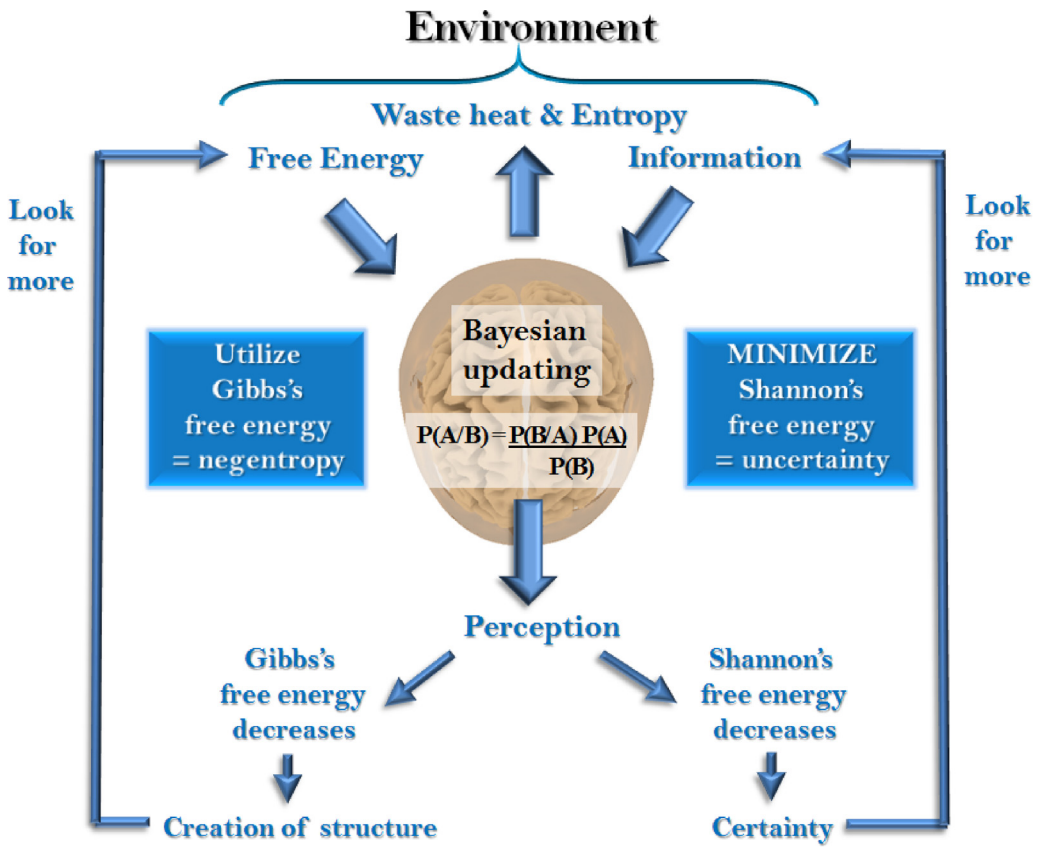

Fig. 2. The Bayesian brain can be conceptualized as a probability machine that constantly makes predictions about the world and then updates them based on what it senses. The brain functions by scanning the environment for information and nutrients in the environment. The purpose of the information is to reduce (Shannonian) free energy, i.e. uncertainty, in order to increases chances of survival. In order to do so, it taps into thermodynamic free energy, i.e. the brain uses glucose. This leads to transient network structure generating perception. Perception increases certainty. After the percept, due to a decrease in thermodynamic free energy, the circle restarts.

increased by tapping into Gibbs' free thermodynamic energy (Costa de Beauregard, 1989) (see Fig. 2).

To reduce the prediction error, one of two things can happen: (1) the brain can either change its prediction or (2) change the way it gathers data from the environment (Friston et al., 2006). In order to do so efficiently, the brain will selectively sample the sensory inputs that it expects, to minimize surprise and minimize free-energy, thereby also maximizing the sensory evidence for the predicted stimulus' existence. In vision, after each fixation, the eye fixates next at the location that minimizes uncertainty (maximizes information) about the stimulus (Renninger et al., 2005), but the eye fixates only the most informative locations, that is, it reduces local uncertainty, not global uncertainty (Renninger et al., 2007). Therefore only locally thermodynamic free energy is decreased, as evidenced by BOLD signal changes in fMRI (Freeman, 2008). Thus active perception, at least in vision, follows the Shannonian free-energy principle.

Since the brain minimizes free-energy (prediction error), both in the firing of neurons as in the wiring between them, it has been proposed that changing connections between neurons to reduce free-energy is formally identical to Hebbian plasticity (cells that fire together wire together) (Friston, 2010). Furthermore, dendritic sprouting can be regarded as a way to minimize free-energy (Kiebel and Friston, 2011). This dendritic sprouting has been proposed to be a kind of Darwinian plasticity (De Ridder and Van de Heyning, 2007), a mechanism to find missing information in the cortical neighborhood. Darwinian plasticity proposes that deafferented neurons, (metaphorically speaking: in order to survive), reorganize, either by opening dormant synapses or via dendritic sprouting (De Ridder and Van de Heyning, 2007).

6. Deafferentation and free-energy

Auditory or somatosensory deafferentation, which leads to sensory deprivation, limits the amount of information the brain can acquire to make sense of the world. In other words, it increases the uncertainty inherently present in the environment.

In order to minimize the free-energy, i.e. to decrease topographically selective uncertainty, the topographically deafferented brain area will look for the missing information or fill in the missing information. This filling in mechanism explains why there is no blind spot in the visual field that corresponds to the lack of light-detecting photoreceptor cells on the optic disc where the optic nerve exits the retina (Komatsu et al., 2000).

The topographically specific deafferentation induces a topographically specific prediction error based on temporal incongruity (De Ridder et al., 2011a), in other words it is inconsistent with what is stored in memory and should be updated. As unpredictable things are difficult to ignore, because it is crucial to experience them to update our understanding of the environment (Fletcher and Frith, 2009), this will increase the salience, the biological relevance, attached to the missing information.

In order to minimize free-energy the brain will try to obtain the missing information. Therefore each cortical area has to be an adaptive processor, altering its function in accordance to immediate perceptual demands (Gilbert et al., 2009).

7. Staged free-energy reduction in sensory deafferentation

The brain can try to obtain the deprived information do so in multiple ways, either (1) via an increase of cortical excitability,

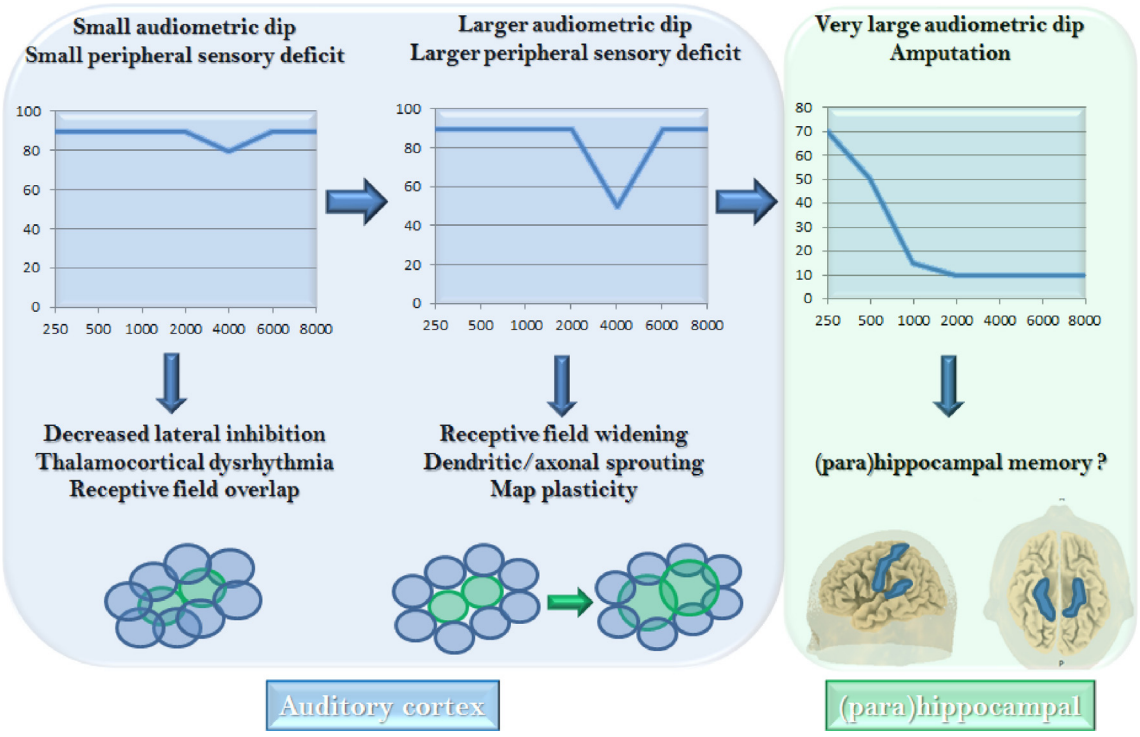

Fig. 3. Staged free-energy reduction. It is proposed that reduction of Shannonian free energy, i.e. uncertainty involves different stages, depending on the lack of information. When the missing information is topographically restricted, the overlap of receptive fields might suffice to obtain the information. If this is insufficient the receptive fields widen, with or without associated sprouting. If the missing information cannot be obtained from the cortical representation of the sensory environment, a parahippocampal mediated memory retrieval is proposed, looking for the missing information in hippocampal memory.

either by increased excitatory tone or by reduced inhibitory tone, (2) via widening receptive fields, (3) via dendritic and axonal rewiring and if that doesn't work by (4) pulling the missing input from memory (see Fig. 3).

7.1. Decrease in lateral inhibition

When the receptor loss is minimal, only a decrease in lateral inhibition, unmasking silent inputs, without topographic map plasticity will suffice (Rajan, 1998). Electrophysiologically this could be analogous to thalamocortical dysrhythmia (Llinas et al., 1999) (see further). In the auditory system neighboring cortical cells will be addressed, and the information can be gathered via the overlapping tuning curves of the neighboring cortical cells.

7.2. Widening of receptive fields and map plasticity

Both synaptic and map plasticity changes are similar in all sensory domains (Buonomano and Merzenich, 1998; Donoghue, 1995; Feldman, 2009; Kaas, 1991). Via the efferent system, tuning curves can widen (Guinan and Gifford, 1988; Zheng et al., 1999) in order to fill the gap, so that map plasticity is not necessary. Indeed sound induced hair cell loss is transiently associated with reversible widening of tuning curves without map plasticity (Chen et al., 1996). Tuning curves can also normalize on regeneration of hair cells (Chen et al., 1996).

In the somatosensory system, deprivation of sensory input by focal xylocaine application immediately increases the size of the receptive fields (Dykes and Craig, 1998; Panetsos et al., 1995).

In the visual system, when visual input is prevented by focal binocular retinal lesions, within minutes after making the lesions, striking increases in receptive field size for cortical cells with receptive fields near the edge of the retinal scotoma are found (Gilbert and Wiesel, 1992). After a few months even the cortical areas that were initially silenced by the lesion recover visual activity, representing retinotopic loci surrounding the lesion (Eysel and Schweigart, 1999; Gilbert and Wiesel, 1992), hereby removing the increased topographic uncertainty. Visual acuity recovery by filling-in the missing information is linked to reorganization of receptive field maps (Komatsu et al., 2000).

Map plasticity is also known in learning. In this setting the map expansion is transient, as described by the expansion–normalization model (Reed et al., 2011). This model posits that cortical map plasticity can enhance perceptual learning. However, auditory cortex map plasticity fades over weeks even though tone discrimination performance remains stable, analogous to what is seen in the visual system (Yotsumoto et al., 2008). This suggests that cortical map expansions associated with perceptual and motor learning are followed by a period of map renormalization without a decrement in performance (Reed et al., 2011). Initial learning generates a population of new dendritic spines and this population is then reduced to a small subset. The skilled performance is maintained by this small but stable subset of new dendritic spines (Xu et al., 2009; Yang et al., 2009).

However in the face of permanent deafferentation this map plasticity seems to remain permanent (Pons et al., 1991; Reed et al., 2011). In both phantom pain (Flor et al., 1995) and phantom sound (Muhlnickel et al., 1998) map plasticity in the respective sensory cortex is present, and the more severe the phantom percept the larger the reorganization (Flor et al., 1995; Muhlnickel et al., 1998). As the map plasticity reverses on clinical improvement of the tinnitus (Engineer et al., 2011) or pain (Theuvenet et al., 1999), this map plasticity might be causally related.

7.3. Dendritic sprouting

Map plasticity can be associated with dendritic sprouting, which reduces free-energy (Kiebel and Friston, 2011), in order to obtain

the information from the cortical neighborhood, via a kind of Darwinian plasticity (De Ridder and Van de Heyning, 2007).

Deafferentation can induce dendritic plasticity in 2 ways: either via sprouting resulting in new dendro-dendritic connections or by reduction in size of the denervated nerve cell dendritic arbor, leading to a relative increase in density of the surviving (though non-sprouting) afferent axon terminals (Takacs and Hamori, 1990). It has been suggested that dendrites are the first to initiate the plasticity response in response to partial deafferentation, followed by the remaining axons (Chen and Hillman, 1990).

The result of these dendritic plastic changes is compensatory, to reduce free-energy and thereby reduce sensory uncertainty. Clinically, it has been shown that auditory receptor loss can be quite extensive without clinically measurable hearing loss. From an information theoretic point of view this is related to redundancy as a protection against errors (37).

7.4. Memory

If reducing uncertainty is impossible by getting the missing information from the cortical neighborhood, the Shannonian free-energy can be minimized by addressing memory.

A brain with a pool of stored information is continually encountering incoming information which duplicates that already stored (Kirkaldy, 1965). This permits an immediate increase of the flow of free-energy to other parts of the brain and body (Kirkaldy, 1965). In other words memory based certainty saves thermodynamic free energy.

This could be mediated via a (para)hippocampal mechanism (De Ridder et al., 2011a). The auditory cortices are anatomically reciprocally connected to the posterior parahippocampal area (Munoz-Lopez et al., 2010). This area has been called the gatekeeper to the hippocampus (Tulving and Markowitsch, 1997), functioning as a sensory gate for incoming irrelevant or redundant auditory input (Boutros et al., 2008). In other words, the parahippocampal area can be considered as the main node of entry for sensory information to the medial temporal lobe memory system, where salient information is encoded into long-term memory (Engelien et al., 2000). As the parahippocampal area has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas, a dysfunction in this mechanism is posited as an explanation for complex auditory phantom percepts such as auditory hallucinations (Diederen et al., 2010) and tinnitus (De Ridder et al., 2011a).

Active perception is biased by potential future costs. For example, in the North American forest, brown bears are more dangerous than black bears. If perception is impoverished, it is better to assume a particular bear-like object is a brown bear (Fleming et al., 2010). Sensory evidence and prospective losses interact in the brain to bias perception via the parahippocampus (Fleming et al., 2010). Thus perception is influenced by predictions of potential future losses which depend on memory, mediated by the parahippocampal area. This might explain why tinnitus and pain, when arisen during life threating stress such as terrorist attacks, war or torture is very prevalent (Fagelson, 2007; Hinton et al., 2006; Raphael et al., 2004).

8. The neuroanatomy of Bayesian phantoms

8.1. Dual pathways for pain and auditory perception

Pain stimuli are processed in parallel (Frot et al., 2008) by 2 pathways: a medial affective/attentional pain pathway and a lateral discriminatory pathway (Kulkarni et al., 2005; Price, 2000; Rainville et al., 1997) (see Fig. 4). The medial pain system is anatomically related to the lateral spinothalamic tract and is triggered by C-fibers, firing in burst mode, and relayed in lamina I of the spinal horn to the mediodorsal and ventromedial nucleus of the thalamus and from there to the anterior cingulated cortex, anterior insula and amygdala. The lateral pain system is anatomically related to the anterior spinothalamic tract and triggered by C-fibers, as well as Aδ and Aβ fibers, firing in tonic mode, and relaying in lamina I and IV–VI of the dorsal horn to the VPL and VPM nucleus of the thalamus and from there to the primary and secondary somatosensory cortex, posterior parietal area (Craig, 2002; Lopez-Garcia and King, 1994; Price, 2000).

There has been no description of a medial auditory processing system, analogous to the medial pain system. Since the mediodorsal nucleus of the thalamus contains auditory processing cells (Tanibuchi and Goldman-Rakic, 2003) and the affective component

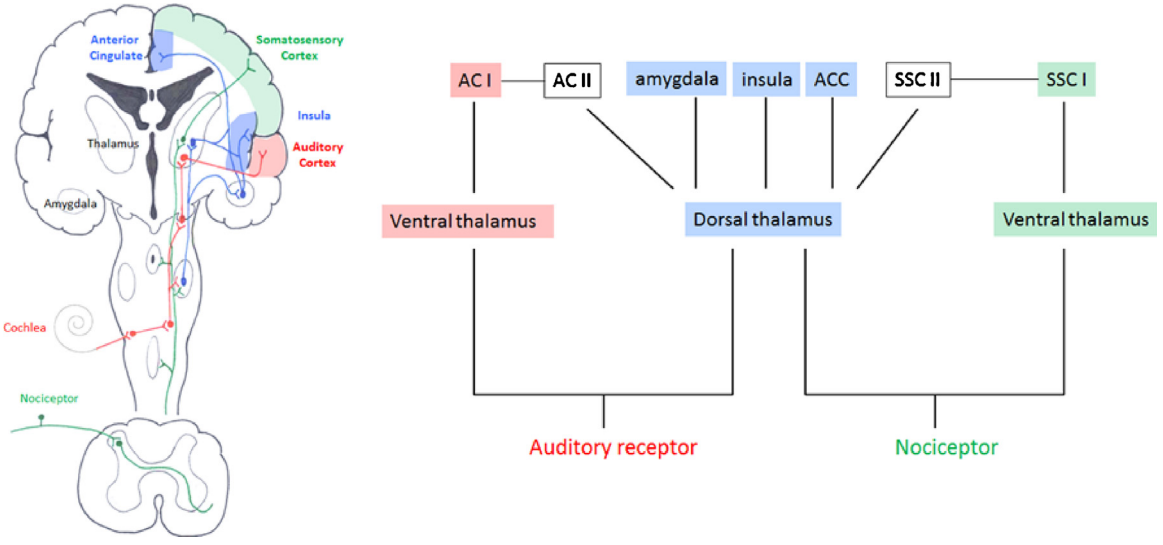

Fig. 4. Simplified version of the auditory and somatosensory pathways involved in phantom perception generation. On the left panel the anatomical location of the structures involved, on the right panel a schematized diagram. The medial pathways (blue) involve the anterior cingulate and insula, and are likely the same used for the somatosensory (green) and auditory (red) pathways. The medial system further involves the amygdala and dorsomedial nucleus of the thalamus. The somatosensory system and auditory system pass via the specific nuclei in the thalamus, respectively the ventral posterior nucleus and medial geniculate body respectively (not shown). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

of sound processing is related in part to activity in the amygdala, dACC and insula (Buchel et al., 1999; Phan et al., 2002; Vanneste et al., 2010), it is possible that such a system exists (Leaver et al., 2011), as has been proposed (De Ridder et al., 2011a) and described by means of functional connectivity studies (Langers and Melcher, 2011).

8.2. Auditory and somatosensory deafferentation

Deafferentation in the auditory and somatosensory system leads to hyperactivity. One possible mechanism that explains this hyperactivity is thalamocortical dysrhythmia (Llinas et al., 1999).

This theoretical concept relates to the presence of persistent pathological coupled low and high frequency thalamocortical oscillatory activity in deafferentation pain and tinnitus. It has originally been posited as a common pathophysiological mechanism for neuropathic pain, tinnitus, Parkinson's disease, depression and slow wave epilepsy (Llinas et al., 1999). This model states that in the deafferented tinnitus state, the dominant alpha rhythm (8–12 Hz) present in normal resting state circumstances decreases to theta (4–7 Hz) (Llinas et al., 1999) band activity. As a result, $GABA_A$ mediated lateral inhibition is reduced (Llinas et al., 2005), inducing gamma (>30 Hz) band activity (Llinas et al., 1999). Gamma band activity in the auditory and somatosensory cortex, respectively, is a prerequisite for auditory (Crone et al., 2001; Joliot et al., 1994) and somatosensory conscious perception and therefore, likely also contributes to the perception of a phantom sound (De Ridder et al., 2011b; van der Loo et al., 2009; Weisz et al., 2007) and pain (Babiloni et al., 2002; De Pascalis and Cacace, 2005; Gross et al., 2007). In neuropathic pain the high frequency component might be more represented by beta (Sarnthein et al., 2006; Stern et al., 2006) rather than gamma activity, possibly reflecting a chronic steady state, a status quo (Engel and Fries, 2010). As theta–gamma coupling also exists in physiological sensory processing (Canolty et al., 2006), the thalamocortical dysrhythmia state can be considered a pathological persistence of normally waxing and waning theta–gamma band coupled activity in specific topographic thalamocortical columns, resulting from sensory deafferentation.

However it has to be considered that both the medial and lateral pain and auditory pathways will be deafferented. Thus a thalamocortical dysrhythmia-like mechanism can be expected in the ACC-insula pathway as well. And indeed neuropathic pain coincides with beta band activity in the somatosensory cortex, but also in the ACC and insula (Stern et al., 2006), as well as gamma activity in the insula (Isnard et al., 2011). The affective component of tinnitus distress is associated with beta activity in the dorsal anterior cingulate (De Ridder et al., 2011c; Vanneste et al., 2010) and delta/gamma band activity in the right insula (van der Loo et al., 2011).

The hyperactivity in the anterior cingulate and anterior insula is involved in the filling in mechanism of the lacking auditory input (Shahin et al., 2009).

8.3. Deafferentation leads to salience

The increased activity in the anterior cingulate and anterior insula also encodes salience (De Ridder et al., 2011a; Seeley et al., 2007). Salience has two separate meanings, one reflecting the physical distinctiveness of a sensory stimulus, mediated via a bottom up mechanism (Fecteau and Munoz, 2006; Itti and Koch, 2001; Knudsen, 2007), the other referring to the functional significance or behavioral relevance of the stimulus, related to the goals and intentions of the subject (Fecteau and Munoz, 2006; Naatanen et al., 1993; Serences and Yantis, 2006). The two meanings for salience cannot always be completely separated from each other since the distinctiveness of a stimulus and the behavioral relevance are often not independent from each other. Only stimuli which substantially affect the observer's beliefs or intentions, which are behaviorally relevant, i.e. salient, yield (Bayesian) surprise, i.e. are different from prediction, irrespectively of how rare or informative (distinctive) in Shannon's sense these observations are (Friston, 2009; Itti and Baldi, 2009), and guide attention (Itti and Baldi, 2009). When an expected reward fails to occur the dorsal ACC and anterior insula are activated (Ullsperger and von Cramon, 2003), but the dorsal ACC neurons respond only when reduced reward leads to a change in behavior (Bush et al., 2002). Thus error detection based on the comparison of representations of the intended response and the actual response appears to involve mechanisms very similar to those seen for error detection based on external feedback (Ullsperger and von Cramon, 2003). This activation orients attention to contextual novel auditory, visual and somatosensory stimuli (Downar et al., 2000; Huettel et al., 2002; Ranganath and Rainer, 2003). Thus, the anterior insula and the anterior cingulate cortex form a "salience network" that functions to segregate the most relevant among internal and extrapersonal stimuli in order to guide behavior (Menon and Uddin, 2010; Seeley et al., 2007), and to bring these behaviorally relevant stimuli such as pain to awareness (Wiech et al., 2010). The activation is context dependent, as threats result in activation of this salience network, resulting in increased pain perception (Ploner et al., 2011; Wiech et al., 2010).

The 'pain matrix' network is activated by painful stimuli and consists of the dACC, anterior insula, secondary somatosensory cortex and thalamus (Legrain et al., 2011). As both somatosensory, pain, auditory and visual stimuli activate this 'pain matrix', this network is not pain specific but should be considered a sensory modality aspecific salience network, essential to bring sensory stimuli to awareness (Legrain et al., 2011; Mouraux et al., 2011). And indeed, spontaneous activity fluctuations in anterior insula and dACC have been shown to influence auditory perception. Higher ongoing activity in the dACC, anterior thalamus and anterior insular cortex prior to the presentation of near-threshold auditory stimuli is predictive of detection performance in the upcoming trial (Sadaghiani et al., 2009). The same mechanism has been shown in pain perception (Boly et al., 2007). Thus the deafferentation induced hyperactivity in the anterior cingulate and anterior insula could lead to both a filling-in of the missing input (Shahin et al., 2009) and bring it to consciousness by simultaneous hyperactivity of the respective sensory cortex (Boly et al., 2007; Sadaghiani et al., 2009), leading to phantom sound (De Ridder et al., 2011b; Llinas et al., 1999) or phantom pain (Llinas et al., 1999; Sarnthein and Jeanmonod, 2008; Stern et al., 2006).

On deafferentation, the parvalbumin positive lemniscal system which supplies auditory information to the primary auditory cortex degenerates (Cervera-Paz et al., 2007). However, the calbindin positive extralemniscal system which involves the anterior cingulate and insula, and might be the anatomical counterpart of the functional medial system, seems to compensate (Forster and Illing, 2000). Similar findings have been described for the somatosensory system in deafferentation: the parvalbumin positive non-nociceptive stem degenerates, whereas the calbindin positive nociceptive system compensates (Rausell et al., 1992). This increase in extralemniscal pathways could potentially partially explain why the tinnitus and pain remain if the deafferentation continues. In transient sensory deprivation, both parvalbumin and calbindin initially increase (Caicedo et al., 1997).

Whereas the anterior cingulate is related more to the attentional and salience component, as evidenced by cingulotomies which distract attention from the pain (Cetas et al., 2008; Cohen et al., 1999a,b; Wilkinson et al., 1999; Yen et al., 2009), likely via removing the salience of the pain, the right insula is more involved in the alertness (Sterzer and Kleinschmidt, 2010) and conscious awareness of the percept (Albanese et al., 2007; Craig, 2003; Isnard et al., 2011). In a similar way the anterior insula is involved in the

meaning and conscious awareness of auditory stimuli (Bamiou et al., 2003; Engelien et al., 1995; Fifer, 1993; Habib et al., 1995).

8.4. Stress and phantom percepts

Stress signifies a potential or actual threat that requires immediate changes in behavior (Joels and Baram, 2009). This means that stress is a signal that important action should be undertaken, involving movement. This will result in a faster changing environment, mandating heightened alertness, and maximal perceptive ability. It has also been proposed that 'stress' should be restricted to conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability (Koolhaas et al., 2011). Thus stress signifies increased uncertainty, which according to the free-energy principle should be minimized.

Under psychological stress, cerebral conscious activity enhances with the decrease of parasympathetic activity and increase of sympathetic activity, associated with an increase in Shannonian entropy (Yu et al., 2009). Stress is associated with sympathetic system hyperactivity, and the sympathetic system is largely controlled by the right anterior insula and anterior cingulate (Critchley et al., 2000, 2002; Oppenheimer, 1993, 2006; Oppenheimer et al., 1992, 1996; Oppenheimer and Hachinski, 1992; Ter Horst et al., 1996), areas which overlap with the uncertainty processing area as well as salience network and filling-in mechanism network.

Psychological stress results in prolonged enhanced functional coupling in the resting state between amygdala, dACC, anterior insula, and the locus coeruleus, resulting in an extended state of hypervigilance that promotes sustained salience and mnemonic processing (van Marle et al., 2010). This could explain both the fact that many patients describe their phantom pain was triggered by a stressful moment in life (Jensen et al., 1985), and tinnitus and pain are more common in patients suffering posttraumatic stress disorder (Hinton et al., 2006; Raphael et al., 2004).

8.5. The Bayesian brain and phantom percepts

Based on information theory and the Shannonian free-energy principle, the Bayesian brain will under deafferentation increase topographically restricted prediction errors, related to memory-based temporal or spatial incongruity. As the brain functions in a way to minimize free-energy or uncertainty it will attempt to reduce the deprived input by filling in mechanisms, mediated by inhibition and/or map plasticity of the respective sensory cortex. Filling in as a repair for missing information also activates the anterior cingulate and insula. Stressful circumstances activate the same areas, increasing salience and turning sensory stimuli into conscious perception. Furthermore these areas determine whether a stimulus is being perceived consciously or not. Thus, under stressful circumstances the associated anterior cingulate, anterior insula and sensory cortex hyperactivity with associated decreased inhibition and/or map plasticity will result in the perception of the deafferented sensory information, as a way to reduce increased topographically restricted uncertainty associated with the deafferentation.

This model suggests that sensory cortex map plasticity might represent a filling in mechanism without phantom pain or phantom sound. When associated persisting hyperactivity is present in the anterior cingulate and anterior insula (and possibly other areas) this filling in could become associated by phantom pain and phantom sound. This is in agreement with the global workspace theory which proposes that changes in one area do not lead to conscious perception, but that co-activated higher order areas are required for a stimulus to be consciously perceived.

In conclusion, the Bayesian updating of knowledge via active sensory exploration of the environment, driven by the Shannonian free-energy principle, provides an explanation for the generation of phantom percepts, as a way to reduce uncertainty, to make sense of the world.

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