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Review article

Adaptive and maladaptive neural compensatory consequences of sensory deprivation—From a phantom percept perspective

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ABSTRACT

It is suggested that the brain undergoes plastic changes in order to adapt to changing environmental needs. Sensory deprivation results in decreased input to the brain leading to adaptive or maladaptive changes. Although several theories hypothesize the mechanism of these adaptive and maladaptive changes, the course of action taken by the brain heavily depends on the age of incidence of damage. The growing body of literature on the topic proposes that maladaptive changes in the brain are instrumental in creating phantom percepts, defined as the perception of a sensory experience in the absence of a physical stimulus. The current article reviews the mechanisms of adaptive and maladaptive plasticity in the brain in congenital, early, and late-onset sensory deprivation in conjunction with the phantom percepts in the different sensory domains. We propose that the mechanisms of adaptive and maladaptive plasticity fall under a universal construct of updating hierarchical Bayesian prediction errors. This theory of the Bayesian brain hypothesizes that the brain constantly compares its internal milieu with changing environmental cues and either adjusts its predictions or discards the change, depending on the novelty or salience of the external stimulus. We propose that adaptive plasticity reflects both successful bottom-up compensation and top-down updating of the model while maladaptive plasticity reflects failure in one or both mechanisms, resulting in a constant prediction-error. Finally, we hypothesize that phantom percepts are generated by the brain as a solution to this prediction error and are thus a manifestation of unsuccessful adaptation to sensory deprivation.

Contents

Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; GABA, gamma amino butyric acid; HAROLD, hemispheric asymmetric reduction in older adults; CRUNCH, compensatory-related utilization of neural circuits.

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1. Introduction

It is generally agreed that the brain creates an internal representation of the environment that it is exposed to (Friston, 2012; Friston et al., 2006). Bottom-up sensory information received by the brain is constantly compared with this internal representation, leading to predictions about the causes of changes in sensory information (Friston, 2005). This process takes place in a hierarchical fashion, such that the beliefs of each level of bottom-up information are estimated by top-down predictions from the succeeding levels (Penny, 2012). Changes in environmental stimuli result in prediction errors (Arnal and Giraud, 2012) between the bottom-up information and top-down predictions (De Ridder et al., 2014b; Friston, 2009; Friston et al., 2006). These changes can be due to an enrichment or impoverishment in environmental stimuli. Damage to peripheral sensory structures or central processing centers leads to sensory deprivation, exposing the brain to decreased sensory input which results in sensory uncertainty. This uncertainty may be minimized by either (a) active sampling of the new environment providing corresponding bottom-up cues and/or (b) appropriate updating of top-down beliefs by the successive levels of the hierarchy (De Ridder et al., 2014b; Friston, 2012; Friston et al., 2006).

In general terms, compensation may be defined as the process of overcoming losses and deficits through one of several neural mechanisms (Dixon and Bäckman, 1999). Evidence for the brain's bottom-up compensatory ability is provided in both neural and cognitive domains. Examples of the brain's bottom-up compensatory techniques include increased activity in sensory and non-sensory regions of the brain (Vanneste and De Ridder, 2012), reorganization of cortical maps following amputation of an extremity (Knecht et al., 1996), extensive cross-modal plasticity of neurons in early loss of a sensory domain (Bavelier and Neville, 2002b; Cohen et al., 1997), and recruitment of bilateral neural resources with aging in cognitively normal adults (Cabeza et al., 2002). Conversely, a top-down compensation mechanism for sensory deafferentation is the successful adjustment of the prediction model at different levels of the hierarchy by learning the changes in bottom-up input (De Ridder et al., 2014b). Updating the prediction model at different hierarchical levels follows a Bayesian statistical approach (Friston, 2005). Empirical Bayes is a method of arriving at statistical inferences by setting prior beliefs based on existing data and updating these beliefs based on new data. This involuntary bottom-up sampling of the environment and top-down updating of prior beliefs is popularly known as the Bayesian brain theory (Friston, 2012), which may be used as a universal construct to explain how the brain adapts to new environments by successfully minimizing sensory uncertainty. Although the brain is very resilient to local and global damages (Alstott et al., 2009; David and Aguayo, 1981; Kaas et al., 1983; Kaiser et al., 2007), the success of both bottom-up and top-down compensatory techniques heavily depends on the time of incidence of the damage. The sensitive or critical period is the time frame in the lifespan of the brain within which it is most susceptible to changes in behavioral and biological development (Kral, 2013). Since the brain is most plastic in the early years of life, compensatory mechanisms for sensory deprivation seem to differ depending on congenital, early, or late-onset of sensory damage.

Adaptive compensation could be achieved through changes in the bottom-up mechanism or top-down updating of a prediction error. However, if these adaptive mechanisms fail, irrespective of the time of incidence of sensory damage, the system needs to compensate for the prevailing uncertainty in alternative ways. This is engineered through maladaptive compensation–by the generation of a phantom percept (De Ridder et al., 2014b). Phantom perception is the experience of a sensory representation (vision, audition, touch, olfaction, gustation, balance, or proprioception) in the absence of an external sensory stimulus (Jastreboff, 1990; Ramachandran and Rogers-Ramachandran, 1996; Schultz and Melzack, 1991; Yanagisawa et al., 1998). The pathways of the different sensory domains from the peripheral receptors to their primary sensory cortices are illustrated in Fig. 1. In general, phantom percepts seem to occur in response to sensory deprivation, specifically damage to peripheral structures such as receptors (Grouios, 2002; Jastreboff, 1990), nerves (Eggermont, 2005; Wrobel and Leopold, 2004), or damage to early stages of sensory processing in the brainstem and cortex (Ramachandran, 1993). They have also been observed as a common after-effect of surgeries such as cataract surgery (Schultz and Melzack, 1991), tonsillectomy (Tomofuji et al., 2005), etc. Although there are ongoing debates about phantom percepts in congenital and early sensory deprivation, their relation to late sensory deprivation is universally accepted.

The aim of this article is to review the literature on bottom-up and top-down adaptive compensatory techniques in congenital, early and late sensory deprivation and phantom percepts in all sensory domains, proposing a universal construct for adaptive and maladaptive compensation of sensory deafferentation. In this article, we will first review different bottom-up and top-down adaptive compensatory techniques employed by the brain in response to congenital, early, and late-onset sensory deprivation. We will then review the phantom percepts in different sensory domains and detail the maladaptive compensatory mechanisms behind their generation. In doing so, we suggest that phantom percepts may be a maladaptive compensatory manifestation to offset the inability of the brain to adapt to decreased sensory input independent of the sensory domain and the time of incidence of deprivation.

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Fig. 1. Sensory pathways to the brain. The figure shows the pathways of the (a) visual, (b) auditory (c) somatosensory, (d) gustatory, (e) vestibular and (f) olfactory systems from the receptors to their respective primary sensory cortices in the brain.

2. Mechanisms of adaptive compensation

Sensory deafferentation results from the partial or complete loss of peripheral and/or central structures causing functional disability to one or more sensory domains. Nevertheless, the brain finds a way to successfully cope with such losses, leading to adaptive changes whose success depends on the age of incidence of the deafferentation. Patients with congenital or early sensory deafferentation cope more successfully than patients who suffer sensory losses later in their life. However, even with late sensory deafferentation, the absence of phantom symptoms still reflects successful adaptation to decreased sensory input. From the vast literature on adaptive compensation of sensory deafferentation, we observe different routes taken by the brain in congenital, early and late sensory deafferentation. These include different bottom-up mechanisms such as cross-modal plasticity (dominant in congenital and early stages and less in the later stages), homeostatic and map plasticity, recruitment of neural reserves, changes in connectivity between sensory and non-sensory areas, thalamic-limbic cancellation of irrelevant stimuli, or top-down mechanisms such as shifting to a new reference point. These different routes of adaptive compensation for sensory loss are described below in detail and summarized in Table 1.

2.1. Cross-modal plasticity

There is much anecdotal evidence supporting better hearing and tactile acuity in the blind and unique communication abilities in the deaf and mute. Research shows that such behavioral manifestations are a consequence of cross-modal plasticity (Bavelier and Neville, 2002b). Cross-modal plasticity is the adaptive reorganization of neurons integrating two or more sensory systems (Kupers and Ptito, 2014; Rauschecker, 1995). Such reorganization is shown to occur extensively in congenital and early deprivation of sensory input and less extensively in late deprivation (Bavelier and Neville, 2002b; Lazzouni and Lepore, 2014). Cross-modal plasticity is observed both in simple organisms such as *C. Elegans* with only 302 neurons and in complex species such as humans (Rabinowitch and Bai, 2016a). Although recent studies report worse performance by congenitally deprived individuals when compared to normal adults in certain tasks (Gori et al., 2014), congenitally blind individuals seem to have better auditory pitch discrimination (Gougoux et al., 2004) and tactile discrimination (Alary et al., 2008) as well as superior odor and taste discrimination abilities (Araneda et al., 2016b; Kupers and Ptito, 2014). Further, congenitally deaf individuals have better visual selective attention and better memory of faces and objects

Table 1
Summary of mechanisms of adaptive plasticity.

Onset of deafferentation	Mechanism	Description
Congenital and early-onset	Cross-modal plasticity	Cross modal recruitment: where remaining intact sensory modalities take over the deprived sensory cortex, functionally and neuro-biologically. This can be explained by the axonal sprouting of the neurons from the intact sensory cortices, populating the regions in the deprived modality. Cross-modal compensation: where changes take place in the remaining intact cortices e.g. expansion of topographic maps to compensate for the loss in the deprived cortex.
	Cross-modal plasticity	Cross-modal plasticity has been shown in late-onset as well; however, there are ongoing discussions about its extensiveness.
Late onset	Homeostatic and map plasticity	Increase in spontaneous firing in the deafferented cortex leading to an increase in "central gain". This may or may not lead to expansion of topographic maps of the deprived cortex.
	Bottom-up cancellation system	Increase in spontaneous activity in the ascending pathways in the presence of a deafferentation is cancelled out at the level of the thalamus by a cortico-limbic cancellation system.
	Neural reserves	Recruitment of extra neural resources to offset sensory deprivation and maintain cognitive competency.
	Functional connectivity	Changes in functional connectivity between different brain areas is witnessed as a compensatory effect of sensory deprivation.
	Top-down modulation system	Successful hierarchical updating of the Bayesian prediction error reflecting successful adaptation of the brain of the changing bottom-up needs.

compared to their normal counterparts (Arnold and Murray, 1998; Bavelier et al., 2000; Dye et al., 2009). Many blind individuals use a phenomenon called echolocation to navigate in space. Echolocation is a special form of spatial hearing, where individuals produce sounds using their mouth, foot, cane etc. to scan the environment and use the subsequent echoes for spatial navigation (Griffin, 1944). Electrophysiological studies in animals and humans show that cross-modal plasticity notably takes two courses: (a) cross-modal recruitment and (b) cross-modal compensation (Lee and Whitt, 2015; Rabinowitch and Bai, 2016a).

2.1.1. Cross-modal recruitment and compensation

Cross-modal recruitment is the recruitment of the deprived sensory cortex by other sensory modalities (Rabinowitch and Bai, 2016a). This is an example of the classical theory of plasticity in which dormant parts of the deprived sensory cortices are populated by neurons of other intact sensory modalities. Evidence for retinotopy and spatial orientation of neurons in the primary somatosensory and auditory cortices of ferrets and hamsters show that cross-modal recruitment of the primary visual cortex may be induced by early surgical intervention (Bavelier and Neville, 2002a; Métin and Frost, 1989; Sur et al., 1988). Cross-modal recruitment of the visual cortex by the auditory cortex has also been demonstrated in congenitally deaf cats (Bavelier and Neville, 2002a; Rebillard et al., 1977). In humans, several neuroimaging studies show cross-modal activation of visual areas to somatosensory stimuli (Büchel et al., 1998; Sadato et al., 1996) and auditory areas to visual (Finney et al., 2001; Nishimura et al., 1999) and somatosensory stimuli (Levänen et al., 1998). Recent studies also show that improved odor detection and awareness may result from parts of the visual area being taken over by the olfactory cortex (Araneda et al., 2016a).

Cross-modal compensation involves compensatory reorganization of the remaining sensory cortices to elevate the performance of the deprived sensory capability (Rabinowitch and Bai, 2016b). The visual (DeYoe et al., 1996), somatosensory (Schott, 1993), auditory (Eggermont, 2006), olfactory (Vosshall et al., 2000), and gustatory (Chen et al., 2011) systems are organized in a systematic way such that sensory input from specific parts of the sensory epithelium are mapped onto specific regions of the primary sensory cortex. In humans, the topographic organization of the striate, somatosensory, and auditory cortices is better understood than that of the olfactory and gustatory cortices. These topographic maps are not hard-wired but rather change with development and learning, thus adapting to the dynamic environment (Reed et al., 2011). Cross-modal compensation manifests as an expansion of the maps of the spared sensory cortices to accommodate the sensory deprivation. Early studies in rats show increased dendritic spine density in the auditory cortex following deafferentation of somatic and visual inputs (Bavelier and Neville, 2002a; Ryugo et al., 1975). Similarly, increased performance in spatial navigation accompanied by expansion of the somatosensory maps of the barrel cortex was observed following removal of the eye in mice (Bavelier and Neville, 2002a; Toldi et al., 1994a,b). Plastic changes were not only found in the primary cortices but also in polymodal association cortices. Congenitally blind cats showed greater tuning of auditory spatial cells in the ectosylvian cortex in addition to superior auditory localization (Bavelier and Neville, 2002a; Rauschecker, 1996, 1995). A similar enhancement in spatial tuning was observed in early-blinded humans, corresponding to changes in auditory evoked response potentials (Bavelier and Neville, 2002a; Röder et al., 1999). Furthermore, larger and faster somatosensory and auditory evoked responses in blind individuals not only provide further evidence for cross-modal recruitment but also support cross-modal expansion of spare modalities in humans (Bavelier and Neville, 2002a; Kujala et al., 1995; Röder et al., 1996).

2.1.2. Cross-modal plasticity in late sensory deprivation

Like congenital and early sensory deprivation, late sensory deprivation may be followed by cross-modal plasticity in the form of both cross-modal recruitment and cross-modal compensation in the presence of extensive deafferentation, such as loss of the entire sensory modality. Animal and human research supports the occurrence of cross-modal plasticity in the deprived adult brain. Electrophysiological recordings from ferrets deafened after their mature age show extensive cross-modal recruitment of somatosensory neurons (Allman et al., 2009). In fact, approximately 84% of their auditory neurons responded to somatosensory input. Similarly, removal of one eye in mature adult rats showed cross-modal innervation by somatosensory inputs (Van Brussel et al., 2011). In humans, indirect cross-modal plasticity was shown through differences in evoked potential responses to deviant tones in posterior areas in late blindness (Kujala et al., 1997). Researchers regard this as the unmasking of existent cortico–cortico connections between different modalities and subsequent recruitment of the deprived cortex by the axonal sprouting of neurons from other modalities (Allman et al., 2009). However, this could also be explained by the concept of "neural Darwinism" which postulates that the dendrites of the neurons from the deafferented cortex actively search for inputs and synapse with neurons of other modalities in order to avoid apoptosis (Edelman, 1993). Other

studies showed cross-modal compensation in the spare cortices, such as expansion of tonotopic maps in the auditory cortex as a compensatory consequence of blindness in the mature adult cortex (Elbert et al., 2002). However, there are also studies that dispute this level of cross-modal plasticity in the adult cortex. Differential patterns of activation between early and late-blind individuals in the striate and extrastriate regions using both PET and fMRI, indicate a decreased extent of cross-modal plasticity in late sensory deprivation (Büchel et al., 1998; Burton, 2003; Cohen et al., 1999; Sadato et al., 2002). Cross-modal activation in late deprivation is suspected to reflect mental imagery of visual stimuli that was formed prior to blindness (Büchel et al., 1998). The extent of cross-modal plasticity is hypothesized to decrease after a period of sensitivity or "critical period". This critical period has mostly been agreed upon as early to mid-adolescence (Cohen et al., 1999; Hensch, 2005; Sadato et al., 2002), after which the brain is hypothesized to become less susceptible to adaptive cross-modal plasticity.

2.2. Homeostatic and map plasticity

In addition to cross-modal innervation of sensory domains, adaptive compensation also involves hyperactivity and plasticity of unimodal sensory representations corresponding to the domain of deafferentation. Homeostasis is the tendency of a physiological system to maintain equilibrium. Homeostatic plasticity in neural circuits is the ability to maintain constant neural activity without becoming hyper or hypo-active (Turrigiano and Nelson, 2004). Increases in activity are corrected by local negative feedback loops that bring the activity back to normal levels (Sterling and Eyer, 1988). In mild sensory deafferentation, increases in the spontaneous rate of neuronal firing in the primary sensory cortex reflect an increase in "central gain" in order to make up for the decreased input from the bottom-up processes (Noreña and Farley, 2013). Homeostatic increases in "central gain" have been shown in various animals (Kotak et al., 2005; Seki and Eggermont, 2003). Homeostatic recruitment of auditory nerve fibers is the rationale behind the sudden increase in perceived loudness of a supra-threshold sound (i.e. hyperacusis) to compensate for deafferentaion (Cai et al., 2009). Such sudden recruitment may lead to the unimodal expansion of topographic maps. In the auditory domain, this map expansion is defined by a shift in characteristic frequency of the deafferented region to the adjacent frequencies (Norena et al., 2003). This has been hypothesized to be the result of changes in the excitation/inhibition balance leading to reduced lateral inhibition of the inputs feeding in from the neighboring frequency bands, thus "unmasking" these connections (Norena et al., 2003). This concept coincides with the classical theory of axonal sprouting of neurons in adjacent areas taking over a deafferented area. A counter-argument was made by De Ridder and colleagues stating that this map plasticity could be the product of dendritic sprouting of neurons from the deafferented area seeking input from the adjacent healthy areas, thereby supporting the hypothesis of neural Darwinism representing the memory of the deafferented areas, termed Darwinian plasticity (De Ridder and Van de Heyning, 2007).

2.3. Cancellation system

Another route taken by the brain to compensate for sensory loss through a bottom-up mechanism is via the thalamic-limbic cancellation system. The thalamus forms an important gateway into the cortex, acting as a relay system and maintaining different states of consciousness (Sherman and Guillery, 1996; Timofeev et al., 2012). Bottom-up input from all the sensory systems except the olfactory system are relayed to the cortex through different thalamic nuclei by means of third-order neurons. Mild, moderate, or severe deafferentation have been proposed to be cancelled out at the level of the thalamus by a sub-cortical limbic cancellation system (Rauschecker et al., 2010a). This prevents any erroneous signals from reaching the cortex. This cancellation system is proposed to consist of the interaction between the serotonergic cells of the sub-cortical limbic structures and the Gamma Amino Butyric Acid (GABAergic) cells of the thalamocortical loop (Rauschecker et al., 2010b). The thalamic reticular nucleus is a reservoir of GABAergic cells that exhibit a strong inhibitory effect on the thalamocortical and cortico-thalamic loops (Pinault, 2004). All sensory modalities, except the olfactory system, are connected to the cortex through the thalamus via thalamic reticular cells. However, a recent study proposed the presence of an olfactory thalamus in the olfactory bulb where the inhibitory role of the thalamic reticular cells is taken over by the granule cells (Kay and Sherman, 2007). Serotonergic cells modulate the cortico-striatal pathways that are responsible for encoding reward, awareness, and motivation. The ventromedial prefrontal cortex–part of the default mode network of the brain that controls the resting state dynamics (Raichle, 2015)–and the nucleus accumbens–part of the ventral striatum (Leaver et al., 2011)–together form a part of the cortico-striatal pathway that modulates the sensory thalamocortical loops. The ventro-medial prefrontal cortex has been shown to exhibit an excitatory influence on the nucleus accumbens (Leaver et al., 2011). Rauschecker and colleagues hypothesize that the interaction of the serotonergic cells of the nucleus accumbens, the ventromedial prefrontal cortex, and the GABAergic cells of the thalamic reticular nucleus produce a powerful inhibitory effect on the thalamic relay cells (Rauschecker et al., 2010b). In the presence of deafferentation, the hyperactivation of the ascending pathways creates a noise signal. A healthy cancellation system would inhibit this noise signal from reaching cortical consciousness, thus explaining the absence of salience even in the presence of deafferentation.

2.4. Brain and cognitive reserve

Different models of modulating cognitive abilities can also explain bottom-up compensation of sensory deafferentation as methods employed by the brain to look for more information. The concept of a reserve was introduced in order to account for the disjunction between the degree of brain damage to its clinical manifestations (Stern, 2009). Reserve can be widely classified into two kinds – active and passive models. Passive models of reserve include the concept of brain reserves which take into account the structural diversity and physical robustness of the brain including neuronal count, size of the brain, number of synapses, etc. (Satz et al., 2011). Brain reserves act as a structural buffer in order to compensate for cognitive capabilities. People having larger brains or higher neuronal count may need a larger extent of brain damage to be cognitively disabled than people with smaller brains would. Active models include the use of top-down cognitive reserves in order to cope with decreased input. Cognitive reserve includes a variety of environmental factors such as education, social activities, hobbies, entertainment, etc. that might be altered by experience, providing a dynamic buffer for cognitive compensation (Barulli and Stern, 2013). Cognitive compensation has been proposed to be governed by two neural mechanisms – neural reserve and neural compensation (Stern, 2006). Neural reserve is the presence of efficient cognitive networks and greater flexibility in network selection in order to overcome deficits in brain damage. Neural compensation is the recruitment of more brain areas or networks in order to maintain cognitive competence (Barulli and Stern, 2013). The concept of brain and cognitive reserve was discussed together for the first time by Nithianantharajah and Hannan wherein they review animal models that investigate the

effects of modifying physical and mental activity and their association with brain and cognitive reserve (Nithianantharajah and Hannan, 2009).

Reduced sensory input to the brain is one of the characteristic effects of aging. With increasing age, there is evidence for increased auditory pure-tone thresholds (Homans et al., 2016), decreased visual function (Martínez-Roda et al., 2016), decreased speech intelligibility in a noisy background (Lu et al., 2016), decreased balance (Santos et al., 2016), decreased olfactory function (Wang et al., 2016), decreased tactile acuity (Lenz et al., 2012), etc. In addition to changes in behavioral parameters, there are also changes in structural and functional patterns in the brain. A decrease in grey matter density (Fjell et al., 2009, 2012; Salat et al., 2004) and white matter integrity (Sexton et al., 2014; Westlye et al., 2009), as well as slowing of stimulus evoked potentials in different sensory domains (Hunter, 2016; Larson et al., 2016) have been observed with aging. However, in healthy aging some of these parameters are not statistically different from healthy young adults, which is evidence for both neural reserve and neural compensation. It is observed that individuals with comparable behavioral thresholds to their younger peers have increased bilateral prefrontal cortex activation compared to unilateral activation in older adults with decreased cognitive abilities (Cabeza et al., 2002). Such asymmetry in neural responses is termed Hemispheric Asymmetric Reduction in Older adults, also known as the HAROLD model, and explains the neural compensatory mechanism for cognitive preservation in older adults (Cabeza, 2002). Although the HAROLD model could explain the recruitment of neural resources, it only provides an explanation for recruitment of bilateral resources. Alternative studies showed an increase in unilateral recruitment of neural resources which can be explained by another recent model, named the Compensatory-Related Utilization of Neural Circuits (CRUNCH) (Berlingeri et al., 2013). CRUNCH posits that neural recruitment does not necessarily involve the contralateral cortex but may also involve recruitment of more areas from the ipsilateral cortex itself.

HAROLD and CRUNCH are models exclusively presented for aging, although recruitment of neural resources is not restricted to aging-related changes. Recruitment of contralateral neural resources is shown in rehabilitation related to stroke, aphasia, and other neurological disorders. A recent study showed that recruitment of neural resources may also be observed in healthy young adults when the difficulty of a task is increased (Du et al., 2014). Thus, recruitment of neural resources may be a compensatory technique to offset cognitive decline due to changing environmental cues.

2.5. Compensation through changes in network connectivity

Deafferentation not only changes the activity but also the functional connectivity between different brain regions sampling the brain for compensatory information for the loss of input. Changes in functional connectivity are not only reflected in regions close to the deafferented site but also in regions that are anatomically distant (Fornito et al., 2015). Changes in functional connectivity between sensory and non-sensory regions have been established after sensory deprivation in almost all sensory domains. Increased connectivity between bilateral primary auditory cortices, auditory association areas, basal ganglia, and insula is observed following sensorineural hearing loss (Liu et al., 2015). Similarly increased functional connectivity was reported between the Broca's area, calcarine sulcus, and extratriate regions such as the inferior and superior occipital gyri with decreased visual input. In addition, these patients also demonstrated increased functional connectivity between Broca's area and the lingual, inferior temporal, and medial parts of the superior frontal gyri in comparison to a control group (Sabbah et al., 2016). Reorganization of networks connecting the somatosensory cortex and the insula is also reported as a result of damage to somatosensory nerve fibers (Čeko et al., 2013). Similarly, changes in functional connectivity between sensory and extra-sensory regions have been reported in cases of vestibular and olfactory deprivation as well (Alsalman et al., 2016; Kollndorfer et al., 2015).

Changes in functional connectivity between different brain areas may constitute an adaptive mechanism to cope with loss of sensory input. Fornito and colleagues propose that such changes can be brought about as a result of one of three mechanisms – (a) compensation (b) changes in neural reserve and (c) degeneracy (Fornito et al., 2015). Compensation is the process of increasing the function of distant unaffected areas by increasing their activity or functional connectivity, to compensate for loss of function at affected sites. Changes in neural reserve involve recruitment of neural resources to preserve functionality in areas associated with the affected site and behaviorally cope with the loss of functionality of the affected site. Degeneracy is the functional overlap of brain regions described as either the phenomenon of a network of regions carrying out the same task or the multimodal ability of certain regions to carry out different tasks. Either way, sensory deafferentation may be adaptively compensated by overlapping functional modules of different brain regions.

2.6. Top-down prediction system

Adaptive compensation of sensory loss may not only be compensated by bottom-up but also by top-down mechanisms. For a long time, it was believed that the aim of bodily functions was simply to maintain homeostasis. Recently, an alternative theory was presented in which the authors argued that trying to maintain a constant set point by every organ would not be a very efficient way to manage bodily resources. On the other hand, it was proposed that bodily resources were managed and distributed to other organs according to their demand by one central control center, namely the brain (Sterling, 2012). According to this theory, the proposed aim of bodily functions is to adjust the internal milieu with respect to changing environmental needs, in other words, allostasis. Allostasis also states that the brain makes predictions about the bodily needs by setting prior beliefs about its environment and updating these beliefs based on bottom-up input (Sterling, 2012). In other words, allostasis refers to the concept of "stability through change" where it creates an 'error' signal when the set prior beliefs are not met and is responsible for involving the whole brain and body to allocate resources in order to minimize this error (Sterling and Eyer, 1988). The concept of allostasis thus goes together with the theory of hierarchical updating of Bayesian prediction errors in the brain in the presence of sensory deafferentation (De Ridder et al., 2014b; Friston, 2009, 2012; Friston et al., 2006). This theory, also known as the theory of the Bayesian brain, also postulates that the brain creates prior beliefs or predictions of the next upcoming input based on its internal representation of the environment it has been exposed to over a period of time (Friston, 2009, 2012; Friston et al., 2006). In the presence of sensory deafferentation, the brain samples the new environment with the aim to provide bottom-up input for the hierarchical updating of prior beliefs. Successful updating of the model would reflect "stability through change" or allostasis. Thus, the theory of the Bayesian brain may be regarded as a mechanism of allostatic plasticity.

It has been shown that the Bayesian prediction-errors between the bottom-up cues and the top-down predictions are encoded by the anterior cingulate cortex, specifically the dorsal anterior cingulate cortex (Hayden et al., 2011; Ide et al., 2013). The dorsal anterior cingulate cortex and the anterior insula have been shown to be a part of the salience network (Seeley et al., 2007) that assigns

top-down goal-directed salience to a prediction error, which determines the relative importance of an external stimulus with respect to the internal environment. This salience is integrated with the reward-system of the brain by other subcortical limbic structures such as the nucleus accumbens, ventral tegmental area, and the ventral striatum (Cooper and Knutson, 2008; Seeley et al., 2007; Yin et al., 2008). Depending on the salience and the associated reward, the hierarchical model is updated in a Bayesian statistical manner in order to minimize the salience and the associated surprise, thereby successfully adapting to a changing environment (Friston, 2009; Friston et al., 2006). The updating has been proposed to be taken care of by the nucleus accumbens, along with the ventral striatum and ventromedial prefrontal cortex, forming a frontostriatal gating system (Rauschecker et al., 2015) for "top-down modulation" of salient stimuli.

3. Mechanisms of maladaptive compensation: generation and compensation of cortical salience

Although the brain tries to sample the new environment using the mechanisms mentioned above, insufficient bottom-up compensatory cues following congenital, early, and late sensory deprivation; failed top-down belief updating; or the inability to integrate multisensory cues – all lead to the prevalence of an uncertainty. The failure of adaptive compensation techniques to accommodate sensory deprivation calls for alternative ways to compensate for sensory uncertainty, such as the generation of a phantom percept.

3.1. Phantom percepts

Phantom percepts primarily occur because of sensory deafferentation and may be a maladaptive solution to compensate for sensory uncertainty. Mechanisms responsible for the generation of these phantom percepts may sometimes result from the failure of adaptive compensatory techniques. The different phantom percepts and their mechanisms of generation are detailed below. Table 2 gives a summary of the phantom percepts in congenital, early, and late sensory deprivation in the different sensory domains.

3.1.1. Visual phantoms

One of the unique qualities of the visual system is that visual phantoms are an everyday experience in all individuals. The location where the optic nerve leaves the retina is deprived of photoreceptors and is called the 'blind spot'. This 'blind spot' is also described as a 'black hole' in the visual field since it forms a natural scotoma (De Weerd, 2006), or a region which receives no visual input (Ramachandran, 1993). The phenomenon of the perception of flawless bifocal vision even in the presence of a natural scotoma is described as the perceptual 'filling-in' of missing information (De Weerd, 2006). Perceptual filling-in is also experienced as the filling of object space with background texture (Ramachandran, 1993), completion of surfaces (Grossberg, 2003), contours (Peterhans and von der Heydt, 1989; von der Heydt et al., 1984), and color (Sasaki and Watanabe, 2004). The perception of impossible shapes such as Penrose shapes, the devil's fork, the Mobius strip, the Dancing elephant, etc. are other famous examples of perceptual filling and how it allows us to make sense of the world around us.

However, other visual phantoms are a product of sensory deprivation. Hallucinations of patterns, disfigured shapes of people, and phosphenes of different colors were reported in patients with lesions to the optic chiasm and optic tract (Cogan, 1973). Partial excision of the frontal lobe due to meningioma could result in patients reporting both simple and complex hallucinations (Cogan, 1973). One of the rare, yet popular visual phantoms is the perception of complex images such as faces of people, landscapes, animals, and trees in inappropriate scenarios following deafferentation of visual input, known as Charles Bonnet Syndrome (Schadlu et al., 2009; Schultz and Melzack, 1991). It most commonly occurs in older people with compromised vision because of macular degeneration (Kester, 2009), surgical removal of tumors, epilepsy, cataract surgeries, or electrical stimulation of the amygdala or temporal cortex (Schultz and Melzack, 1991).

Table 2
Summary of phantom percepts in different sensory domains.

Onset of deafferentation	Sensory domain	Cause	Phantom percepts
Congenital and early-onset	Vision	Early-onset blindness	Charles Bonnet syndrome
	Audition	Early-onset deafness	Tinnitus
	Somatosensory	Congenital or early amputation, contradicting visual input from someone with intact body schema	Phantom limb syndrome
Late-onset	Vision	Surgical causes: Enucleation, evisceration, exteneration, cataract surgery, electrical stimulation Lesions to central processing centers such as tumors, infarcts and trauma Degenerative causes: Macular degeneration, epilepsy	Phosphenes; kaleidoscopic vision in color and black and white; pleasant images of flowers; horrific images of coffins; Charles Bonnet syndrome
	Audition	Noise-induced, hidden or age-related hearing loss Moderate to severe deafness, focal brain lesions	Continuous subjective tinnitus Musical hallucinosis
	Somatosensory	Damage to peripheral nerves, spinal cord Amputation of an extremity	Neuropathic pain Phantom limb pain
	Olfaction	Conductive losses: obstruction to nasal air flow, chronic rhinosinusitis, polyps, nasal tumors Sensorineural damage: head trauma, infection to upper respiratory tract, damage to olfactory receptor neurons	Phantosmia – smelling pleasant and unpleasant odors Parosmia – change in the smell of items.
	Gustation	Sensorineural damage: Head trauma, damage to thalamus, brainstem, infection of upper respiratory tract, exposure to toxic substances Surgical effects: Surgery of chorda-tympani, glossopharyngeal or vagus nerve, tonscillectomy	Phantogeusia – persistent bitter or metallic taste Dysgeusia – change in the taste of items.
	Vestibular	Surgical causes: Resection of vestibular schwannoma Changes in gravitational environment Caloric and galvanic vestibular stimulation Damage to otocania, decreased multisensory integration	Dizziness, Mal de debarquement, "room-tilt" illusion, mis-ownership of body parts, autoscopic phenomenon – autoscopic hallucinations, heautoscopy, feeling of presence, out of the body experience

There are accounts of the occurrence of Charles Bonnet Syndrome in early visual deprivation as well (Schwartz and Vahgei, 1998).

3.1.2. Auditory phantoms

Auditory phantoms are the perception of simple or complex sounds in the absence of external auditory input (Jastreboff, 1990; Vanneste et al., 2013). Simple auditory phantoms such as the intermittent or continuous perception of a ringing, buzzing, or hissing sound are collectively called tinnitus (Jastreboff, 1990; Møller et al., 2010). Although tinnitus may be caused due to temporary inconsistencies in the auditory periphery (Møller et al., 2010), it is believed to be a result of deafferentation of auditory input, either by means of noise trauma (Attias et al., 1993; Axelsson and Sandh, 1985; Jansen et al., 2009) or due to progressive hearing loss due to aging (Nicolas-Puel et al., 2002; Rosenhall and Karlsson, 1991; Szymiec et al., 2002).

A more complex type of phantom auditory sound, called musical hallucinosis, is the perception of vocal or instrumental music perceived in the absence of an external stimulus (Berrios, 1990; Keshavan et al., 1992). This phenomenon is attributed to be the auditory analogue of Charles Bonnet Syndrome (Evers, 2006; Evers and Ellger, 2004; Griffiths, 2000; Hosty, 1994). Although there are several etiologies to the incidence of musical hallucinosis (Evers, 2006; Evers and Ellger, 2004), moderate to severe deafness and focal brain lesions have been identified to be the most common causes of the disorder (Baurier and Tuca, 1996; Griffiths, 2000; Hammeke et al., 1983; Warren and Schott, 2006). Other lesion-deficit studies also report the incidence of musical hallucinosis in patients with brainstem lesions (Baurier and Tuca, 1996; Gordon, 1997), thalamocortical radiation infracts (Woo et al., 2014), and resection of insular gliomas (Isolan et al., 2010). Interestingly, several reviews and case studies suggest that the music heard by the patients are repetitive verses from songs that are familiar to the patients or other people (Hammeke et al., 1983; Inzelberg et al., 1993; Miller and Crosby, 1979; Vitorovic and Biller, 2014; Warren and Schott, 2006).

3.1.3. Somatosensory phantoms

Phantom sensations in the somatosensory domain could result from damage to the peripheral nerves, damage to the spinal cord (Baron, 2006; Woolf and Mannion, 1999), or the amputation of an extremity (Flor, 2002, 2008; Ramachandran, 1993; Rasmussen et al., 2011). Damage to peripheral nerves or the spinal cord could result in a condition called neuropathic pain (Baron, 2006; Woolf and Mannion, 1999). Amputation of an extremity that is mapped to the somatosensory cortex such as arms, legs, parts of the face, fingers, toes, genitals, eyes, etc. could lead to one of the most famous somatosensory phantoms, phantom limb pain (Flor, 2002, 2008; Ramachandran, 1993; Rasmussen et al., 2011). Similar to the phantom limb phenomenon in adults post-amputation, phantom limbs have been reported in early amputation in children (Melzack et al., 1997; Poeck, 1964) and even in people born with congenital aplasia (Poeck, 1964; Saadah and Melzack, 1994; Weinstein et al., 1964).

Like phantoms in other domains, phantom limb pain and neuropathic pain have been categorized as disorders of the central nervous system resulting from peripheral damage (Flor et al., 2006). In addition to activation of the primary somatosensory and motor cortices (on movement of the phantoms), there is also evidence for the activation of non-somatomotor brain areas in phantom and chronic neuropathic pain. Neuropathic pain has hence been proposed to be a connectivity disorder, where aversive memory networks fill in for the missing somatomotor information because of aberrant functional connections (De Ridder et al., 2011). On the other hand, phantom pain has been proposed to be the result of competing somatomotor and visual inputs, wherein visual input is used to reinforce the position of the phantom (Chan et al., 2007; Deconinck et al., 2015; Ramachandran et al., 1998).

3.1.4. Smell and taste phantoms

Olfactory disorders provide important clues about endocrinologic changes in the body (Levy and Henkin, 2003) and act as precursors to damage to brain structures due to head trauma (Callahan and Hinkebein, 2002) or ischemia (Beume et al., 2015). Gustatory cues are important in evaluating loss of appetite, malnutrition, and unintended weight loss (Maheswaran et al., 2014) and also accompany smell disorders most of the time (Stevenson and Langdon, 2012; Wrobel and Leopold, 2004). Damage to peripheral structures in both sensory domains leads to diminished or total loss of functionality, often leading to phantom perceptions in both domains (Stevenson and Langdon, 2012).

Phantosmia is the phantom perception of a smell, usually unpleasant, in the absence of an external odorant stimulus (Grouios, 2002; Leopold et al., 2002). This could be caused due to a disruption in olfactory function by conductive losses which include obstruction of the nasal airflow due to chronic rhinosinusitis (Cowart et al., 1997; DiFabio et al., 2009; Wrobel and Leopold, 2004), polyps, or nasal tumors (Cowart et al., 1997; Wrobel and Leopold, 2004). This damage may also occur due to sensorineural impairment such as loss of olfactory receptor neurons, insult to the olfactory bulb due to head trauma in accidents, infection of the upper respiratory tract, or other forms of damage to the olfactory receptor neurons (Cowart et al., 1997; Grouios, 2002; Leopold, 2002; Schechter and Henkin, 1974; Wrobel and Leopold, 2004). Although phantosmia does not critically impair a person's quality of life, it still impairs the social gratification of consuming tasty food or experiencing pleasant odors (Levy and Henkin, 2003). In addition to damage to peripheral structures, there are also some centrally-observed changes that accompany phantom smelling (Stevenson and Langdon, 2012).

Similarly, disruption in taste perception may result in parageusia (perception of a different taste for an item) or phantogeusia (perception of a taste without the presence of an external taste stimulant) (Cowart et al., 1997; Maheswaran et al., 2014; Wrobel and Leopold, 2004). Taste phantoms mostly co-occur with decreased or complete loss of taste sensitivity (Bartoshuk et al., 2005). Taste phantoms that occur alongside olfactory phantoms are caused due to similar reasons such as head trauma and resulting damage to the thalamus, brainstem, and ventrotemporal lobes; infection of the upper respiratory tract; chronic rhinosinusitis; exposure to toxic substances; etc. (Hummel et al., 2011). They can also be an anesthetic or post-operative effect of surgery to either the chorda tympani nerve (Bartoshuk et al., 2005; Yanagisawa et al., 1998), the glossopharyngeal nerve, or the vagus nerve (Bartoshuk et al., 2005; Hummel et al., 2011), all of which innervate the oral/throat region. A survey of case studies looking at the post-operative effects of tonsillectomy revealed that one of the most common after-effects was the incidence of taste disorders accompanied by phantogeusia (Kim et al., 2006; Leong et al., 2007; Scinska et al., 2008; Temporale et al., 2013).

3.1.5. Vestibular phantoms

Mal de debarquement is a pure vestibular phantom phenomenon where the memory of a certain vestibular event, such as the rocking feeling when going on a boat, is replayed in resting state (Moeller and Lempert, 2007). In healthy adults, alterations in gravitational environment create illusions of tilted extrapersonal space called the "room-tilt illusion" (Brandt and Dieterich, 1999; Querner et al., 1999). Room-tilt illusions occur due to the mismatch between the visual and vestibular 3D maps at the cortical level (Brandt, 1997). Cosmonauts flying in orbit in outer space and flyers

in parabolic flight report illusions of feeling upside down in a canonically upright space due to the lack of vestibular input in microgravity in an eyes-closed condition (Graybiel and Kellogg, 1967; Kornilova, 1997). These illusions may also occur in patients with pathological conditions such as vestibulocerebellar lesions, lesions to the parieto-occipital or frontal cortices (Malis and Guyot, 2003), or due to a lack of peripheral vestibular input (Malis and Guyot, 2003; Tiliket et al., 1996).

Indirect vestibular phantoms involve conflict between multisensory systems and inaccurate integration of multiple sensory domains, leading to phantom perception in multiple sensory domains (Lopez, 2013). Mis-ownership of body parts can also be invoked by providing conflicting visual and tactile input to the brain in the presence or absence of vestibular stimulation (Lopez et al., 2010). This is famously called the "rubber-hand illusion" where simultaneous tactile stimulation of a rubber hand and the invisible hand of the participant at the same time could cause the participant to attach phantom ownership to the rubber hand (Lopez et al., 2010). A more complex phenomenon of disembodiment combined with altered body ownership as a result of faulty multisensory integration is called the autoscopic phenomenon (Blanke and Mohr, 2005). These are visual hallucinations of the self with or without a sense of disembodiment. One of the famous variations is the 'out-of-the-body experience' which is the visual hallucination of one's own supine body from an elevated position involving both the occurrence of a double and the complete displacement from one's self-referential point (Blanke et al., 2004; Blanke and Mohr, 2005; Lopez et al., 2008). Neuroimaging (Lopez et al., 2008) and neurostimulation (De Ridder et al., 2005) studies reveal that stimulation/lesions to bilateral temporo-parietal junctions and orbito-parietal cortices (Lopez et al., 2008) may result in the autoscopic phenomenon.

Phantom percepts may be generated as a result of a dysfunctional bottom-up compensatory system that failed to rapidly sample the environment and/or a dysfunctional top-down compensatory system that failed to update its prediction resulting in the prevalence of constant salience (De Ridder et al., 2014a). Congenital and early age phantoms are argued to be generated due to a prediction error due to competition between decreased bottom-up input and either an intact body schema, the activity of mirror neurons activated while looking at someone's intact body schema, or increased bottom-up input due to the use of prosthesis competing with maladaptive cross-modal plasticity. In late sensory deprivation, both failed bottom-up processes such as aberrant thalamocortical rhythms, maladaptive map plasticity, maladaptive changes in functional connectivity, dysfunctional thalamic limbic-cancellation, and dysfunctional top-down processes such as updating to a new reference point may be responsible for the generation of phantoms. These concepts are detailed below and summarized in Table 3.

3.2. Disruption of body schema and neuro-matrix

Some scientists believe that the occurrence of congenital and adult phantoms can be attributed to the development of body schemas and neuro-matrices. The concept of body schema stems from the idea of having both self-awareness of our body and a representation of the different parts of the body in the brain. Body schema is defined as the internal, dynamic representation of the spatial and biomechanical properties of one's body (Giummarra et al., 2007). The body schema is developed from the activity triggered in the muscles during intrauterine muscle movements (Bromage and Melzack, 1974). Researchers propose that this schema or body representation in the brain is plastic and can constantly change with learning, use, and environmental stimuli (Oouchida et al., 2016). The body schema is proposed to be modified by sensory inputs from the somatomotor system, proprioceptive system, vestibular system, visual system, and an efference copy of all motor commands that are delivered to the different limbs (Giummarra et al., 2007).

The concept of the "neuro-matrix" was proposed by Melzack in 1990 to explain the occurrence of phantoms in congenital aplasia. The neuro-matrix is considered an extension of the concept of body schema wherein the awareness of one's body parts is produced by the activity of neurons within the brain (Melzack, 1990). This activity can also be triggered by input from different sensory domains. The neuromatrix concept proposes that although learning is an integral part of the development of body schema, there is still a genetic component to the formation of neural circuits that governs the structure and functionality of different body parts

Table 3
Summary of mechanisms of maladaptive plasticity.

Onset of deafferentation	Mechanism	Description
Congenital and early-onset	Disruption to body schema and neuromatrix	The organization of the topographic maps has a genetic aspect. Disruption of this organization may be caused congenitally.
	Mirror-neurons	Mirror neurons trying to imitate the movements of an intact body schema may not be integrated with the internal body schema of the person.
	Cross-modal plasticity	Extensive cross-modal recruitment can hinder domain-specific plasticity in the deprived cortex to aid the use the of prostheses.
Late onset	Thalamocortical dysrhythmia	Presence of wide-spread low-frequency activity in the cortex in the wake state accompanied by a halo of high frequencies. This results from increased synchronization of the thalamocortical loop due to de-inactivation of T-type Ca^{2+} channels and decreased lateral inhibition due to reduction in GABA receptors.
	Map plasticity	Increased spontaneous activity may also trigger changes in topographic map organization. This could either follow axonal sprouting of neurons from the adjacent entities into the deafferented site (classical theory) or dendritic sprouting of deafferented neurons into the adjacent entities (neural Darwinism). Either way there is increased expression of deafferented area.
	Functional connectivity	Changes in functional connectivity between sensory and non-sensory areas have been reported in several phantoms.
	Failed bottom-up cancellation	Failure of the cortico-limbic cancellation system due to structural or functional changes to the ventromedial prefrontal cortex or the nucleus accumbens may lead to "unmasking" of the erroneous bottom-up input, which is then relayed to the cortex by the thalamocortical loop.
	Failed top-down modulation	Structural or functional changes to the subgenual ACC/ventromedial prefrontal cortex lead to an inability to make successful adjustments to the top-down belief-system based on the changing bottom-up information. This results in the creation of constant salience
	"Filling-in" missing information	Faulty integration of sensory signals or constant salience may be compensated by "filling-in" the missing information by pulling it out from the sensory memory.

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(Melzack, 1990). The neuro-matrix is hypothesized to consist of thalamo-cortical and limbic loops whose inputs and outputs shape the characteristic structure and function of the neuro-matrix, also called the "neuro-signature" (Giummarra et al., 2007; Melzack, 1990). With the concept of the neuro-matrix, Melzack proposes that the general structure of the topographical patterns of each sensory domain may be laid out even before birth rather than built up neuron-by-neuron. Although learning and sensory experience may change the topographic organization of sensory maps, his theory proposes that the genetic aspect of the development of topographic maps may be responsible for the occurrence of congenital phantoms. In other words, his theory claims that congenital phantoms are reflections of an intact body schema that was formed even before birth. Some scientists support this concept of a pre-conceived neural signature of the body schema (Ramachandran et al., 1998), and some scientists refute the idea, saying that learning and sensory exposure is a prerequisite to the development of topographic sensory maps (Eggermont and Kral, 2016).

3.3. Failed integration of self-referential and external sensory input

In a comprehensive perspective article, Price argues that although the theory of a 'hard-wired' neuro-matrix solves the mystery of congenital phantoms, it creates redundancy in the creation of a body image, which is inefficient from an evolutionary perspective (Price, 2006). Thus, as an alternative theory to the generation of congenital phantoms, a proposition for the presence of "mirror-neurons" in the human brain was made (Price, 2006). The theory of mirror-neurons was first proposed in monkeys in order to explain the similarities in the firing pattern of neurons in the pre-motor cortex when monkeys performed a goal-directed task compared to seeing someone else do the same task (Rizzolatti et al., 1988). On the other hand, mirror-neurons in humans were observed not only while performing a motor task but also in the sub-threshold firing of neurons while observing a particular task (Fadiga et al., 2005). Furthermore, mirror-neurons were shown to fire in response to the sound or vision of a particular action (Kohler et al., 2002). Conversely, audiovisual mirror-neurons are shown to be instrumental in recognizing an action that is associated with a particular sound (Keysers et al., 2003). In addition, mirror-neurons have also been reported to be important in imitations, which play an important role in the cognitive development of infants (Iacoboni, 2009).

The theory of mirror-neurons postulates that visual input from the movement of intact limbs of people with intact bodies may trigger postural or somatic empathy, creating a discrepancy in the body image of the self that is brought to consciousness at an age when a person is more aware of his/her surroundings (Price, 2006). The mirror-neuron system is also hypothesized to be responsible for reinforcing an intact body image in various sensory representations that may lead to the perception of a phantom in congenital aplasia patients following habitual visual input from external sources (Brugger, 2006; Brugger et al., 2000; Funk et al., 2005).

3.4. Maladaptive cross-modal plasticity

Although the theory of the neuro-matrix and mirror neurons support the possibility of phantoms in congenital loss of sensation, some researchers argue that extensive plasticity of sensory maps within the critical period and the significant contribution of the environment in shaping sensory experience make the occurrence of phantoms within the critical period extremely improbable. In their review, Eggermont and Kral comprehensively describe how somatotopic sensory maps are developed based on somatic memories and how the tonotopic map in the auditory system is developed majorly based on both genetic factors and intrauterine auditory experience (Eggermont and Kral, 2016). They explain that in the presence of unilateral deafness, extensive cross-hemispheric plasticity takes over the somatotopic organization in the deaf side and that no somatic memories will be formed since the deaf side has never been exposed to auditory experience. Taking this into consideration, Eggermont and Kral argue that tinnitus in congenital deafness is highly improbable. Thus, successful compensation of the deprived sensory experience by cross-modal plasticity may result in successful adaptation of the brain to the reduced sensory input, making phantoms in congenital deprivation improbable.

As much as cross-modal plasticity helps to compensate for the missing sensory representation, it can also be a hindrance to individuals trying to use prostheses. There are reports of phantom sensations in congenitally deprived individuals following use of prostheses (Eggermont and Kral, 2016; Weinstein et al., 1964). This is hypothesized to be the result of dis-integration of contradicting bottom-up input provided by the prosthesis and the top-down information provided by successful rewiring of neurons from another sensory domain (Campbell and Sharma, 2016). Use of prostheses has also been reported to reinforce the altered body schema as a result of amputation, leading to reinforcement of phantom perceptions (Giummarra et al., 2007).

3.5. Thalamo-cortical dysrhythmia

Maladaptive bottom-up compensation in late-deprivation may be witnessed in aberrant thalamocortical rhythms. In healthy adults, the thalamocortical rhythm in wakefulness is maintained in alpha oscillations, wherein meaningful stimuli are relayed to the cortex and redundant information are suppressed (Klimesch, 2012). Thalamocortical synchrony at lower frequencies such as delta and theta are established only in sleep or minimally conscious states (Lee et al., 2005; Timofeev et al., 2012). However, in the presence of deafferentation, there is wide-spread low-frequency activity at the cortical level delivered by aberrant thalamocortical synchrony in the wake state (Llinás et al., 1999). This is proposed to be brought about by de-inactivation of the T-type calcium channels of the thalamic relay cells, leading to hyperpolarization of the cell membrane (Llinás et al., 2005; Llinás and Steriade, 2006). This results in the synchronization of the thalamocortical loop, leading to widespread low frequency theta oscillations at the level of the cortex and a decrease in alpha oscillations (Llinás et al., 2005). This in turn results in decreased lateral inhibition, producing an increase in cortical high frequency gamma oscillations around the edge of the low-frequency theta oscillations (Llinás et al., 1999). Thalamocortical dysrhythmia can also result from a reduction in Gamma Amino Butyric Acid (GABA) receptors in cortical interneurons, producing a similar edge effect and spontaneous hyperactivation in the sensory cortices (Llinás et al., 2005; Shore et al., 2016). Although the olfactory system is not relayed through the thalamus, it is proposed that the olfactory bulb serves as a similar gateway to the cortex. The granular cells have been proposed to take over the role of the inhibitory thalamic reticular cells, and the glomerular cells are proposed to take over the role of the thalamic relay cells, thus exercising homologous gating and relay control of the olfactory system (Kay and Sherman, 2007).

Increased activity in the sensory cortices has been shown in the case of all phantoms from single-cell recording, EEG, and fMRI data. This could result from aberrant thalamocortical synchrony, which can be viewed as one of the initial mechanisms in the compensation of cortical salience. Low-frequency theta oscillation is said to represent negative symptoms such as loss of vision, hearing, and somatomotor capabilities, whereas increases in

synchronized gamma activity are said to reflect positive symptoms such as phantom images, sounds, music, and limbs (Llinás et al., 2005; Llinás and Steriade, 2006). Although no direct evidence has been presented from the olfactory, gustatory, or vestibular systems, we can hypothesize a similar turn of events following disinhibition in their respective sensory cortices. The gamma frequency has also been related to conscious perception or keeping a stimulus "online" (Dehaene et al., 2006). In the case of phantom percepts, increased gamma activity also keeps the phantom "online", leading to continuous perception.

3.6. Maladaptive map plasticity

The thalamocortical dysrhythmia model is in direct relationship with changes in neuronal activity in the different sensory cortices. The decreased inhibition in the sensory cortices due to the reduction in Gamma amino butyric acid receptors (Berrios and Brook, 1984; Levy and Henkin, 2004; Llinás et al., 2005; Paulig and Mentrup, 2001) results in an increase in spontaneous activity, which may or may not trigger plasticity of topographic maps (Rajan, 1998). Changes in map organization due to decreased sensory input in the different sensory domains may sometimes be maladaptive and result in the generation of a phantom percept. Phantoms, especially in the auditory (Eggermont, 2006), visual, and somatosensory (Flor, 2008; Flor et al., 2006; Oouchida et al., 2016) domains, have been shown to accompany maladaptive expansion of topographic, visual field-size, and tonotopic map organization as a compensatory mechanism to the memory of the deafferented region.

In the auditory domain, it has been shown that reversal of map expansion is correlated with improvement in phantom perception (Engineer et al., 2011). Although changes in map plasticity seem to be a neural correlate of phantom percepts, there is still an ongoing debate as to whether map plasticity always follows deafferentation. There is evidence from the auditory and somatosensory literature that this is not always true (Langers et al., 2012; Makin et al., 2013), and indeed a significant loss of receptors could be induced without causing changes in cortical maps (Rajan, 1998). Secondly, even if map plasticity does follow deafferentation, does it always lead to the creation of a phantom? Although map plasticity is well understood in the animal literature, there is substantial criticism in human literature due to the lack of imaging techniques to look at single cell recordings or microscopic maps. We still lack clarity as to whether increased cortical excitation as reported by EEG and fMRI relates directly to increases in spontaneous activity at the neuronal level or reflects change in overall synchronized activity of neuronal cell populations, thus bringing into question the incidence of map plasticity in humans at the macroscopic level.

3.7. Maladaptive changes in functional connectivity

Changes in functional connectivity may not only be adaptive, but also maladaptive. Maladaptive changes in functional connectivity have been the focus of recent literature in phantom percepts of different domains. Extensive research in the auditory (Husain and Schmidt, 2014; Shore et al., 2016) and somatosensory (Makin et al., 2015) domains reveals changes in functional connectivity between sensory, limbic, and frontal regions depending on the amount of deafferentation (Vanneste and De Ridder, 2016), chronicity (Zhang et al., 2015), and distress (Vanneste and De Ridder, 2015) associated with the phantom percept. Auditory phantom percepts are proposed to be an integration of multiple subnetworks, in which each symptom is hypothesized to be encoded by a specific subnetwork (De Ridder et al., 2014c). Thus, trying to modify the percept may involve disintegration of multiple separable subnetworks (Mohan et al., 2016). This hypothesis may be extended to phantoms of other domains, encouraging further research in terms of analyzing changes in functional and causal connectivity between sensory and extra-sensory regions.

Like mechanisms of adaptive changes in functional connectivity, Fornito and colleagues also propose different ways of manifestation of maladaptive changes in functional connectivity. They propose that maladaptive changes in functional connectivity may feature three mechanisms: (a) Diachisis, (b) transneuronal degeneration, and (c) dedifferentiation (Fornito et al., 2015). Diachisis is defined as the maladaptive changes affecting specific areas of a particular network which are remote to the region of deafferentation. This has been shown by changes in activity and functional connectivity of regions such as the limbic and frontal regions in phantoms of different domains. Transneuronal degeneration has been explained as a longitudinal version of diachisis. Transneuronal degeneration can be identified with changes in functional connectivity with increased chronicity of the syndrome. Lastly, dedifferentiation is proposed to be an imbalance between excitation and inhibition that causes the break-down of segregated neural activity. This has been shown in both the thalamocortical dysrhythmia model and changes in the balance between integration and segregation in phantom percepts.

3.8. Failed cancellation and top-down prediction mechanisms

As explained before, the cancellation system plays a very important role in tuning out unwanted signals created by deafferentation at the level of the thalamus, thus providing adaptive compensation of bottom-up cues (Rauschecker et al., 2010b). However, malfunctioning of the cancellation system would be responsible for the inefficient filtering of erroneous signals and maladaptive sampling of bottom-up cues leading to erroneous signals sent to the cortex. This may be followed by increased firing in the nucleus accumbens, inducing excitotoxicity in the serotonergic cells of the nucleus accumbens (Rauschecker et al., 2010b). In addition, changes in the levels of serotonin in individuals genetically predisposed to decreased levels of neurotransmitters may experience a decline in functionality of the cancellation system even earlier than others who don't possess the same genetic vulnerability (Rauschecker et al., 2010b). The up-regulation of serotonergic cells and the increase in serotonergic activity has been evidenced in the generation of phantom percepts (Caperton and Thompson, 2011). The resulting erroneous signal would result in a discrepancy between the top-down beliefs and the bottom-up cues thus producing a prediction error at different levels of the hierarchy.

Although erroneous signals may reach cortical consciousness due to a malfunctioning cancellation system, successful updating of hierarchical prediction errors could still prevent the generation of a phantom. However, structural and functional changes to the regions involved in the encoding and updating of the prediction error could still lead to the generation of phantom percepts. As mentioned earlier, the dorsal anterior cingulate cortex, a very important hub in the salience network, encodes the hierarchical prediction error. Several studies report changes in activity and connectivity in the salience network and specifically in the dorsal anterior cingulate cortex in the presence of phantom percepts (Vanneste and De Ridder, 2015; Vanneste et al., 2010). In addition to updating prediction errors, top-down influence is also evidenced by the association of a positive or negative affect to the salience attached to sensory uncertainty. As discussed previously, the fronto-striatal gating system inhibits the negative affect that is attached to salience caused as a result of deafferentation (Rauschecker et al., 2015). Thus, a decrease in grey matter volume and an increase in activity in the subcallosal anterior cingulate cortex, ventromedial prefrontal cortex, and the

nucleus accumbens (Leaver et al., 2011) may not only lead to the generation of a phantom due to decreased interaction with the thalamocortical loop but may also be responsible for assigning a negative affect to the phantom percept.

3.9. Compensation of cortical salience: the "filling-in" mechanism

The different mechanisms explained in the previous subsections result in maladaptive plasticity, leading to the generation of constant cortical salience which the brain tries to minimize by creating a phantom to compensate for the missing information (De Ridder et al., 2014b). This theory is similar to the one discussed in the different sensory domains as a "filling-in" mechanism. In the vestibular system, although there is some evidence supporting the occurrence of vestibular phantoms following damage to the vestibular periphery, salience could also result from conflicting input from different sensory systems. Thus, phantom perceptions could be regarded as the compensatory solution to the failure of the adaptation of the Bayesian brain to decreased sensory input (De Ridder et al., 2014a).

Cortical salience may also be compensated for by recalling stimuli from the sensory memory. In many sensory domains, phantoms reflect on past experiences. People with Charles Bonnet Syndrome see well-formed images of faces, landscapes, animals, etc. (Pang, 2015). The pitch of tinnitus may be identified by the edge frequencies of patients' hearing loss (Sereda et al., 2015). People with musical hallucinosis usually recognize the tunes as parts of songs they have heard before (Vitorovic and Biller, 2014). Patients with phantom limb pain usually report paralysis of the phantom in the position the actual extremity was in prior to amputation (Ramachandran et al., 1998). People with smell and taste phantoms may recognize the scents and flavors from past experiences (Henkin et al., 2000) and people with vestibular phantoms, especially Mal de debarquement, continue to experience the rocking sensation from the particular incident preceding the onset of symptoms (Moeller and Lempert, 2007). Although this is explained as a part of the "filling-in mechanism" in the visual, olfactory, gustatory, and vestibular systems, a more comprehensive explanation is provided in the auditory and somatosensory systems (De Ridder et al., 2011). In patients with substantial amounts of deafferentation, the brain recalls the missing information from memory by involving structures such as the hippocampus and the parahippocampus (Vanneste and De Ridder, 2016). The parahippocampus acts as a sensory gate-keeper to the hippocampus, disregarding redundant stimuli (Tulving and Markowitsch, 1997). With an increase in sensory deafferentation, compensation by increased hyperactivity in the primary sensory areas becomes less effective and hence the brain recruits the network responsible for storing auditory memory in order to compensate for the hearing loss (Vanneste and De Ridder, 2016). Although the published work talks specifically about the auditory domain, this opens avenues for further research in the other

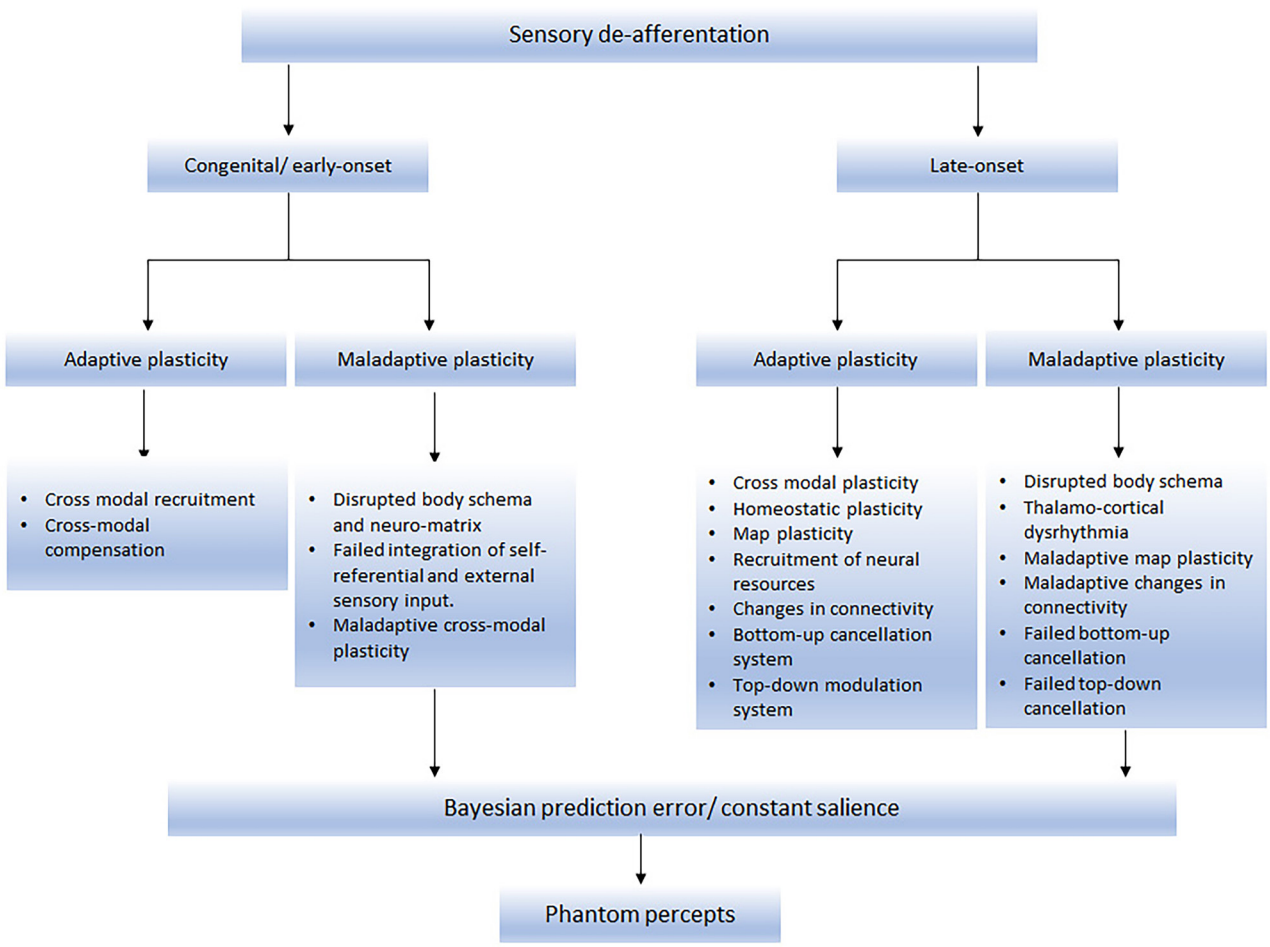

Fig. 2. The universal construct for adaptive and maladaptive compensation for sensory deprivation. The dendrogram serves as a visual summary to the article outlining the different adaptive and maladaptive compensatory mechanisms employed by the brain in congenital, early and late-onset sensory deprivation. It also postulates that the adaptive and maladaptive compensatory mechanisms fall under a universal construct of Bayesian prediction-error coding where phantoms are a maladaptive manifestation of unsuccessful adaptation.

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sensory domains. In addition, well-formed hallucinations involve severe damage to the corresponding association cortices, also responsible for making sensory memory. This supports the hypothesis that the occurrence of phantoms may stem from recalled memories as a possible compensatory mechanism for severe deafferentation.

Fig. 2 summarizes the article by categorizing the adaptive and maladaptive mechanisms employed by the brain in order to compensate for sensory deafferentation. The maladaptive mechanisms ultimately lead to the creation of a prediction error between bottom-up stimuli and top-down prediction, leading to the generation of cortical salience, which is maladaptively compensated by a phantom percept.

4. Clinical applications and future directions

Maladaptive changes in the brain have been tackled for a long time by means of medications (Palumbo et al., 2015), prostheses (Eggermont and Kral, 2016; Weinstein and Sersen, 1961; Weinstein et al., 1964), mirror therapy (Deconinck et al., 2015), etc. Today however, the therapeutic field is shifting towards non-invasive and invasive neuromodulation targeting different nerves and brain areas (Langguth et al., 2012). Thus, the knowledge of the different manners of adaptive and maladaptive compensation of the brain to sensory deafferentation opens avenues to better understand the outcomes of non-invasive techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) etc., and invasive stimulation techniques such as occipital nerve stimulation, vagus nerve stimulation, and deep brain stimulation. Neuromodulation is a relatively new field that is gaining traction with its vast application and attraction to temporarily or permanently reverse maladaptive plasticity. Several studies until now have shown varying results of efficacy in improvement in patient symptoms over one and several sessions of neuromodulation (Langguth et al., 2012). However, not all patients report a uniform change in their percept. Thus, the current article better informs us of the various ways a system may potentially dysfunction, exposing us to a range of targets for neuromodulation. Further, knowing which brain regions fall under the different mechanisms reviewed in this article also gives us a better understanding of the underlying mechanisms that are being altered.

5. Conclusion: the universal construct of adaptive and maladaptive neural compensation of sensory deafferentation

Although different mechanisms for adaptive and maladaptive compensation have been discussed in the current review article, these compensatory mechanisms may all be explained by the

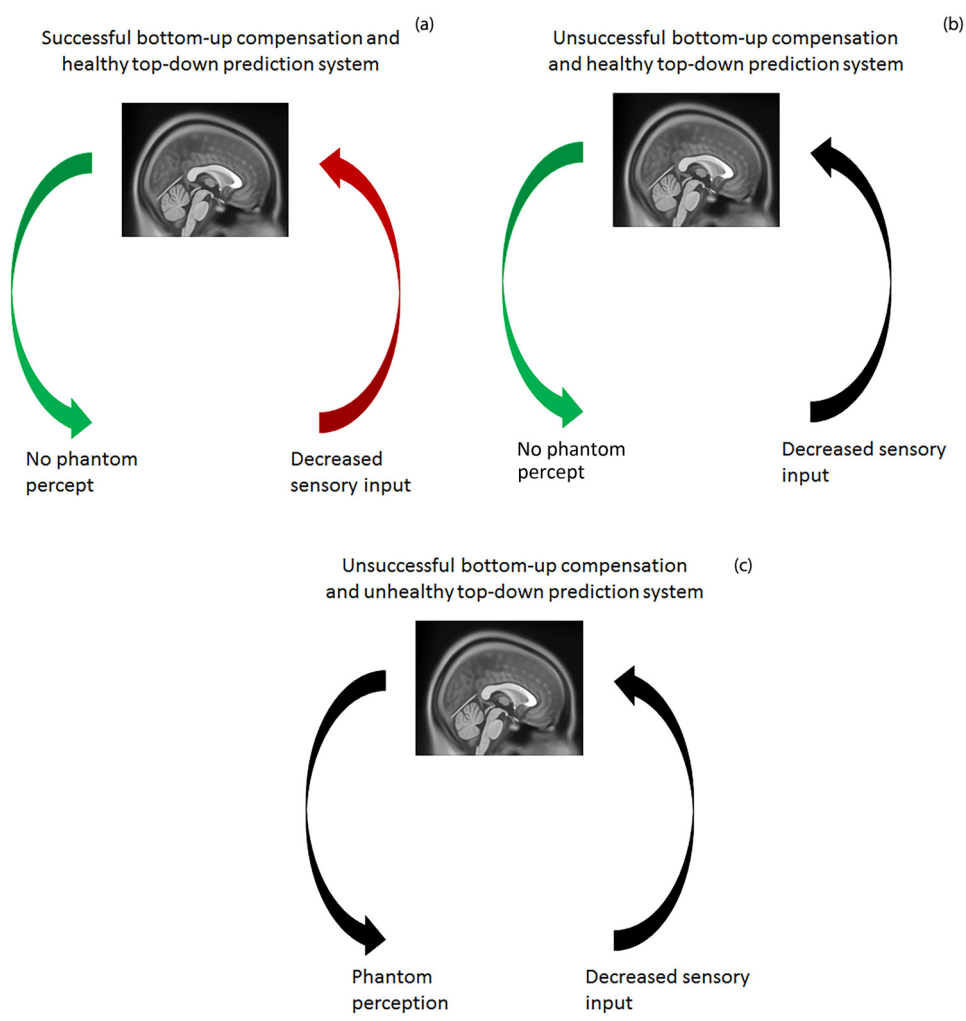

Fig. 3. Mechanism of action of complementary compensation systems. The figure outlines the mechanism of action of the bottom-up and top-down compensatory mechanisms in the presence of sensory deafferentation. The bottom-up system is shown in red, the top-down system is shown in green and failure of a system is shown in black. (a)–(c) show different variations of successful and unsuccessful bottom-up and top-down compensation of sensory deafferentation.

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universal construct of Bayesian hierarchical prediction coding. As introduced earlier in this article, it is hypothesized that the brain maintains an internal representation of the external environment. The internal and the external environment are constantly compared and any salient changes in the environment are updated in a series of hierarchical Bayesian predictions. In the presence of sensory deafferentation, irrespective of congenital, early, or late-onset, the bottom-up cues are reduced, owing to the sensory deprivation the brain is exposed to. Thus, the brain employs one or more of the bottom-up compensatory techniques in order to actively sample the new environment. These techniques include recruiting cross-modal inputs, increasing activity in sensory areas through homeostatic plasticity, expanding sensory maps, recruiting bilateral neural resources, increasing activity in other sensory cortices, or modifying connections between different sensory and non-sensory areas. If there is still any residual erroneous signal remaining, the brain employs a sub-cortical limbic cancellation system to prevent the signal from reaching cortical consciousness (Fig. 3a). In the event of a failure of bottom-up compensation, a fully-functional top-down error monitoring system may be able to ensure successful adaption to sensory deprivation. Efficiently updating the model based on the new input provided by these different bottom-up compensatory mechanisms minimizes sensory uncertainty (Fig. 3b).

However, sensory deafferentation may also lead to maladaptive compensation which may result from a combination of unsuccessful sampling of the environment, disrupted body schema, unsuccessful integration of stimuli from different sensory domains, maladaptive map and cross-modal plasticity, undesired functional connectivity, failed bottom-up cancellation, or failed top-down prediction – which represent different forms of maladaptive bottom-up and top-down compensation techniques (Fig. 3c). As a result, maladaptive plasticity results in the prevalence of continuous sensory uncertainty leading to the generation of top-down goal-directed cortical salience. It is hypothesized that this top-down, goal-related salience is compensated by the generation of a phantom percept which “fills-in” the missing sensory information. Consequently, the way phantom percepts are generated may be proposed as the maladaptive compensatory consequence and manifestation of constant salience in the brain stemming from unsuccessful adaptation to sensory deprivation.

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