Opinion

Frontostriatal Gating of Tinnitus and Chronic Pain

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Tinnitus and chronic pain are sensory–perceptual disorders associated with negative affect and high impact on well-being and behavior. It is now becoming increasingly clear that higher cognitive and affective brain systems are centrally involved in the pathology of both disorders. We propose that the ventromedial prefrontal cortex and the nucleus accumbens are part of a central ‘gatekeeping’ system in both sensory modalities, a system which evaluates the relevance and affective value of sensory stimuli and controls information flow via descending pathways. If this frontostriatal system is compromised, long-lasting disturbances are the result. Parallels in both systems are striking and mutually informative, and progress in understanding central gating mechanisms might provide a new impetus to the therapy of tinnitus and chronic pain.

Tinnitus and chronic pain (see Glossary) are highly-disabling medical conditions for millions of people. Between 20 and 30% of the adult population suffer from chronic pain [1], and tinnitus prevalence can reach 30% depending on age [2]. Both disorders are difficult to treat and the associated burden for the individual patient and the healthcare system are substantial [3,4].

The similarities between tinnitus and chronic pain have been discussed for some time [5–7]. Both are abnormal and variable subjective sensations often linked to, but not sufficiently explained by, an initial peripheral lesion. Owing to the absence of an external physical stimulus, they are often referred to as ‘phantom sensations’, even though they are very real experiences. Tinnitus and chronic pain are frequently associated with hypersensitivity to sensory stimulation (hyperacusis/misophonia versus hyperalgesia/allodynia). Moreover, patients suffering from these two conditions often share the same psychological profile with an increased tendency to anxiety, fatigue, and depression [8,9], which seems to vary in lockstep with the sensory disorder. In fact, depression is ranked as one of the strongest predictors for low back pain, and intensity of back pain correlates with severity of depression [10]. Similarly, patients identified with depression or anxiety disorder at the onset of tinnitus are more likely to develop severe incapacitating tinnitus [11]. Finally, some data suggest that there is a tendency for increased tinnitus prevalence in chronic pain patients [12].

However, there are also important differences between tinnitus and chronic pain. For example, in its acute and physiological form, pain signals a threat and thus fulfills vital protective functions. Pain has thus an inherently negative value. By contrast, auditory signals do not necessarily have a predefined value and may only become bothersome if perception persists over extended periods of time, as in the case of tinnitus. Moreover, different forms of tinnitus and chronic pain exist, and their pathologies may differ. Nevertheless, the striking similarities and associations indicate that tinnitus and chronic pain share common pathophysiological mechanisms.

The understanding of the pathophysiology of tinnitus and chronic pain has changed considerably with the advent of human brain imaging over the past decades. While it was long thought...
that mainly peripheral (or spinal) processes underlie these disorders, a major involvement of brain and cognitive processes has been recognized in recent years. In both disorders, the experienced discomfort often exceeds the extent expected from the underlying pathophysiological causes, and symptoms can persist well past the time of the original insult. Such observations have led to research focusing on processes beyond peripheral or spinal components, and even beyond early sensory brain regions. Currently, the role of higher-order brain areas and associated cognitive and affective functions in the development and maintenance of tinnitus and chronic pain are the focus of much work. We outline below how remarkably similar structures and functional systems are involved in both disorders, and how findings converge onto a central role of frontostrial circuits. We postulate that this system acts as a central ‘gatekeeper’, which evaluates the relevance and affective meaning of sensory stimuli and modulates information flow via descending (and corticocortical) pathways.

**Brain Structure and Function in Tinnitus and Chronic Pain**

Neuroimaging and neurophysiological studies have revealed extensive changes of brain structure and function in tinnitus and chronic pain, as shown by altered measures of grey and white matter as well as local and network activity. Figure 1 illustrates how remarkably-similar structures are involved in both disorders.

**Structural Changes: Grey Matter**

The advent of voxel-based techniques in structural MRI permitted the measurement of morphometric changes in the living brain. Several studies have compared grey matter volume between tinnitus patients and normal controls. In tinnitus patients, a striking grey matter reduction was first detected in the subcallosal area of ventromedial prefrontal cortex (vmPFC) using whole-brain analysis corrected at both voxel and cluster level [13]. This finding was reproduced in two independent samples [14,15] and has led to the ‘central gating hypothesis’ of tinnitus [16]. Initial attempts by other groups to replicate the grey matter loss in vmPFC of tinnitus patients were unsuccessful (e.g., [17]; reviewed in [18]), but new studies are currently underway.

**Glossary**

- **Alloodynia**: pain due to a stimulus that does not normally provoke pain.
- **Chronic pain**: pain that persists past healing time, lasts or recurs for more than 3–6 months, and lacks the warning function of acute pain.
- **Hyperacusis**: decreased tolerance or heightened sensitivity to specific sound frequencies beyond a particular volume. Can lead to pain while not being a normal individual.
- **Hyperalgesia**: increased pain from a stimulus that normally provokes pain.
- **Misophonia**: intense aversion to sound. A condition in which an individual shows an extreme reaction to specific everyday sounds.
- **Tinnitus**: perception of sound in the absence of an external auditory stimulus. Sometimes referred to as ‘phantom’ auditory sensation.
- **Tonotopic map**: topographic organization according to sound frequency observed in the auditory system.

Figure 1. Schematic of Brain Structures Involved in Tinnitus and Chronic Pain. Block diagrams of relevant brain structures are shown for tinnitus (A) and chronic pain (B). Please note that the diagrams primarily show the structures and connections most relevant in the context of the proposed concept, but are not exhaustive. Abbreviations: A1, A_, primary and nonprimary auditory cortex; Amyg, amygdala; Hc, hippocampus; M/ACC, mid/anterior cingulate cortex; NAc, nucleus accumbens; PFC, prefrontal cortex; S1, S2, primary and secondary somatosensory cortex; vmPFC, ventromedial prefrontal cortex.
One of the above studies [15] found a second subcallosal region with grey matter reductions near the anterior cingulate cortex (scACC), which was distinct from the first region in vmPFC (Figure 2A). Whereas grey matter decreases in vmPFC correlated with actual tinnitus loudness, decreases in scACC correlated with tinnitus distress, anxiety, and depression [15]. In addition, a positive correlation between tinnitus distress and cortical thickness was found in the anterior insula [15]. Other studies added a reduction of grey matter volume in the hippocampus and an increase in entorhinal regions to the list of morphometric changes in tinnitus [15,17,19,20]. Within the auditory system, moderate reductions of grey matter volume were observed in the auditory cortex [19–21], although one study suggested that this may be due to hearing loss [20]; other studies reported a grey matter increase in posterior thalamus of tinnitus patients compared to healthy controls [13,17]. Overall, there is clear evidence for volume loss in mPFC, and specifically in the subcallosal region of tinnitus patients, as this has now been reproduced several times in independent studies. However, the variability of VBM results across different labs remains disconcerting, indicating the need not only for more standardized conditions and analysis techniques [18,22] but also for more attention to possible functional differences in distinct subregions of the mPFC.

A large number of studies have also shown grey matter changes in the brain of chronic pain patients. Recent meta-analyses revealed that grey matter decreases preferentially affect medial prefrontal, ventral striatal, and cingulate areas [23–25]. Some changes were also found in insular and thalamic regions [23–25]. Different forms of chronic pain syndromes differ in their patterns of grey matter changes as well as in the dynamics of brain reorganization [26]. However, although not identified in every single study (e.g., [27]), the changes show a substantial overlap in medial prefrontal cortex (mPFC) similar to those observed in tinnitus (Figure 2B). Most interestingly, the observed grey matter changes in vmPFC co-vary interindividually with the intensity and duration of pain [23], and are at least partly reversible when pain resolves [28–30], indicating plasticity and adaptiveness of these changes (Box 1).
Box 1. Volume Loss in Ventromedial Prefrontal Cortex (vmPFC): Morphological Bases and Ultimate Causes

One of the overarching findings in structural imaging studies of patients with tinnitus and chronic pain is a loss of grey matter in ventromedial prefrontal cortex (vmPFC), as determined by voxel-based morphology (VBM) (see main text and Figure 2). Most authors tacitly assume that a volume loss corresponds to cell death or atrophy of neurons, occasionally even prompting calls to count age-dependent tinnitus and chronic pain among the rubric of neurodegenerative disease [140]. However, this interpretation is anything but certain. VBM-related volume changes can be related to functional–behavioral changes, such as learning a new motor skill [141], and volume losses can be reversible [142]. Indeed, some studies report that a volume loss can recede as individuals recover from chronic pain [28–30]. This suggests that volume losses are at least not wholly related to atrophy, but should be seen more appropriately as plastic changes in the morphology of neurons, dendrites, and axonal arbors, or may even include changes in neuron-glia interactions. Ultimately, the validation of VBM methods and the identification of their morphological basis await parallel studies with histological–anatomical means, either in postmortem human tissue or in animal models.

What drives the morphological changes that underlie the volume loss in tinnitus and chronic pain is a different question. Some models (e.g., [16]) discuss the possibility that hyperactivity in NAc (or in sensory regions of the brain, such as auditory cortex in tinnitus), is relayed to vmPFC and exerts an excitotoxic effect on neurons there. The problem with this explanation is that neurons in NAc or auditory cortex do not seem to die at the same rates, or do not die at all. A more likely interpretation is, therefore, that morphological changes in vmPFC, including any atrophy or cell death, are caused by factors that are independent of the process leading to hyperactivity in sensory areas. One such factor could be stress, which is known to modulate both tinnitus and chronic pain [5], and which can even lead to their onset. Indeed, extensive studies in animal models have demonstrated that specifically vmPFC undergoes dramatic structural modification when animals are exposed to long-lasting stress [143]. Interestingly, dopamine release upon stress is increased in the PFC and inhibited in the NAc [144].

Prolonged sleep-deprivation and insomnia are also inversely correlated with grey matter volume of the brain in humans, specifically orbitofrontal cortex and hippocampus [145]. These effects may relate to dysregulation in cortisol levels [143] which could, in tinnitus subjects, reflect a disturbance of the neuroendocrine reaction to stress [146]. There is indeed a high prevalence of organic sleep disorders in tinnitus patients [147,148] and restoration of normal sleep patterns may be helpful for the treatment of tinnitus and chronic pain.

Structural Changes: White Matter

The number of studies measuring structural connectivity changes in tinnitus patients with diffusion tensor imaging (DTI) is still very limited. Results mostly involve reductions in white matter integrity (as measured by fractional anisotropy) within the auditory system, including auditory cortex, but these seem to relate to the patients’ hearing loss rather than to their tinnitus [31–33]. Three other studies provide some evidence for changes of structural connectivity within auditory–limbic brain circuits specific for tinnitus: two of the studies report enhanced connectivity [34,35], while another reports deteriorated connections [19]. This seemingly contradictory pattern may be due in part to the intricacies of the DTI technique, but it may also be due to the presence of confounding factors that are not well controlled. Further studies will be necessary to assess the consistency of these findings, which at present should be considered preliminary until several technical challenges have been overcome [35]. On the other hand, the study by Seydell-Greenwald et al. [35] shows very convincingly that fractional anisotropy in the vmPFC region is significantly correlated with tinnitus loudness, but not with depression or anxiety, thus echoing the grey matter morphometric data [15].

In individuals with chronic pain, the observed changes in white matter predominantly affect connections between frontal and limbic brain areas [36–39]. A recent longitudinal study revealed that white-matter fractional anisotropy at onset of acute back pain predicts the later transition to chronic pain [39], indicating that structural connectivity reflects a causally-relevant predisposition for the development of chronic pain. Interestingly, the relevant white matter changes included connections between prefrontal cortex and the nucleus accumbens (NAc), matching the grey matter changes in frontostrital circuits.

Functional Changes: Local Brain Activity

Most studies of functional brain changes in tinnitus have concentrated on the auditory system. Early positron emission tomography (PET) studies demonstrated tinnitus-related activity in
primary and secondary auditory cortex [40–42], as well as in auditory association cortex [41,43–47]. Correspondingly, numerous fMRI studies of tinnitus have revealed increases of sound-evoked activity for cortical [14,48,49] and subcortical stations along the auditory pathway [50–52]. Besides mere changes of activity levels within the auditory system, studies using magnetoencephalography (MEG) report abnormal activity in different frequency bands [53], which has been embedded in the concept of abnormal thalamocortical oscillations as a mechanism underlying tinnitus and chronic pain [54]. Furthermore, tonotopic map reorganization in auditory cortex has been observed [55], consistent with lesion-induced plasticity after hearing loss [56]. Several studies demonstrate that functional plasticity in tinnitus also affects limbic brain regions [41,47,57]. In particular, one carefully controlled fMRI study has for the first time been able to identify highly-significant stimulus-evoked hyperactivity of the NAc in tinnitus patients that was independent of age and hearing loss [14]. Compared to other brain structures, such as auditory cortex, the NAc exhibited the greatest degree of hyperactivity, specifically to sounds frequency-matched to the tinnitus of the patients. NAc hyperactivity in tinnitus patients was present in the single-voxel analysis (Figure 1A of that paper), in which hearing loss was a ‘nuisance’ covariate, as well as in separate regions of interest (ROI) analysis in which age was a covariate. In addition, NAc hyperactivity persisted in an ROI analysis restricted to the four youngest patients. The same study replicated a corresponding volume loss in vmPFC (see above).

In chronic pain, studies with PET [58–61] and arterial spin labeling MRI [62–65] show increases of blood flow and metabolism in prefrontal, cingulate, and insular cortices and in the striatum as well as decreases in the thalamus. Some of these blood-flow changes positively relate to pain intensity (e.g., [61,65]) and are reversible with treatment [58]. More recent electroencephalography (EEG) and fMRI studies consistently indicate that mPFC plays a central role in the encoding of ongoing experimental [66] and clinical pain [27,67,68]. Moreover, an fMRI study shows, as in tinnitus, activation of the NAc by noxious stimuli [69]. Finally, studies on chronic pain using MEG and EEG indicate activity increases in the theta frequency band [54,70,71], which can be localized to prefrontal, cingulate, insular, and somatosensory cortices [71], and which are again at least partly reversible with treatment [70,71].

Functional Changes: Network Activity
Resting-state fMRI studies have shown changes of functional brain connectivity in tinnitus [72–76]. Specifically, increased interactions between auditory and limbic regions have been observed [72–74,77–79]. Among the limbic regions, the subgenual or subcallosal ACC (scACC)/vmPFC region can be considered an important dysfunctional node, consistent with the structural changes found with voxel-based morphometry (VBM) [13,15]. Indeed, a recent study performed a blind source separation of resting-state EEG activity in tinnitus subjects. The independent components obtained were organized into two fully-independent network modules related to either tinnitus loudness or tinnitus-associated distress. Results showed that these two modules were linked through a pathological functional connection involving the scACC/vmPFC region in highly distressed tinnitus subjects [80]. Similarly, greater connectivity within the so-called ‘default-mode network’ (DMN [81]) and between DMN and scACC was related to focusing on negative aspects of tinnitus and on ‘catastrophizing’ [82]. Modifications of brain connectivity within auditory cortex [78] as well as across a widely distributed network of brain regions have been observed with MEG [77]. The relative prominence of auditory–sensory areas decreases with longer duration of tinnitus, whereas the participation of non-auditory brain regions increases [83]. Moreover, when looking at effective connectivity measures, modification of activity in the auditory cortices seems to be driven by activity in the cingulate cortices and left insula in tinnitus subjects [78]. Overall, tinnitus is related to functional connectivity changes in multiple brain regions including, but not limited to, the fronto–limbic–striatal system.
Similarly, functional connectivity changes in chronic pain particularly affect the mPFC, which is part of the DMN [84–88]. Greater connectivity between DMN and insula was related to more spontaneous pain [88] and was reduced after successful pain treatment [87]. Interestingly, greater functional connectivity between NAc and prefrontal cortex predicted the development of chronic back pain [27,88], again indicating a causal role of frontostriatal circuits in the transition from acute to chronic pain. A further longitudinal study showed that brain activity associated with ongoing pain shifts from sensory pain-processing regions to more emotion-related brain regions, including mPFC, with the transition from acute to chronic pain [88].

**Mechanisms of Frontostriatal Gating**

Converging lines of evidence, as outlined above, indicate that tinnitus and chronic pain are associated with structural and functional brain changes that overlap remarkably between the two conditions (Figure 1). The changes predominantly affect frontostriatal circuits including vmPFC and NAc, with possible additional roles for the thalamus and for medial temporal lobe structures, such as amygdala and hippocampus. Frontostriatal circuits with their closed-loop structure are anatomically well-positioned to integrate sensory information for use in executive functions. MPFC in particular has been found to estimate subjective value [89,90] or affective meaning [91] across different stimuli, tasks, and modalities. The ventral striatum is considered the key component of the brain’s ‘reward value system’ [92,93]. Changes of these circuits have not only been observed in tinnitus and chronic pain but appear to be a general feature of neuropsychiatric disorders associated with a negative emotional state, such as depression [94,95].

Thus, we hypothesize that, together, NAc and vmPFC assign subjective value or affective meaning to sensory signals, whether generated externally or internally, and together act as a ‘gatekeeper’ system, which triggers action to minimize signals with negative values. An internal signal corresponding to pain carries exclusively negative values; an internally generated tinnitus signal has at best a value of zero and neutral affective meaning (‘irrelevant’), but could turn increasingly negative as time goes on. The frontostriatal system ultimately serves to nullify such disturbing signals: NAc and vmPFC are centrally involved in the valuation of the signal and the initiation of appropriate modulation, as studies on both tinnitus and chronic pain suggest [10,14–18]. Other authors have couched this function of the frontostriatal system as ‘prediction error signaling’ in a Bayesian sense [96]. According to this view, the frontostriatal system signals a deviation from the predicted state of the body and/or the environment, in other words a prediction error, which serves to update predictions and to motivate appropriate behavioral responses. Tinnitus and chronic pain can thus be conceptualized as a continuous and persistent prediction error. This interpretation would also be consistent with a role for the cerebellum in both disorders, as postulated recently [97,98].

The modulatory role of the frontostriatal system is effected via lower levels of the neural hierarchy using descending pathways (‘top-down modulation’). In the pain system, these levels range from the cerebral cortex and the thalamus down to the spinal cord dorsal horn, as proposed in the seminal gate control theory of pain [99]. For tinnitus, related gating theories have been proposed to explain tinnitus as the failure of a central ‘noise cancellation’ process involving NAc and vmPFC, whose decisions may be effected via the thalamic reticular nucleus (TRN) [16]. The TRN has been singled out in this hypothetical gating process because it controls information flow between thalamus and cortex [100,101] and can inhibit specific thalamic neurons in a highly-selective and frequency-specific manner [102].

Compromised function of the frontostriatal gating system could thus affect perception of a sensory signal in two different ways, which are not mutually exclusive (Figure 3, Key Figure). First, damage to the descending projection originating in vmPFC (Figure 3, left loop) would result in a
lack of suppression of irrelevant sensory signals [14–16]. Second, damage to the NAc/vmPFC–scACC circuit or changes in its input systems could result in a dysfunctional valuation process and abnormal assignment of negative meaning to a neutral stimulus (Figure 3, right loop). This process has often been thought of as a learned ‘reaction’ to the tinnitus or pain signal [103,104], and could be related to particular forms of aversive conditioning in rats, for which the circuits are well characterized and vmPFC and ventral striatum play a central role [105,106]. Dysfunctional valuation and gating mechanisms could initiate and maintain self-perpetuating processes, which in turn result in further dysbalances of frontostriatal circuits and compromised gating processes at lower levels of the neural hierarchy. At the cognitive level, such self-perpetuation has been conceptualized as an abnormal learning process [107], which also depends on frontostriatal circuits [108–110].

**Neurotransmitter Systems Involved in Frontostriatal Gating**

Figure 3 demonstrates that the frontostriatal gating and valuation process is under the control of two major transmitter systems: dopamine and serotonin.
Decreasing dopamine activity seems to reduce tinnitus perception [111]. Furthermore, serotonin has long been hypothesized to play a role in tinnitus and its comorbidity with depression and insomnia [112,113]. In addition, the proposed loss of inhibition in tinnitus has been suggested to be due to lowered γ-amino butyric acid (GABA) levels along the auditory pathway [114,115]. However, none of these hypotheses are sufficiently elaborate to explain the neurochemical basis of tinnitus, let alone lead the way towards possible drug treatment.

Neurochemical changes and potential ensuing therapeutic interventions have been studied in greater detail for chronic pain than for tinnitus. Serotonergic modulation is an important and well-established therapeutic tool in chronic pain [116]. Some evidence for the therapeutic potential of dopamine is also available [117–119] but is rarely recognized, even though dopamine has been shown to play an important role for the processing of pain [120]. Experimental studies in animals using microdialysis and microinjections, as well as PET studies in humans, have mostly concentrated on the dopaminergic [120] and opioidergic [121] systems, which closely interact [122]. These neurochemical changes show remarkable overlap with the structural and functional changes reviewed above. Reduced levels of dopamine and weakened dopamine responses to pain have been observed in ACC, thalamus, and striatum [123–125]. In the ventral striatum, dopaminergic activity has been linked to valuation, motivation, and learning [126–129]. It has therefore been claimed that dopamine and the ventral striatum particularly relate to the valuation of pain, which might influence the development of pain into a chronic condition [110]. In the opioidergic system, altered endogenous opioid activity has been reported in limbic brain areas, including prefrontal and insular cortices, as well as in striatum, amygdala, and hippocampus [121] for review. Interestingly, opioid-sensitive neural pathways from prefrontal and insular cortex, amygdala, and hypothalamus via the brainstem to the spinal cord dorsal horn play a key role in the descending modulation of pain [130]. A recent meta-analysis indicates that chronic pain is associated with changes in these descending pain modulatory pathways [131], which might result in abnormal gating functions and thereby contribute to the development and maintenance of chronic pain [132–134]. Indeed, the efficiency of pain modulation has been shown to predict the development and treatment of chronic pain [134], which indicates a causal role of descending pain modulation and gating processes in chronic pain. It remains to be seen if equivalent effects can be demonstrated for tinnitus.

**Concluding Remarks and Clinical Implications**

As discussed in this review, a central and causal role of frontostriatal circuits for the development and maintenance of tinnitus and chronic pain is emerging. We specifically propose that the ventromedial prefrontal cortex and the nucleus accumbens are part of a central ‘gatekeeping’ system, which evaluates the relevance and affective value of sensory stimuli and controls information flow via descending pathways.

Having identified the frontostriatal gating system as crucial for the development and maintenance of tinnitus and chronic pain, the problem now shifts to the next stage: why do some individuals seem to have a predisposition for developing these disorders, whereas others show great resilience under the same circumstances? For instance, people with the same amount of loud-noise exposure and the same resulting level of hearing loss may or may not develop tinnitus. Presumably, genetic factors or gene–environment interactions produce both vulnerability and resilience, but at what level do they exert their effects? It appears likely that persons with tinnitus or chronic pain have a systemic vulnerability in one or more transmitter systems, such as dopamine or serotonin or their interaction, as described for other disorders [135]. The mechanisms are likely to be multifactorial, and genetic vulnerability, developmental insults, and environmental stressors may be synergistic contributors [136]. Resilience is a complex multidimensional construct, and the study of its neurobiology is a relatively young area of scientific investigation [137]. Understanding the mechanisms of resilience in healthy individuals is one of...
the major challenges of both research fields. This could include, for instance, repair mechanisms protecting against damage done by stress to neurons in the mPFC (or reversing it). Deep-brain stimulation may also help to restore lost function in frontostral disorders [138].

Although numerous open questions still need to be addressed (see Outstanding Questions), the integration of these findings might give a new impetus to the prevention and treatment of these disorders. Because prevention significantly depends on individual predispositions, a standardized assessment of the individual susceptibility and resilience to tinnitus and chronic pain is desirable. Such an assessment could include psychophysical, psychological, genetic, and brain-based (neuroimaging) measures. For example, psychophysical assessment of susceptibility to chronic pain could comprise standardized sensory testing [139], including testing for the efficacy of pain modulation [134]. Brain-based measures could include the structure and function of frontostral circuits during rest and/or pain challenges [27,39]. If increased vulnerability is found, and considering that self-perpetuating learning processes may play a role, treatment should be initiated early to prevent or reverse these abnormal processes. Such strategies might include cognitive-behavioral therapy and physiotherapy as well as pharmacotherapy. Dopaminergic neurotransmission might represent a promising pharmacological target.

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