Phantom percepts: Tinnitus and pain as persisting aversive memory networks

Dirk De Ridder[a], Ana Belen Elgoyhen[b,1], Ranulfo Romo[c,1], and Berthold Langguth[d]

[a]*Tinnitus Research Initiative, Brain Research Center Antwerp for Innovative and Interdisciplinary Neuromodulation, and Department of Neurosurgery, University Hospital Antwerp, 2650 Edegem, Belgium;* [b]*Instituto de Investigaciones en Ingeniería Genética y Biología Molecular, Consejo Nacional de Investigaciones Científicas y Técnicas and Tercera Cátedra de Farmacología, Facultad de Medicina, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina;* [c]*Instituto de Fisiología Celular-Neurociencias, Universidad Nacional Autónoma de México, 04510 Mexico D.F, Mexico; and* [d]*Interdisciplinary Tinnitus Clinic, Department of Psychiatry and Psychotherapy, University of Regensburg, 93053 Regensburg, Germany*

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Phantom perception refers to the conscious awareness of a percept in the absence of an external stimulus. On the basis of basic neuroscience on perception and clinical research in phantom pain and phantom sound, we propose a working model for their origin. Sensory deafferentation results in high-frequency, gamma band, synchronized neuronal activity in the sensory cortex. This activity becomes a conscious percept only if it is connected to larger coactivated "(self-)awareness" and "salience" brain networks. Through the involvement of learning mechanisms, the phantom percept becomes associated to distress, which in turn is reflected by a simultaneously coactivated nonspecific distress network consisting of the anterior cingulate cortex, anterior insula, and amygdala. Memory mechanisms play a role in the persistence of the awareness of the phantom percept, as well as in the reinforcement of the associated distress. Thus, different dynamic overlapping brain networks should be considered as targets for the treatment of this disorder.

A fundamental concept in psychology and philosophy of the mind is the notion of perception: The act of interpreting and organizing a sensory stimulus to produce a meaningful experience of the world and of oneself. A stimulus produces an effect on the different sensory receptors, inducing sensation. Further processing of this sensory stimulation generates an internal representation of the outer and inner world called a percept. Since the first days of psychology, two challenging questions have existed: How is sensory information encoded and, in particular, how is this represented information transformed into the individual awareness of a conscious percept (1)? Our understanding of sensory encoding, perception, and consciousness is challenged with a further degree of complexity in the case of phantom perception, the conscious awareness of a percept in the absence of an external stimulus. Deciphering the underlying neural correlates of phantom perception is a scientific endeavor that will aid in understanding the active processes of selecting, organizing, and interpreting information, which ultimately lead to the formation of a conscious percept within the brain.

Although some cases of phantom percepts have been described for the visual, olfactory, and gustatory systems, the vast majority of sensory phantoms are those present in the somatosensory (phantom limb perception/phantom limb pain and neuropathic pain) (2) and auditory (tinnitus) (3) modalities. Upfront we are challenged with the following questions: In the absence of an external sensory stimulus, where and how in the brain is the conscious percept generated? In addition, are the neural substrates underlying the generation of a conscious phantom percept similar for the auditory and somatosensory modalities? If so, can we advance in our understanding and treatment of tinnitus on the basis of what is known for phantom limb and phantom pain perception and vice versa? Here, we address these questions and propose a working model of how phantom perceptions arise from activity in the brain.

Phantom Pain–Phantom Sound Analogy

Activation of nociceptive pathways can trigger brain responses without necessarily causing the feeling of pain, and pain can occur in the absence of activation of nociceptors (4). Neuropathic pain is pain resulting from lesions of the peripheral or central nervous system (5), and phantom limb pain belongs to the group of neuropathic pain syndromes (2). Acute nociceptive pain and neuropathic pain have distinct although overlapping brain activation patterns in the insula, anterior cingulate cortex (ACC), prefrontal cortex, secondary somatosensory cortex, and thalamus (6). After limb amputation almost all people experience a phantom limb (2), whereas 70% suffer from severe phantom pain (2).

In a similar way, stimulus-evoked auditory cortical activation does not necessarily produce conscious auditory perception (7), and auditory perception is possible in the absence of auditory input: More than 80% of people with normal hearing perceive phantom sounds when placed in a soundproof room (8). In addition, deprivation of auditory input can result in an auditory phantom phenomenon called tinnitus. Whereas some people just perceive the phantom sound without being bothered, others suffer severely from their tinnitus (9).

Thus, a clear clinical analogy exists between phantom pain and disabling tinnitus (10, 11): (*i*) Both symptoms are wholly subjective perceptions and may change in character and quality and (*ii*) both symptoms occur in the deafferented area. The frequency spectrum of the tinnitus reflects the individual's hearing loss (12), neuropathic pain is felt as coming from the area that was initially innervated by the injured neural structure (2), and phantom pain is perceived in the missing body part (2, 13). The latter has to be differentiated from residual limb (or stump) pain in the still-present body part, adjacent to the amputation or deafferentation line (2). (*iii*) Both symptoms can be transiently masked and relieved by electrical stimulation of their respective sensory cortex (14) and (*iv*) similar characteristic symptoms exist in tinnitus and phantom pain (11). For example, a touch stimulus to the skin in patients with neuropathic pain can create a painful sensation (allodynia) and tinnitus patients frequently perceive specific sounds as unpleasant or painful (misophonia). A painful stimulus in neuropathic pain patients often generates an explosive and prolonged reaction to the stimulus (hyperpathia), similar to the hyperacusis seen in some tinnitus patients. Furthermore, a feeling of anxiety and stress responses is often encountered in both

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[1]To whom correspondence may be addressed. E-mail: abelgoyhen@gmail.com or rromo@ifc.unam.mx.

phantom pain and tinnitus patients, which can lead to sleep disturbances, concentration problems, fatigue, depression, anxiety disorders, and sometimes even to suicide in both clinical conditions (11).

However, there are also differences between pain and tinnitus. Whereas specific nociceptive pathways lead to physiological nociceptive pain, no analogous physiological tinnitus pathways exist. This observation might account for the fact that, in general, analgesics that are quite efficient for acute physiological body pain are not efficient for the treatment of tinnitus (15). Also, medications such as antiepileptics and antidepressants, which are effective in the treatment of neuropathic pain (15), are generally ineffective for tinnitus (16).

Primary Sensory Cortex and Beyond: Conscious Perception

Herman Melville's Captain Ahab following the loss of his leg in a skirmish with the big white whale Moby Dick perceives a phantom leg and phantom pain, and Ludwig von Beethoven, after losing his hearing, perceives tinnitus constantly, resulting in a "wretched life." Deprivation of sensory input triggers changes in the central nervous system, resulting in phantom percepts.

Both animal (17) and human functional neuroimaging studies (2) demonstrate that phantom limb pain is associated with cortical map plasticity resulting in somatosensory cortex reorganization and that the more pronounced the reorganization is, the more severe the phantom pain (2, 18). Similarly, animal (19) and human data (20) demonstrate that cortical map plasticity in the auditory cortex is associated with tinnitus and that the more pronounced the reorganization is, the more severe the tinnitus is perceived (20). Furthermore, these remapping changes normalize when the pain (21) or the tinnitus improves (22). Topographic development and reorganization in all sensory areas of adult cortex are governed by similar/common mechanisms of synaptic plasticity (23), likely explaining the analogy between phantom pain and tinnitus.

Magnetoencephalography (MEG) studies have demonstrated that nociceptive stimuli induce gamma oscillations in the primary somatosensory cortex (S1) and that they vary with objective stimulus intensity and subjective pain intensity (24). MEG studies have also shown that auditory stimuli elicit gamma band activity in the auditory cortex (25, 26) and that γ-band activity in the sensory cortex correlates with phantom pain (27) and tinnitus (27, 28). Moreover, electroencephalography studies have demonstrated that γ-band activity in the auditory cortex reflects the tinnitus intensity (29), analogous to intensity coding in normal auditory perception (30). The γ-band activity noted in tinnitus patients goes along with decreased α (31) and increased θ activity (27, 32). This coupled θ–γ activity coordinates activity in distributed cortical areas, providing a mechanism for effective communication between these distributed areas (33). The θ–γ coupling has also been shown on intracranial recordings in a patient with tinnitus, which disappears when tinnitus is suppressed by electrical stimulation of the auditory cortex (34). The thalamocortical dysrhythmia model provides an explanation for the emergence and persistence of such a pattern as a consequence of sensory deafferentiation (27).

Are these map plasticity and oscillatory changes in the primary sensory cortices the neural correlate of the conscious phantom percept? More detailed data derived from recordings of the somatosensory system in nonhuman primates indicate that S1 is not sufficient for the generation of a percept and have implicated association cortex and frontal lobe involvement in perception (35), analogous to what has been described for the visual (36) and auditory systems (37). Thus, it has been demonstrated that the activity of S1 neurons covaries with the stimulus strength but not with the animal's perceptual reports. In contrast, the activity of frontal lobe neurons does not covary with the stimulus strength but does so with the animal's perceptual reports (38). Moreover, the transition from sensation to perception gradually builds up across cortical areas, starting at the somatosensory cortex and ending in the premotor areas of the frontal lobe, which might have a hidden sensory function (39). Consistent with this interpretation is the fact that the artificial activation of clusters of S1 neurons is sufficient to drive the full cascade of cognitive events leading to somatosensory perception (40). In addition, very recent studies performed in monkeys are giving hints that what has been described for the somatosensory cortex can be extrapolated to the auditory cortex (41). According to these observations, we could speculate that weak transitions in activity of deafferented sensory cortices trigger abnormal processing across cortical circuits, leading to phantom perceptions. However, phantom perceptions are not necessarily induced only by the triggering signals of sensory cortices. Perceptual systems are formed by interconnected circuits forming distributed systems (42) and therefore phantom perceptions could be generated in any part of the distributed system.

Human imaging studies have given further insight into the neural correlates of conscious perception. For example, brain activity and functional connectivity in patients in a persistent vegetative state, a condition where patients are awake but without awareness and without conscious percepts (43), show that loss of awareness is associated with decreased metabolism in the anterior and posterior cingulate, precuneus, and frontoparietotemporal areas in comparison with that in normal subjects (43). These "awareness areas" anatomically overlap with the brain's default network areas (44), which might also be involved in self-awareness (44, 45). In these persistent vegetative state patients, pain stimuli activate the thalamus and S1, but this primary cortex is functionally disconnected from the secondary somatosensory cortex as well as from the abovementioned awareness areas (43, 46, 47). Similarly, in these patients activation induced by auditory stimulation is restricted to the primary auditory cortex (A1) bilaterally, without functional connectivity to the inferior parietal cortex, the hippocampus, the anterior cingulate, and the posterior cingulate (43, 48, 49).

Taken together, these results indicate that the function of the primary sensory cortices is mainly to generate an appropriate neural discriminatory representation of the sensory input, which does not lead to conscious perception. A stimulus becomes conscious only when functionally connected to a network of frontal and parietal areas. This network, together with the posterior insula (50), is relevant for the integration of sensory experiences in bodily self-consciousness (51, 52). The posterior insula triggers the pain network and the resulting emergence of subjective pain experience (53), possibly because of its involvement in the genesis of our sense of limb ownership and self-awareness (54). Furthermore, a pain (55) or an auditory stimulus (56) delivered near threshold becomes consciously perceived only when the dorsal ACC (dACC) and anterior insula are activated, i.e., when the stimuli are salient (4, 57), meaning behaviorally relevant or functionally significant (58). This concept is consistent with the "global workspace model" of consciousness proposed by Baars (59) and further elaborated by others (36, 60), on the basis of studies of the visual system.

Neuroimaging studies have confirmed the relevance of the coactivation of frontal and parietal areas together with A1 in tinnitus (61, 62). Nonpainful phantom phenomena have been shown to be more closely related to activation of S1 and the posterior parietal cortex, without activation of the secondary somatosensory cortex (63) and without cortical reorganization (64), whereas phantom limb pain is related to activation of the thalamus, the ACC, and the lateral prefrontal cortex (65), similarly to neuropathic pain in general (6), and is associated with plastic

changes in S1 (50, 64). The reorganization of A1 in tinnitus (20) and the activation of the ACC and the lateral prefrontal cortex in bothersome tinnitus (9) therefore suggest that distressing tinnitus and phantom pain are more similar than nonbothersome tinnitus and nonpainful phantom phenomena.

Incongruence, Pain, and Tinnitus

Multisensory mechanisms involving cross-modal congruency are involved in bodily self-consciousness (66–68), and cross-modal illusions are observed in most conditions in which there is incongruence among two or three stimuli of different modalities (auditory, visual, somatosensory) (69). Whereas synchronous stimulation of external objects, such as a rubber hand, can lead to the illusion of body ownership (70), asynchronous stimulation in one sensory modality or between the senses can lead to abnormal sensory perception (71, 72). On the basis of this concept it has been proposed that inappropriate cortical representation of proprioception may falsely signal incongruence between motor intention and movement, resulting in pathological pain in the same way that incongruence between vestibular and visual sensation results in motion sickness (73). This sensorimotor conflict can also induce pain in healthy volunteers (72). In this sense, phantom limb pain could hypothetically be related to a temporal incongruence between what is stored in memory (the presence of the limb) and deprivation of sensory input (the absence of the limb). Thus, when a mirror box is used to reinstate the congruence between what was stored in memory and what is seen, the pain can disappear (74).

Incongruence between auditory and visual input can alter auditory perception, as in the well-known McGurk effect (75). Whether multisensory incongruence is involved in tinnitus has not been investigated yet.

Beyond Sensory Percepts: The Affective Dimension

Pain has sensory (discriminative) and affective (the "unpleasantness") dimensions and can induce an avoidance behavior (76). Likewise, hearing has a sensory and an affective component and can induce avoidance behaviors. Moreover, affective disorders such as anxiety and depression frequently occur together with tinnitus (77). Data based on evoked potentials in humans with implanted electrodes in several brain structures indicate that painful stimuli are processed in parallel in the somatosensory cortex and dACC (78), suggesting that the affective and discriminatory aspects are processed simultaneously and not serially.

MEG studies are aiding toward delineating the network connectivity underlying the affective components of phantom perception. Thus, the presence of distress in tinnitus is related to a network activity, lateralized to the right hemisphere (79). The amount of distress is reflected by functional alterations in a network consisting of the medial temporal lobe (amygdala and hippocampus), parahippocampal areas, insula, and subgenual ACC (sgACC) and dACC (9). This network activation seems to be nonspecific, because pain distress but also distress in dyspnea (80) or social rejection (81) activate the ACC and anterior insula (9).

It is of interest to note that the areas related to the salience network and the distress component of pain and tinnitus overlap with brain areas involved in central control of the autonomic system, which include sgACC, dACC, insula, hypothalamus, and amygdala (82). This overlap supports the idea that the autonomic system is also involved in bringing the phantom percepts to consciousness, flavored by an emotional component, as described in the neurophysiological model for tinnitus (83) and similar pain models (2, 84).

Phantom Percepts and Memory

Almost every amputee experiences a phantom percept (13), but not everybody perceives the phantom as aversive or painful (2, 13). Likewise, not every tinnitus patient experiences tinnitus as aversive or bothersome. In addition, many patients describe their phantom pain as triggered by stressful life events (85), and tinnitus is more common in patients suffering post-traumatic stress disorder (86).

What mechanism turns a phantom percept into an ongoing aversive phenomenon that cannot be extinguished? Behaviorally relevant or functionally significant experiences tend to be well remembered. This observation is reflected by coactivation of the dACC and the anterior insular cortex that form a salience network (57). Functional connectivity studies demonstrate a prolonged enhanced functional coupling in the resting state between amygdala, dACC, anterior insula, and the sympathetic locus coeruleus after psychological stress, resulting in an extended state of hypervigilance that promotes sustained salience and mnemonic processing (87). Thus, the efficient encoding of aversive emotional memories can lead to the formation of a strong, aversive memory trace (88). Pain can induce single-event learning, the memory of which can last for the rest of life. A negative emotional context increases pain perception and this is concomitantly associated with increased neural activity in the anterior insula mediated

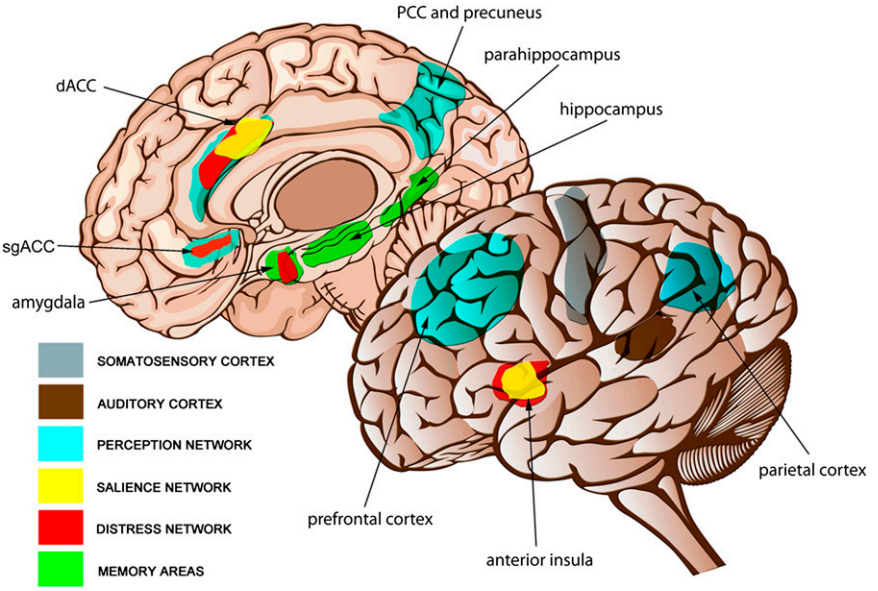

Fig. 1. Brain networks involved in phantom perception. Sensory deafferentation causes neuroplastic changes resulting in increased activation of the primary sensory cortex: somatosensory cortex (gray) in the case of phantom pain and auditory cortex (brown) in the case of tinnitus. Awareness of the stimulus arises when this activity is connected to a larger coactivated awareness or perceptual network. This perceptual network involves subgenual (sgACC) and dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (PCC), precuneus, parietal cortex, and frontal cortex (blue). Salience to the phantom percept is reflected by activation of dACC and anterior insula (yellow). As a consequence of a constant learning process, the phantom percept becomes associated to distress, which is reflected by a nonspecific distress network consisting of the anterior cingulate cortex (sgACC and dACC), anterior insula, and amygdala (red). The persistence of the phantom percept is due to memory mechanisms involving the parahippocampal area, amygdala, and hippocampus (green).

by the amygdala and parahippocampus (89). In this regard, many people with amputations report phantom limb pain that is similar in both quality and location to pain experienced before the amputation. Moreover, pain experiences before the amputation are powerful predictors and elicitors of phantom limb pain (2). These observations point to the existence of a pain memory system that entrains the chronically persisting phantom pain. The continuous experience of pain produces continuous aversive emotional associations and does not provide an opportunity for extinction of the memory of pain (84). This self-reinforcement process is similar to what has been described in posttraumatic stress disorder, where anxiety and distress are perpetuated by an overactive emotional memory in the amygdala together with a lack of contextual memory in the hippocampus (88).

In the case of tinnitus, enhanced activity of the amygdala is evidenced by c-fos expression in animal models (90, 91), by source-localized electroencephalography (9), by positron emission tomography imaging (92), and by transient tinnitus diminution after suppression of the amygdalohippocampal complex by amytal (93). Hippocampal deficits have been documented in animal models of tinnitus and structural imaging in tinnitus patients has demonstrated a decrease in gray matter in the hippocampus (94). Structural deficits have also been observed in the sgACC/nucleus accumbens area (sgACC/Nac) and, on the basis of these findings, it has been postulated that tinnitus is the result of a deficient sensory attentional gating mechanism, originating in the sgACC/Nac and acting on the reticular thalamic nucleus (95). This nucleus accumbens-related inhibitory system is analogous to the nucleus accumbens-based antinociceptive system implicated in pain suppression (96). This sensory gating deficiency is likely mediated via the parahippocampal area, which has a sensory gating function for irrelevant or redundant auditory input (97). The parahippocampal area has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas, and a dysfunction in this mechanism is posited as an explanation for complex auditory phantom percepts such as auditory hallucinations (98). As the parahippocampal area is involved in tinnitus and tinnitus distress (9), a similar mechanism could be proposed for tinnitus. Moreover, chronic stress is known to reduce neuroplasticity in the hippocampus and to reduce connectivity between hippocampus and sgACC (99). Thus, we suggest that the deficient thalamic gating function emerges as a consequence of an aversive tinnitus memory together with chronic stress and represents an additional factor contributing to the perpetuation of the phantom percept.

In brief, we hypothesize that both tinnitus and phantom pain are perceptual states of continuous learning, where—in the absence of an external input—the phantom percept is reinforced and the connection with aversive emotional associations is continuously updated.

Working Model

We propose that phantom perception arises as the consequence of multiple parallel overlapping dynamic brain networks (Fig. 1). Thus, any altered activity across these brain networks could generate a phantom perception for any sensory modality. This interpretation casts doubts concerning the sole participation of only one critical circuit in phantom perception. Phantom percepts result from sensory deafferentation and reach awareness only when increased neuronal activity in the primary sensory cortex is connected to a larger coactivated awareness or global workspace brain network, involving frontal and parietal areas. Activity in a salience network consisting of the dACC and anterior insula is required for the percept to reach consciousness. This salience network overlaps with a central autonomic control system and also influences limbic–auditory and –somatosensory interactions that are essential for maintaining the percept into consciousness. These interactions are mediated by the sgACC/Nac and amygdala, modulating the reticular nucleus of the thalamus and thereby potentially further contributing to thalamocortical dysrhythmia. Memory mechanisms play a role in the persistence of the awareness of the salient phantom percept, as well as in the reinforcement of the associated distress. Through the involvement of learning mechanisms, the phantom percept becomes associated to distress, which in turn is reflected by a simultaneously coactivated nonspecific distress network consisting of the parahippocampal area, ACC, anterior insula, and amygdala. Thus, different dynamic and overlapping brain networks should be considered as targets for the treatment of this disorder.

Looking Forward

Our understanding of phantom perception has evolved from a "peripheral," to a "primary sensory cortex," into a "static network," reaching a "dynamic multiple parallel overlapping network" problem. Although scientific understanding has advanced in the last decade, much more has yet to be discovered. There are several research directions that promise interesting results in the near future. Application of new structural connectivity techniques such as diffusion tensor imaging and diffusional kurtosis imaging and correlating these to functional connectivity measures would shed light on information flow within and between the parallel networks involved in phantom perception. These connectivity studies could be further evaluated by applying network science methodology (100) and thus could lead to identifying ideal targets and stimulation designs for neuromodulation. Finally, interventional studies using known and new drugs or known and new stimulation designs will enable researchers to prove and refine the proposed working model.

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