



## Review

Role of attention in the generation and modulation of tinnitus<sup>☆</sup>Larry E. Roberts<sup>a,\*</sup>, Fatima T. Husain<sup>b,c,d,1</sup>, Jos J. Eggermont<sup>e,f,2</sup><sup>a</sup> Department of Psychology, Neuroscience, and Behaviour, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4K1, Canada<sup>b</sup> Department of Speech and Hearing Science, University of Illinois at Urbana-Champaign, 901 South Sixth Street, Champaign, IL 61820, USA<sup>c</sup> The Neuroscience Program, University of Illinois at Urbana-Champaign, Champaign, IL, USA<sup>d</sup> The Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Champaign, IL, USA<sup>e</sup> Department of Physiology and Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada<sup>f</sup> Department of Psychology, University of Calgary, 2500 University Drive N.W., Calgary, AB T2N 1N4, Canada

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## ABSTRACT

Neural mechanisms that detect changes in the auditory environment appear to rely on processes that predict sensory state. Here we propose that in tinnitus there is a disparity between what the brain predicts it should be hearing (this prediction based on aberrant neural activity occurring in cortical frequency regions affected by hearing loss and underlying the tinnitus percept) and the acoustic information that is delivered to the brain by the damaged cochlea. The disparity between the predicted and delivered inputs activates a system for auditory attention that facilitates through subcortical neuromodulatory systems neuroplastic changes that contribute to the generation of tinnitus. We review behavioral and functional brain imaging evidence for persisting auditory attention in tinnitus and present a qualitative model for how attention operates in normal hearing and may be triggered in tinnitus accompanied by hearing loss. The viewpoint has implications for the role of cochlear pathology in tinnitus, for neural plasticity and the contribution of forebrain neuromodulatory systems in tinnitus, and for tinnitus management and treatment.

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\* Corresponding author. Tel.: +1 (905) 525 9140x24052; fax: +1 (905) 529 6225.

E-mail addresses: [roberts@mcmaster.ca](mailto:roberts@mcmaster.ca) (L.E. Roberts), [husainf@illinois.edu](mailto:husainf@illinois.edu) (F.T. Husain), [eggermont@ucalgary.ca](mailto:eggermont@ucalgary.ca) (J.J. Eggermont).

<sup>1</sup> Tel.: +1 (217) 333 7561.

<sup>2</sup> Tel.: +1 (403) 220 5214.

## 1. Introduction

Individuals experiencing a persistent tinnitus (chronic ringing of the ears) commonly report that their awareness of tinnitus decreases when they focus on activities that are absorbing and do not require processing of signals in the auditory domain. Modulation of tinnitus awareness can fluctuate rapidly, suggesting either that the neural activity underlying tinnitus is dynamically altered or that its access to consciousness is gated by brain mechanisms that are sensitive to context or task demands. Brain mechanisms that direct the focus of consciousness are commonly described as those that perform top-down attention-like functions. In contrast, studies of neural plasticity in the auditory cortex (Fritz et al., 2003; Weinberger, 2007) and other sensory systems (Ramanathan et al., 2009) indicate that cholinergic neuromodulators deployed to the cortex from the basal forebrain gate synaptic plasticity for unexpected and behaviorally relevant stimuli, performing a bottom-up attention-like function. Attention has been cited as a factor contributing to the development and/or modulation of tinnitus by several models of this condition (Jastreboff, 1995; Jastreboff and Jastreboff, 2006; Zenner et al., 2006; Searchfield et al., 2012b) and as a possible factor contributing to the findings of research studies (Gu et al., 2010; Husain et al., 2011; Hoare et al., 2012). However, the mechanisms by which attention is called and how its role is expressed in the neural changes underlying tinnitus remain a topic of discussion (Roberts et al., 2010).

In this paper we discuss how attention may be involved in the generation of tinnitus and its modulation by task demands. A qualitative model for a role of attention in tinnitus is presented and recent evidence is discussed in the light of it. A key assumption of the model is that in tinnitus there is a disparity between what the brain predicts it should be hearing (this expectation influenced by neural activity underlying the tinnitus percept) and the acoustic information that is delivered by the ear to the brain, when cochlear damage indexed by the audiogram or more sensitive measures is present. The disparity between the predicted and obtained inputs activates mechanisms of auditory attention that may contribute to the establishment and persistence of tinnitus and to its modulation by competing tasks.

## 2. Neural mechanisms for attention

Understanding how attention might be involved in tinnitus is assisted by a provisional understanding of how attention systems are organized in the normal hearing mammalian brain. Brain regions that show differential activity between a condition in which sounds are attended to, and a condition in which they are not, can be variable depending on the sound attribute to be detected, the prevailing multisensory context, and the significance of the sound including its predictive value and the mental or behavioral operations to be performed (Fritz et al., 2007). This variability arises in part because auditory attention does not operate in isolation of brain networks for other functions that may be engaged by a task, such as comparing task stimuli to those in memory, organizing behavioral responses, and processing feedback from them. The question of how brain networks concerned with auditory attention relate to networks that perform such functions or to those that underlie conscious executive control processes is the topic of extensive ongoing research (Palva and Palva, 2012; Sadaghiani et al., 2009; Dehaene and Changeux, 2011). Also debated are the neural and synaptic mechanisms by which the effects of attention are achieved. Detailed discussions of these topics are found in recent reviews (Fritz et al., 2007; Palva and Palva, 2012; Dehaene and Changeux, 2011) which have provided a backdrop for the discussion to follow. It may be that one should speak not of a single

mechanism for attention, auditory or otherwise, but of multiple such mechanisms depending on the sensory modality and stimulus attributes to be attended to and the conditions of testing. Alternatively, top-down and bottom-up forms of attention may share neural resources sufficient to speak of a single system for attention, even though its expression in brain network activity may depend on the specific task stimuli that are present and the behavioral and cognitive performance requirements of the task procedure.

### 2.1. Top-down and bottom-up auditory attention

Notwithstanding this question, there is a consensus that several brain structures are active in auditory attention in the normal hearing brain, and that auditory attention can be called by bottom-up as well as by top-down signals. Effects attributable to top-down auditory attention are revealed by tasks that direct the focus of attentive processing to auditory signals when bottom-up sensory input and other task variables are held constant. Contrasts comparing brain activations between a silent baseline condition and a condition in which sounds are presented passively have found increased blood oxygen level dependent (BOLD) responses in primary (A1, postero-medial Heschl's gyrus) and nonprimary (A2, surrounding auditory belt and parabelt cortex) auditory regions that reflect stimulus driven activity occurring in these regions (Hall et al., 2000; Johnson and Zatorre, 2005; Petkov et al., 2004; Tzourio et al., 1997), although the possibility of some degree of attention being drawn to the sounds cannot be excluded. When the same sounds are explicitly processed in attention to fulfill a task requirement, brain activity increases further in these auditory regions (Grady et al., 1997; Degerman et al., 2006; Paltoglou et al., 2009), although the pattern of auditory activation may depend on the nature of sounds that are attended. For example, attention to simple spoken syllables (Jäncke et al., 1999) or amplitude modulated pure tones (Gander et al., 2010a,b) has been reported to activate A1 and A2, whereas attention directed to melodies activated posterior regions of the superior temporal gyrus (STG) where more complex forms of auditory processing are believed to take place (Johnson and Zatorre, 2005, 2006; Petkov et al., 2004). Supporting evidence for the view that these activations serve an attentional role is found in the observation that baseline BOLD activity in these auditory regions is elevated when subjects listen in silence for an impending sound (Voisin et al., 2006) and when subjects consciously detect a target noise burst on a discrimination task (hits) compared to trials on which the same sound is not detected (misses; Sadaghiani et al., 2009). In the latter study the anticipatory BOLD increment was larger for hits than misses suggesting that neurons coding for the target sound had been sensitized by attention, although a contribution from behavioral response preparation cannot be ruled out. Interestingly, in the latter study neural activity in two non-auditory brain networks, one consisting of brain regions functionally connected in baseline resting states (the frontal/parietal "default mode" network; Raichle et al., 2001; Raichle, 2010) and the other of non-auditory brain regions functionally coupled during the maintenance of task set (the "intrinsic alertness network" including the anterior cingulate gyrus and anterior insula; Dosenbach et al., 2006, 2007), was also elevated prior to target detection, while activity in a third network (the dorsal attention system, consisting of the right inferior parietal cortex and frontal eye fields; Corbetta and Shulman, 2002) was suppressed. Modulation of these additional networks may reflect the discriminative requirements of the detection task and the need to link behavioral responses with specific auditory signals. Overall the results support the view that distinct auditory areas (A1 and A2) are engaged by the specific stimulus content of sounds when top-down auditory attention is called, but that other brain regions can also be modulated. The dorsal attention system associated with vision is activated by sounds that have a spatial

attribute (Shomstein and Yantis, 2006; Wu et al., 2007), underscoring that the specific brain regions associated with top-down auditory attention can be task dependent.

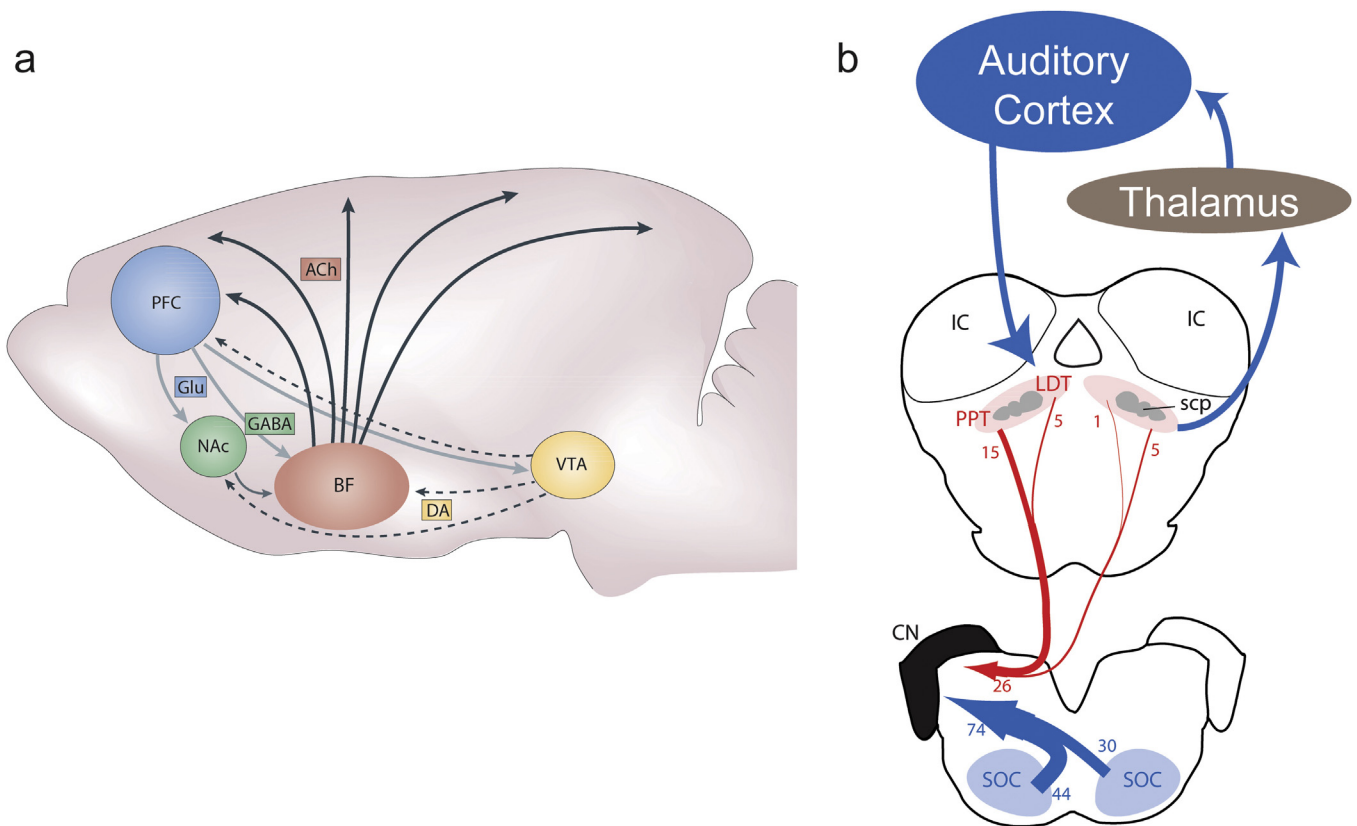
Unlike top-down effects of attention that are directed by task objectives, bottom-up effects of attention are driven by stimuli that occur outside of a task focus. Such stimuli are usually moderately intense or are not predicted by the current context. Nonetheless, although the initiating event (the task or stimulus) is different in the two attention types, bottom-up stimuli appear to engage (at least in early processing) the same networks that support top-down auditory attention. Sounds that deviate in some attribute from a repetitive standard evoke the mismatch negativity (MMN), a difference wave in the electroencephalogram (EEG; deviant minus standard) that reaches its peak over a latency window 100–250 ms after the occurrence of the deviant sound. However, while the MMN is a long latency response, deviance is expressed at least as early as the Nb auditory middle latency response (latency ~40 ms), which is within the range of early cortical processing and suggests that a series of events underlies generation of the MMN waveform (Grimm et al., 2011). Consistent with this view, fMRI studies of the MMN and source modeling of the MMN EEG waveform (Schönwiesner et al., 2007) have identified generators for this response in A1 (Heschl's gyrus) and in A2 (superior temporal gyrus and planum temporale), as well as in regions of mid-ventrolateral prefrontal cortex that have been implicated in top-down attentional or executive control in primates (Petrides et al., 2002). A latency difference of ~60 ms between the temporal and prefrontal responses suggests that change-related activity in frontal regions may rely on afferent projections from the temporal lobes, although reciprocal communication between the regions is also possible (Schönwiesner et al., 2007). In addition to this pathway the reticular activating system (RAS) sends projections from the brain stem to the superficial neocortical laminae (Eggermont and Moore, 2012) that bypass the thalamus and may modulate early cortical responses such as the Nb when driven by arousal-worthy (unpredicted) sounds. Activation of the cortex by unpredicted signals may provide access to higher order memory representations that may be needed to assess novel sensory inputs. The variable nature of these representations may contribute to the variability in the latency of the MMN that is seen across different tasks and stimulus procedures (Grimm et al., 2011).

## 2.2. Role of basal forebrain and tegmental cholinergic systems

The involvement of prefrontal regions in top-down and bottom-up attention is worthy of note, because this region is reciprocally innervated by the basal forebrain (BF) cholinergic system which has also been implicated in attention-like functions (Sarter et al., 2005). Cholinergic efferents originating from nuclei in the BF (see Fig. 1a, adapted from Sarter et al., 2009) project to all regions of the neocortical mantle in a coarse regional topography (Mesulam et al., 1983; Jiménez-Capdeville et al., 1997), including prefrontal, parietal, and allocortical structures implicated in attentional processing as well as the “Global Neuronal Workspace” proposed by Dehaene and Changeux (2011) to be active in conscious processing. This projection is believed to make the targeted pyramidal neurons more sensitive to their afferent inputs by promoting the extrasynaptic release of acetylcholine on muscarinic and nicotinic receptors (Metherate and Ashe, 1993; Metherate, 2011) or by acting on heteroreceptors to achieve function-specific effects (Sarter et al., 2009). A parallel GABAergic innervation has been described (Freund and Meskenaite, 1992) targeting inhibitory cortical interneurons suggesting a synergistic effect on cortical processing. A cholinergic projection from the BF to the reticular nucleus of the thalamus has also been described, which alters thalamic neuron response patterns evoked by previously trained sounds and may play a role

in modulating thalamocortical transmission based on the learning history of the animal (Hallanger et al., 1987). The overall effect of activating the BF cholinergic system is to shift the balance of excitation and inhibition in cortical networks, facilitating the processing of thalamocortical relative to local intracortical inputs to the neocortical mantle (Sarter et al., 2005). The BF cholinergic system is driven bottom-up by auditory and other sensory inputs via thalamic afferents conveyed through the amygdala as well as by dopaminergic reward systems in the ventral tegmental area (VTA); in return, the BF system receives top-down projections from prefrontal cortex (PFC) either directly or mediated by the nucleus accumbens (NAc; see Fig. 1a). This dual innervation by bottom-up and top-down inputs implicates the BF as a key structure in both types of attention. Distributed projections from the BF to the neocortical mantle could enable highly specific brain activations driven by the specific content of environmental stimuli, without the need for specialized attention systems for different sensory attributes.

Attentional modulations arising from a mechanism of this type would be expected to depend on the learning history of the organism. Passive immersion in a distinctive sound environment has been shown to lead to substantial changes in cortical map organization for the exposure frequencies in the immature brain (de Villiers-Sidani et al., 2007; Zhang et al., 2001) and more recently in mature animals as well (Noreña et al., 2006; Pienkowski and Eggermont, 2009, 2010, 2011, 2012; Zhou and Merzenich, 2012). Although the rules of this form of plasticity are only partly established, evidence suggests that passive exposure-induced plasticity in developing and adult animals may share common mechanisms but differ in the constraints applied to these mechanisms after the closure of developmental sensitive periods (Pienkowski et al., 2013). Cholinergic projections from the BF to the neocortical mantle are also developmentally dependent, reaching maturity in the rat brain at a time corresponding approximately to adolescence in primates (Kiss and Patel, 1992). While its role in passive learning is not presently known, the BF cholinergic system is involved in gating neural plasticity on active learning tasks, in which adult animals are trained to respond to specific auditory signals to obtain reward (Weinberger, 2004). The spectrotemporal receptive fields of auditory neurons are precisely sculpted by such training to represent the specific sound attributes contained in the signal (Dahmen and King, 2007), including best frequency (Recanzone et al., 1993; Weinberger, 2007), amplitude and frequency modulations (Kilgard et al., 2001; Fritz et al., 2005), and temporal patterning (Kilgard and Merzenich, 1998, 2002). Changes occurred only when the trained sounds signaled important goals such as a food pellet or an impending electric shock, implicating a role for attention; presentation of the same sounds while the animal performed a task requiring attention to a different sensory modality did not alter cortical representations for the auditory stimuli (Recanzone et al., 1993; Buonomano and Merzenich, 1998) although there is evidence that perceptual performance can improve without substantial map changes (Brown et al., 2004). Following auditory training on multiple spectrotemporal tasks in ferrets, the tuning properties of A1 neurons are rapidly modulated by changes in the task context suggesting acquired top-down attention-like effects (Fritz et al., 2007). These changes are coherent with neural responses recorded simultaneously from regions of PFC cortex that are homologous with prefrontal regions implicated in top-down attention in primates (Fritz et al., 2010). While the specific mechanisms underlying these observations are not fully known, control of the neural responses by task cues established by their learning histories is likely to have acted through the BF cholinergic system (Weinberger, 2007). Consistent with this hypothesis, plastic changes that are induced in cortical forelimb representations by skilled forelimb training in rats were prevented when the BF cholinergic projection was ablated by a neurotoxin, although map reorganization produced by passive



**Fig. 1.** Cholinergic neuromodulatory systems. (a) The basal forebrain cholinergic system (shown for the rat, adapted from Sarter et al., 2009, with permission). Cholinergic neurons originate from the nucleus basalis of Meynert, the substantia innominata and the vertical and horizontal nuclei of the diagonal band of Broca (collectively termed the BF) and innervate all cortical areas and layers. The prefrontal cortex (PFC) is the only cortical region, in rodents and primates, that is known to project back to the BF both directly and indirectly through the nucleus accumbens (NAc). This organization provides an avenue for top-down control of the BF by the PFC. The BF, PFC and NAc are further innervated by dopaminergic neurons from the ventral tegmental area (VTA, dashed lines), while dopaminergic neurons are in turn contacted by PFC projections allowing interactions between attention and reward/arousal pathways. Not shown are projections to the BF from thalamic sensory nuclei via the amygdala, return projections to thalamic and subcortical structures, or parallel GABAergic projections from the BF targeting inhibitory cortical interneurons (Freund and Meskenaite, 1992). (b) Pontomesencephalic cholinergic system. Subcortical cholinergic projections from the pontomesencephalic tegmentum (PMT, shaded pink) and superior olivary complex (SOC, shaded blue) to the cochlear nucleus (CN) are shown. Arrows indicate projections from the SOC and two nuclei of the PMT, the pedunculopontine tegmentum nucleus (PPT) and the laterodorsal tegmental nucleus (LDT), to the CN. Also depicted are ascending projections from the PMT to the thalamus and cortex, and return projections from layer V pyramidal cells in auditory cortex to the PMT which provide a pathway for top-down influences. (Adapted from Mellott et al., 2011, with permission; SCP: superior cerebellar peduncle; IC: inferior colliculus.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

deafferentation in the same animals (facial motor nerve transection) was not affected by this procedure (Ramanathan et al., 2009).

Cholinergic projections to the neocortical mantle from the BF thus appear to perform an attention-like function, gating neural plasticity in accordance with the significance of environmental sounds and other task stimuli. A second cholinergic pathway in subcortical structures has been identified in the pedunculopontine (PPT) and laterodorsal (LDT) nuclei of the midbrain tegmentum, referred to collectively as the pontomesencephalic tegmentum (PMT; Motts and Schofield, 2010; see Fig. 1b, adapted from Mellott et al., 2011). Although the PMT is considered to form part of an ascending arousal system that modulates the flow of information through the thalamus in various stages of the sleep–wake cycle (Edeline, 2003; Hennevin et al., 2007), its functional and anatomical connectivity also suggest a role in gating sensory stimuli in the alert animal (Schofield and Motts, 2009). In addition to sending cholinergic projections to several auditory subcortical nuclei including the medial geniculate body, inferior colliculus, and dorsal cochlear nucleus (Motts and Schofield, 2010), the PMT receives direct projections from layer V pyramidal neurons in primary auditory cortex, which could exert a top-down influence on neural processing in subcortical auditory structures (Schofield and Motts, 2009). Electrical stimulation of cholinergic inputs to the dorsal cochlear nucleus in vitro modulates the sign of spike-timing

dependent plasticity (STDP) in this structure, converting Hebbian long-term potentiation to anti-Hebbian depression in parallel fiber-fusiform cell synapses through retrograde endocannabinoid signaling (Zhao and Tzounopoulos, 2011). It has been suggested that anti-Hebbian depression of these synapses forms a negative image of ongoing auditory nerve activity occurring in the parallel fiber system (Zhao and Tzounopoulos, 2011). Because parallel fibers convey somatosensory information from the region of the head and neck including the vocal tract and pinnae (Kanold and Young, 2001), this mechanism could perform a filtering, attention-like function, by suppressing auditory responses to one's own vocalizations relative to those that arise from external sound sources. Inputs from the tegmental and BF cholinergic systems converge at the level of the thalamus (Hallanger et al., 1987) where jointly they may influence the transmission of information to the cortex during attentive processing and learning. A further subcortical cholinergic projection from the superior olivary complex (SOC) to the cochlear nucleus (CN) is thought to play a role in gating input from the ear via olivocochlear efferents (Mellott et al., 2011; see Fig. 1b). Olivocochlear efferents from the lateral superior olive (LSO) release dopamine onto inner hair cells, regulating their sensitivity and protecting against glutamate excitotoxicity in the presence of loud sounds (Lendvai et al., 2011). After cochlear damage induced by noise trauma cholinergic activity in the ventral (VCN) and



dorsal (DCN) cochlear nucleus is upregulated for up to 2 months (the longest duration studied), suggesting a role for this pathway in adaptations that occur in hearing loss (Jin et al., 2006; Kaltenbach and Zhang, 2007; Meidinger et al., 2006).

Given the role of the BF and pontomesencephalic cholinergic systems in gating sensory stimuli and in modulating neural plasticity, it is plausible to ask whether auditory attention acting through these systems may be involved in the neural changes that underlie tinnitus. If auditory attention is involved, how is the attention system involving these structures signaled, and how might it contribute to the generation and/or maintenance of tinnitus? In the next section we address these questions, starting with an account of the neural changes associated with tinnitus and their relation to hearing loss. In later sections the role of other neuromodulatory systems is also considered.

### 3. Auditory attention and tinnitus

Most cases of tinnitus are associated with hearing loss expressed either in the audiogram or putatively detected by more sensitive measures. When subjects are asked to rate several sound frequencies for similarity to their tinnitus, similarity judgments typically commence near the edge of normal hearing in the audiogram and increase in proportion with the depth of hearing loss, yielding a tinnitus spectrum that spans the hearing loss region (Noreña et al., 2002; Roberts et al., 2006; Sereda et al., 2011; Zhou et al., 2011). It is also known that band-pass masking sounds that produce a post-masking suppression of tinnitus (residual inhibition, RI) do so optimally in proportion to the extent to which their center frequencies (CFs) are in the same frequency region (Roberts et al., 2008). These results suggest that aberrant neural changes taking place in the hearing loss regions of central auditory structures underlie tinnitus, and disrupting these changes suppresses it (see Fig. 2a). Research in animal models of hearing loss has begun to identify some of the neural changes involved.

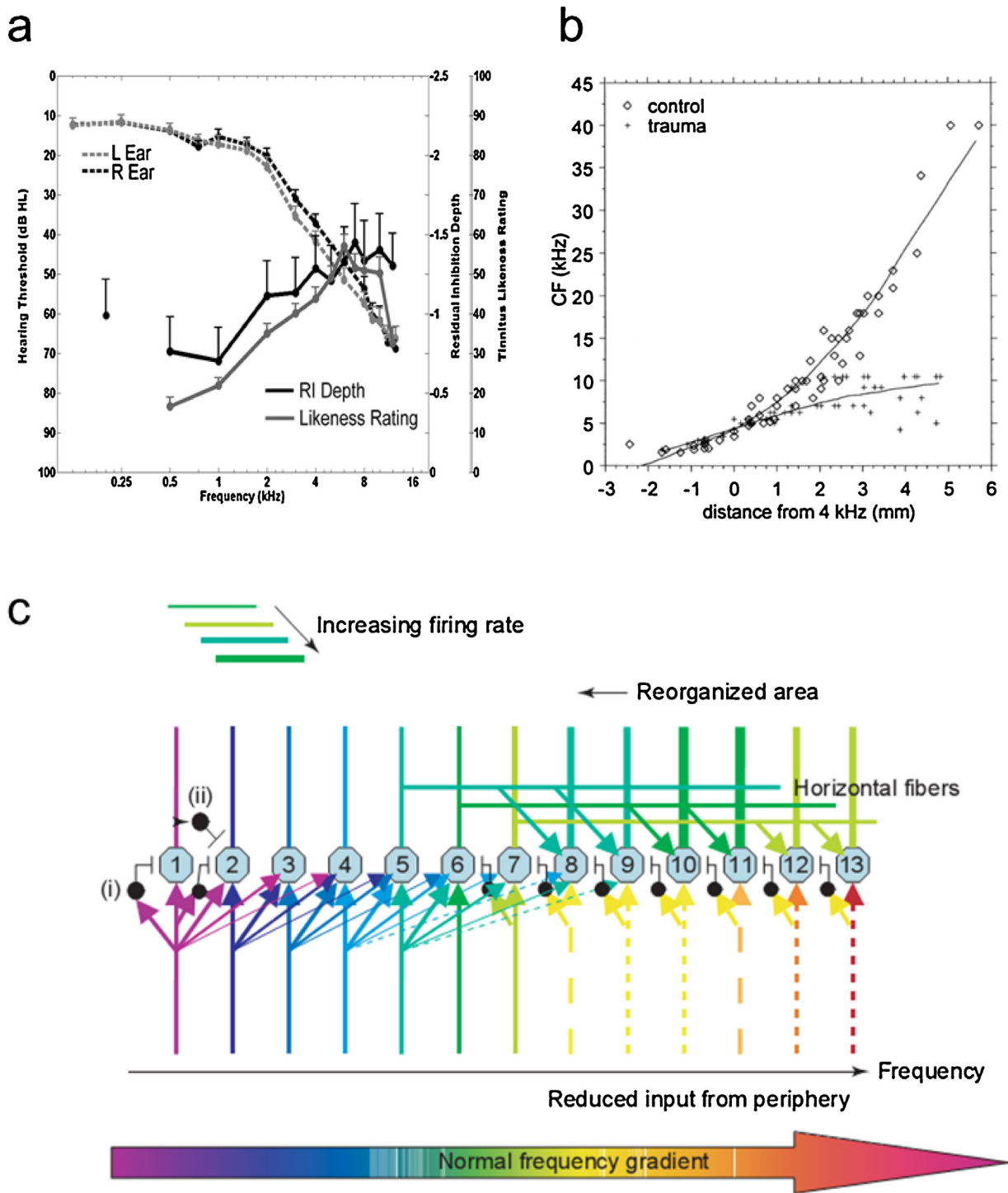
#### 3.1. Neural changes in tinnitus

One of the neural changes consequent on hearing loss is tonotopic map reorganization, in which neurons in the hearing loss region of primary auditory cortex (A1) begin to express the tuning preferences of their unaffected neighbors thereby augmenting the representation of neighboring frequencies in the cortical place map (Rajan and Irvine, 1998a; Eggermont and Komiya, 2000; Fig. 2b). Map reorganization in A1, which has been observed in human tinnitus sufferers with hearing loss (Wienbruch et al., 2006), suggests that pre-existing inputs on lateral connections to neurons in the hearing loss region now have a stronger influence on these neurons than do surviving inputs from thalamocortical pathways (Eggermont and Roberts, 2004; Fig. 1c). Other hearing loss induced changes include shifts in the balance of excitation and inhibition in auditory cortical networks (Scholl and Wehr, 2008), increased spontaneous activity of neurons in central auditory structures (Kaltenbach et al., 2004; Noreña and Eggermont, 2003; Dehmel et al., 2012), increased burst firing in some of these structures (Noreña and Eggermont, 2003; Finlayson and Kaltenbach, 2009), and increased synchronous activity among cortical neurons affected by hearing loss (Noreña and Eggermont, 2003). Changes in central gain in auditory pathways, in which the input/output functions of auditory neurons affected by hearing loss are amplified to compensate for diminished input from the cochlea (Noreña, 2011; Schaette and McAlpine, 2011; Chrostowski et al., 2011; Dehmel et al., 2012), may contribute to these changes and to hyperacusis (increased sensitivity to sounds) that often accompanies tinnitus and may be an early marker for the condition. Although the specific

contribution of these various neural changes to tinnitus percepts is not fully understood, enhanced neural synchrony in the auditory cortex is a likely proximal neural correlate of tinnitus, because it is largely confined to the hearing loss frequencies (Noreña and Eggermont, 2003) which is the frequency range where human subjects also localize their tinnitus percepts (Noreña et al., 2002; Roberts et al., 2008). Computational factors also point to a role for synchrony, since phase locked output from a network of neurons is more likely to depolarize a postsynaptic target than is temporally incoherent input to the same neurons (Niebur et al., 2002; Singer, 1999; Stevens and Zador, 1998).

Forms of neural plasticity are believed to contribute to these neural changes following hearing impairment. Cochlear damage in an animal model of hearing loss is followed within 2 weeks by an upregulation of somatosensory inputs to auditory neurons in the DCN, one of the early processing stages in subcortical auditory pathways (Zeng et al., 2009, 2012). This change is believed to reflect a form of plasticity called homeostatic plasticity, which acts to preserve the global firing rates of deafferented neurons in cortical and subcortical structures within a prescribed dynamic range (Turrigiano and Nelson, 2004; Pozo and Goda, 2010). Evidence for homeostatic plasticity operating in tinnitus is found in recent reports of differences between individuals with and without tinnitus in components of the auditory brain stem response (ABR), when hearing thresholds are normal in both groups. Compared to controls with normal hearing Wave I of the ABR (latency ~2 ms, reflecting output from the cochlea) is reduced in tinnitus sufferers with normal audiograms, implying undetected damage to the cochlea such as that attributable to loss of high threshold ribbon synapses on inner hair cells (IHCs) following noise exposure (Kujawa and Liberman, 2009) or cochlear dead regions missed by conventional audiometry (Weisz et al., 2006). However, ABR wave V (latency ~6 ms, originating from generators in the auditory mid-brain) is either not reduced (Schaette and McAlpine, 2011) or even augmented (Gu et al., 2012), suggesting compensatory changes in the intervening central auditory structures. At the cortical level an undesirable consequence of homeostatic plasticity may be an increase in the spontaneous and driven activity of auditory neurons following hearing impairment (Noreña, 2011; Schaette and McAlpine, 2011; Chrostowski et al., 2011), setting the stage for the development of tinnitus and abnormal sound level tolerance or hyperacusis which is experienced by many tinnitus sufferers (Noreña, 2011; Gu et al., 2010; Hébert et al., 2013).

Increased neural synchrony, which may play a crucial role in the generation of tinnitus percepts, is a further neural correlate of tinnitus that may result from neuroplastic mechanisms (Eggermont and Roberts, 2004; Weisz et al., 2007a,b). Following hearing loss and diminished intracortical inhibition, cortical neurons in the regions affected by hearing loss begin to discharge in phase locked patterns (Seki and Eggermont, 2003; Noreña and Eggermont, 2003) likely mediated by their lateral connections or by other shared inputs such as rhythmic local field potentials arising from recurrent corticothalamic activity disinhibited by hearing loss (Llinas et al., 2005). Subsequently such cortical network activity may be forged into larger functional assemblies by spike-timing dependent plasticity (STDP) in the cortical hearing loss region (cf. Yao and Dan, 2001), giving rise to tinnitus sounds. Changes in spontaneous activity (occurring either intrinsically in the auditory cortex or conveyed from subcortical auditory structures) induced by cochlear damage could provide a substrate for the development of such network activity. If this process continues unabated over a period of time, chronic functional changes may result in a tinnitus that is dependent wholly on central mechanisms and resistant to therapeutic intervention (Noreña and Farley, 2013). Although it is not known whether STDP or some other neuroplastic process is involved, a progression to dependence on central mechanisms has been



**Fig. 2.** Psychoacoustic properties and cortical map reorganization in tinnitus. (a) The group-averaged audiogram, tinnitus spectrum, and RI function for 47 participants with chronic bilateral tinnitus are shown. To obtain the tinnitus spectrum, participants rated each of 11 sounds differing in center frequency for similarity to their tinnitus (a likeness rating >40 indicated a sound beginning to resemble tinnitus). The RI function shows the suppression of tinnitus reported after cessation of band-limited noise sounds differing in center frequency (−5 equaled “tinnitus gone;” 0, no change; +5, tinnitus worse). The RI function is plotted negative up to show its similarity to the tinnitus spectrum. WN, white noise (from Roberts et al., 2008, with permission). (b) In the normal hearing cat (diamonds), the characteristic frequency tuning of neurons at low sound intensity shows an orderly gradient from low to high frequencies across the surface of A1 (tonotopy). In cats exposed to noise trauma (+), neurons in the hearing loss region (above 8 kHz in this example) responded preferentially to sound frequencies at the edge of normal hearing (from Eggermont and Komiya, 2000, with permission). (c) Model for map reorganization in primary auditory cortex. The dashed lines represent diminished thalamocortical input to cortical cells in the hearing loss region. A few inhibitory feedforward connections are indicated (one is labeled i) that suppress the same cells receiving thalamic inputs after one synaptic delay. Feedback inhibition is indicated by one example (ii). Hearing loss reduces excitation and feedforward inhibition arising from thalamocortical pathways, such that the affected neurons begin to respond preferentially to inputs from their unaffected neighbors via horizontal connections in the tonotopic map. The output of the affected neurons remains intact and is heard in terms of their original cochleotopic tuning as the tinnitus percept.

From Eggermont and Roberts (2004), with permission.

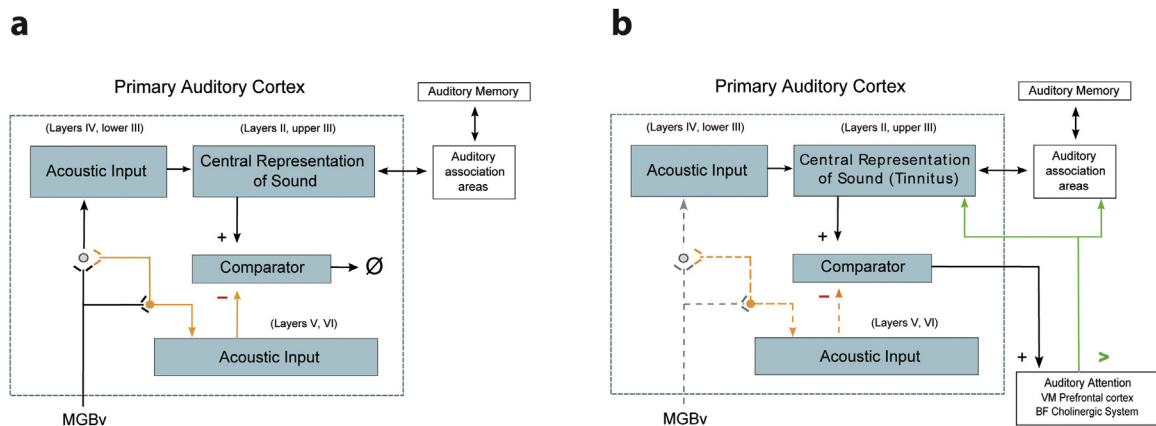
described in subcortical auditory nuclei following cochlear damage induced by noise trauma. In the inferior colliculus (IC) of guinea pigs increased spontaneous activity induced by cochlear damage is reduced by stimulating olivocochlear efferents or by cochlear ablation up to about 6 weeks after noise trauma, demonstrating that in its early stage IC hyperactivity is at least partially dependent on continued afferent input from the ear (Mulders et al., 2010). However, after about 8 weeks cochlear ablation no longer had any effect on IC hyperactivity, indicating a transition to mechanisms intrinsic to the IC or in auditory regions projecting to this structure had occurred over this time window (Mulders and Robertson, 2011; Robertson et al., 2013).

### 3.2. Role of auditory attention in tinnitus

Given its role in modulating the sensitivity of cortical neurons to their afferent inputs and its consequences for neural plasticity, a mechanism for auditory attention (particularly one involving the basal forebrain cholinergic system) could be expected to play a role in forging neural network activities that underlie tinnitus percepts. Zenner et al. (2006) similarly proposed a role for attention in establishing the neural changes underlying tinnitus, although a specific mechanism for attention and the circumstances leading to its engagement were not described. In Fig. 3 we describe a qualitative model of how attention and tinnitus might be linked.

Briefly, this model proposes that a principal role of the auditory cortex is to construct dynamic representations of the acoustic environment that integrate current auditory input with the organism's past history with sound. These representations serve as templates for filtering and predicting sensory state and in the model of Fig. 3 are read out as a pattern of excitation on a bank of pyramidal neurons that perform a comparator function. Sounds that are present in the environment generate a pattern of inhibition conveyed to the same neurons. In normal auditory perception (Fig. 3a) the predicted representation is built on current auditory input interacting with information contained in memory about the history of sounds

the organism has heard and their correlates in the current context. If this representation is congruent with afferent input arriving from auditory pathways, the patterns representing predicted and obtained inputs cancel each other and neural processing continues uninterrupted in accordance with the history of the organism in its current auditory environment. However, should an unexpected auditory event occur, the predicted and obtained patterns no longer match and a signal is generated, calling auditory attention which facilitates building a new and more accurate representation of the auditory scene. In normal hearing where cochlear function is intact, this process may require one or two hundred milliseconds or more for completion (Ross et al., 2002). But in the case of tinnitus where cochlear pathology is presumed to be present (illustrated in Fig. 3b), the outcome is different. Here the sound representation generated by the auditory cortex incorporates aberrant synchronous neural activity occurring in the hearing loss region that is part of the organism's history and has been encoded in memory in auditory association areas or higher centers. Because this representation is not congruent with bottom-up input arriving from auditory pathways, the mismatch of top-down and bottom-up information results in a persisting deployment of auditory attention. The BF cholinergic system which projects densely to the neocortical mantle may be a key element in this attention system, although a role for pontomesencephalic cholinergic or other neuromodulators cannot be excluded. Cholinergic modulation by the BF system would be expected to exert a powerful effect on synaptic plasticity, broadening the tuning properties of the targeted neurons and fostering the formation of spike-timing dependent linkages among them (Sarter et al., 2009; Pawlak et al., 2010). Because cholinergic modulation alters the balance of excitation and inhibition toward excitation in central auditory structures, it could also increase the spontaneous firing rates of auditory neurons in these structures. An exception to this scenario may occur when the sound frequencies contained in the auditory environment correspond more closely with those predicted by higher auditory centers. Under these conditions (such as during masking yielding residual inhibition) the



**Fig. 3.** A qualitative model for the role of attention in normal hearing and in tinnitus. The model is adapted from the canonical neocortical circuit described by Douglas and Martin (1990) from neuroanatomical data, in which excitation is delivered preferentially to pyramidal neurons in the superficial neocortical layers and feedforward inhibition preferentially to pyramidal neurons in the deep layers after one synaptic delay. (a) In normal hearing predicted sounds may be read out as a pattern of excitation (black) on a bank of pyramidal neurons where each neuron performs a comparator function. This prediction is determined by integration of a running memory of inputs from the intact ear and output from auditory association areas that provide feedforward information about acoustic inputs that are expected in the prevailing auditory context. Sounds that are present in the environment generate a pattern of inhibition (red) that is conveyed to the same comparator neurons. Although here feedforward inhibition is assigned this role (Creutzig et al., 2010), any inhibitory process could perform it provided that it contains sufficient spectrotemporal specificity to represent the sound environment. In normal hearing the two inputs match and cancel each other, provided that the auditory scene is reasonably stable, such that current sound representations continue to guide intracortical processing and behavior in accordance with the recent history of the organism. (b) In tinnitus, aberrant synchronous activity forged by neural plasticity in frequency regions affected by ear loss (this pattern stored in auditor memory) generates a pattern of excitation on comparator cells that is not canceled by inhibition arising from damaged auditory pathways (broken lines, red inhibitory, black excitatory). The mismatch between predicted and experienced inputs calls auditory attention which is expressed in primary and secondary auditory regions and prefrontal cortex as the cortex attempts (unsuccessfully) to construct a more accurate representation of the acoustic environment. Cholinergic neuromodulation may reinforce persistent aberrant neural synchrony underlying the tinnitus percept (green > facilitatory). (MGBv – ventral medial geniculate body in the thalamus; BF – basal forebrain; VM – ventromedial prefrontal cortex) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

predicted and obtained spectral patterns of auditory input correspond more closely with each other, and the experience of tinnitus may subside only to return when the congruent sound frequencies are no longer present in the acoustic scene.

It will be noted that the viewpoint described here proposes a key role for the auditory cortex in the generation and maintenance of tinnitus percepts (Eggermont and Roberts, 2004; Eggermont, 2012). Auditory cortex or more generally the thalamocortical system is likely necessary for perceiving tinnitus; without it there is usually not a conscious auditory percept, and likely not the annoyance aspect. Furthermore, the thalamocortical system does more than just relay information from the midbrain to cortical association areas. More than 90% of neural inputs to a cortical neuron are from other cortical cells; even in the input layers of auditory cortex at most 10% of the inputs are of thalamic origin (Abeles, 1991). It is thus likely that auditory cortical neurons work mostly on their intrinsic cortical inputs. The output of the auditory cortex to the thalamus far outweighs the input the thalamus receives from the auditory midbrain, at least if it parallels the visual system (Van Horn et al., 2000), which suggests that corticofugal feedback from the auditory cortex exerts a control function on subcortical structures. These anatomical features suggest a cortex that is more of a representational and information processing system than a passive recipient of bottom-up acoustic input. It has a “world-view” that can only be changed when input from the environment violates its expectations, in accordance with a trusted principle adopted by well-known rules that describe associative learning in several species and contexts (Rescorla and Wagner, 1972; Esber and Haselgrove, 2011). This sensitivity to change is also reflected in several forms of event-related potentials that are generated by violations of expectation. The pre-attentive MMN discussed above is one such potential, but others reflecting change detection in cortical networks at different levels of processing include long latency P300 odd-ball responses or language-related deviants signaling semantic (N400) and syntactic (P600) violations (Friederici, 2002) which may require long latency top-down input from higher cortical memory centers in order to form predictive representations.

In addition to its representational capacity, other features of auditory cortical processing that may be important in tinnitus pertain to how its dynamics are altered by deafferentation and how neural plasticity is expressed there. Although forms of neural plasticity are expressed at multiple levels of the auditory projection pathway (Zeng et al., 2009; Zhao and Tzounopoulos, 2011), cortical auditory receptive fields are known to be highly pliable through learning and are rapidly modulated by training contexts to reflect previous learning histories (Fritz et al., 2003; Polley et al., 2006). As discussed above, long-term passive exposure to low-level background sounds without signal value can also alter the response properties of auditory neurons over wide swaths of cortical territory that persist at least on the order of months after exposure (Pienkowski and Eggermont, 2009). In the latter experiments changes in cortical activity were achieved through exposure to external sounds, whereas in tinnitus auditory intracortical activity may have a different source (deafferentation); nonetheless in both cases sustained intrinsic activity appears to produce neural changes in the auditory cortex that are persistent, although the source of intrinsic activity and its perceptual consequences may not be the same. Because it fosters communication across wide regions of the auditory cortex, possibly enabling spike-timing dependent neuroplastic changes affecting this region, tonotopic map reorganization may be a contributing factor in enabling maladaptive plasticity after hearing loss. Map reorganization in adult animals occurs in the auditory cortex (Rajan et al., 1993; Rajan and Irvine, 1998a) and auditory thalamus (Kamke et al., 2003) following noise trauma or mechanical damage to the cochlear hair cells, but not in the auditory midbrain (Irvine et al., 2003) or cochlear nucleus

(Rajan and Irvine, 1998b). Homeostatic plasticity is a further established mechanism operating in deafferented auditory pathways (Zeng et al., 2009) that may increase central gain and the spontaneous and driven responses in auditory neurons. This mechanism is a putative source of increased sensitivity to external sounds (hyperacusis) observed in tinnitus patients (Hébert et al., 2013). However, as discussed earlier, increased neural synchrony in corticothalamic regions affected by hearing loss may be especially important for the experience of tinnitus. Increased neural synchrony coincides with tonotopic map changes and the region of impairment in animal models of hearing loss (Noreña and Eggermont, 2003), while in humans tinnitus spectra and residual inhibition functions similarly track the region of threshold shift (Noreña et al., 2002; Roberts et al., 2008).

The model of Fig. 3 is intended to illustrate how predicted auditory events might be evaluated at the level of primary auditory cortex. Although input from auditory pathways to the cortex is presumed to be impaired in tinnitus, leading to prediction failure, the output of cortical neurons representing the tinnitus sound remains intact, such that the predicted pattern of auditory activity may be conveyed corticofugally to subcortical structures as well as corticopetally to higher association areas, enabling the prediction to be assessed at multiple levels of the auditory projection pathway. Prediction has been proposed by several authors as an operating principle in the auditory system (see Winkler et al., 2009 and Bendixen et al., 2012 for reviews) and in other domains (Schultz and Dickinson, 2000). In the model of Winkler et al. (2009), which is concerned with auditory scene analysis, attention is considered to be a factor modulating the detection of prediction failure (detection of deviance) and promoting the stimulus driven binding of sensory attributes to form new auditory objects in dynamic auditory environments. Like the current model of the role of attention in tinnitus, Winkler et al. (2009) suggest that prediction failure (the detection of deviance from predicted representations) is signaled by EEG mismatch responses. Biological implementations of deviance detection have been studied most intensively in visual and sensorimotor systems where a representation of the expected consequences of the organism's actions (corollary discharge or efference copy) is used to detect errors and guide correction in primate ocular and motor behavior (Wurtz et al., 2011; Webb, 2004; Guillery and Sherman, 2011; Rauschecker, 2011; Shadmehr et al., 2010) or to cancel sensory signals that are generated by self-movement in the capture of prey by electric fish (Harvey-Girard et al., 2010). Computations performed by the parallel fiber-fusiform network in the dorsal cochlear nucleus cited earlier (Zhao and Tzounopoulos, 2011) may be another example of context-dependent, predictive filtering performed by central auditory structures. The wide range of latencies characterizing different forms of mismatch response is consistent with predictive filtering conducted at different levels of neural processing (Bendixen et al., 2012) including a role for top-down inputs from memory structures in forming predicted neural representations (Winkler et al., 2009). Although the specific mechanisms underlying these responses are only partially known, Bendixen et al. (2009) found that the evoked potential elicited by omission of a fully predicted tone (but not the evoked potential elicited by an unpredicted omitted tone) was identical to that evoked by the tone itself up to the time of processing in the auditory cortex (~50 ms, the P1 evoked potential) but not thereafter. This suggests that early cortical or subcortical processing had generated a prediction (neural representation) of the input that was expected, and that subsequent processing in higher cortical centers (Schönwiesner et al., 2007) was evoked when prediction failure occurred.

A final aspect of the model of Fig. 3 concerns the nature of the attention system that is activated when prediction failure occurs. The BF cholinergic system (possibly accompanied by activation of



tegmental cholinergic projections) may be a key component of this system. However, the BF cholinergic system receives top-down input from the PFC and in turn projects to all primary and secondary cortical sensory regions facilitating neural processing in these regions. In principle top-down inputs to the BF system could reflect the outcome of processing in other sensory domains, so that involvement of this system is not unique to auditory attention. Because the BF system is known to play a crucial role in learning and memory (Sarter et al., 2005; Ramanathan et al., 2009), its engagement by perceptual disparities in other sensory modalities may account for the close relationship between attention and learning seen in a wide range of tasks (Biferno and Dawson, 1977; Roberts et al., 1984). Other modulatory systems are also known to be sensitive to expectancy violations and may support attention-like functions (a topic we discuss further in Section 5.2). Summarizing data for effects of expectancy failure in modulatory systems, Yu and Dayan (2005) proposed a model in which cholinergic and noradrenergic neuromodulators act in tandem to direct top-down attention and learning under conditions of stimulus and task uncertainty.

#### 4. Evidence of a role for auditory attention in tinnitus

These considerations based on the neural changes that are seen in tinnitus and mechanisms for neural plasticity give reason to consider a role for an auditory attention network in the generation and maintenance of tinnitus. What does the evidence suggest? At present, it must be acknowledged that definitive studies on the question are lacking. However, several lines of evidence can be interpreted to suggest a role for attention in the development and maintenance of tinnitus, which are reviewed here.

##### 4.1. Behavioral studies

That tinnitus is itself a persistent audible percept could be taken as *prima facie* evidence for an involvement of auditory attention mechanisms. Although few systematic studies have addressed the question, their findings add weight to the hypothesis. If an S1 stimulus consisting of a standard sound and an infrequent deviant is presented to one ear, with each S1 signaling the subject to correctly categorize an S2 stimulus presented to the other ear, performance of the S2 task is impaired following the deviant S1 compared to the standard S1 (Schröger, 1996). This has been taken to suggest that the deviant S1 draws or “captures” attention away from the S2 ear. Cuny et al. (2004) found that in patients with unilateral tinnitus attentional capture was reduced when the S1 and S2 stimuli were presented in the nontinnitus and tinnitus ear respectively, rather than in the reverse arrangement. They suggested that auditory attention was automatically directed to the tinnitus ear, such that a deviant S1 stimulus could not draw attention away from it. Cuny et al. (2004) repeated this procedure with normal hearing subjects who did not experience tinnitus, but a tinnitus-like external sound was played in one ear. Performance of the S2 task did not differ between the two ears, suggesting that it is not the presence of a sound in one ear that modulates attentional capture but whether the sound is an auditory phantom. The model of Fig. 3b could be taken to suggest that the disparity between a tinnitus sound and input from the damaged ear aroused attention to the affected ear in unilateral tinnitus. Evidence for ear-specific auditory attention has been reported by Müller et al. (2009) in normal hearing subjects, although under the conditions of their test modulation of brain activity by the ear of attention reached significance only in the left hemisphere and only for a sound AM at 20 Hz.

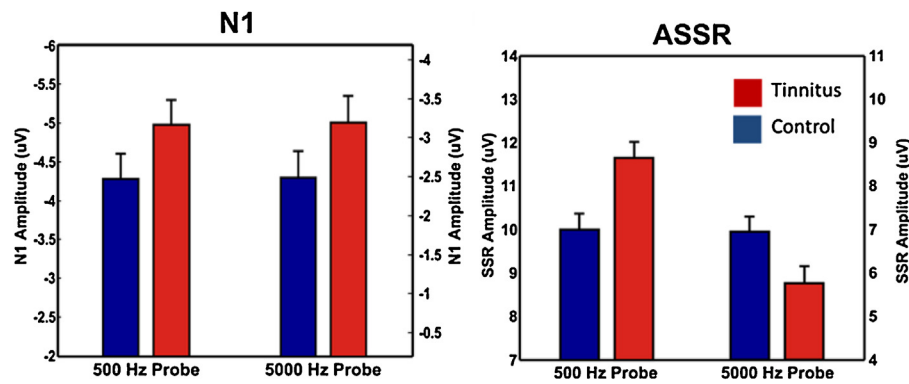
In another study relevant to the attention hypothesis, Knobel and Sanchez (2008) placed 66 normal hearing volunteers in a silent sound booth where they performed three tasks in a mixed

consecutive order, consisting of the Tower of Hanoi task requiring problem solving and working memory, a simple visual task asking subjects whether they noticed changes in illumination, and a simple auditory task asking subjects whether they heard sounds in environment. Unknown to the subjects, the visual (room illumination) and auditory (silence) conditions remained constant on all tasks. When probed after each task, auditory perceptions were reported by 68.2% of the subjects after the auditory task, 45.5% of subjects after the visual task, and 19.7% of subjects after the Tower of Hanoi, but reports of visual perceptions were infrequent overall (<16% of subjects) indicating that the subjects were making discriminated judgments. These findings suggest either that phantom auditory sounds are facilitated when the task calls attention to auditory signals, or that tasks that require non-auditory cognitive resources are most suppressive of phantom sounds that are otherwise perceived in a silent environment. Complementary evidence from studies of tinnitus sufferers indicates that persistent, attention-demanding tinnitus interferes with complex information processing. Individuals with chronic tinnitus perform more poorly on cognitive tasks that require selective attention and working memory than do individuals without tinnitus, even when the effects of hearing level, anxiety, and depression are regressed out (Stevens et al., 2007; Rossiter et al., 2006). The results suggest that tinnitus-related neural activity possibly supported by auditory attention remains a fierce competitor for access to the global workspace supporting such tasks.

##### 4.2. Electrophysiological evidence

Following a different approach, Roberts and Bosnyak (2010) asked subjects with tinnitus and age and hearing-level matched controls to adjust the intensity of a 5 kHz 40-Hz amplitude modulated (AM) sound (in the region of tinnitus and hearing loss) and a similarly AM modulated 500 Hz sound (in the range of normal hearing and below the tinnitus frequency range) to match the loudness of a 1 kHz sound presented at 65 dB SL (this sound also below tinnitus frequencies and in the range of normal hearing). The aim of this procedure was that the 500 Hz and 5 kHz sounds should be equal in perceived loudness for all subjects regardless of the different carrier frequencies, the presence of threshold shifts, and possible hyperacusis consequent on altered gain changes. The tinnitus and control subjects were then probed (in separate groups) with the 500 and 5 kHz 40-Hz AM sounds (a train of 12 0.5 s probes presented at 0.4 Hz, each train separated by 60 s of silence) under conditions in which the tinnitus subjects would have heard their tinnitus. Two EEG responses, one localizing to primary auditory cortex and the other to secondary auditory regions (the stimulus driven 40-Hz steady-state response or ASSR, and the N1 transient response, respectively), were measured. Both of these responses have been shown in previous research to be highly sensitive to auditory attention in normal hearing subjects (see Gander et al., 2010a,b, for reviews).

The results of the study depended on the response measured and on probe frequency. N1 amplitude was elevated in both tinnitus groups at both probe frequencies (Fig. 4, left panel,  $p < 0.03$ ), consistent with aroused auditory attention in tinnitus experienced under baseline conditions. ASSR amplitude was also elevated in the tinnitus group, but only for the 500 Hz probe ( $p = 0.003$ ), consistent with an attention effect expressed at this frequency (Fig. 4, right panel). At 5 kHz the group difference was reversed, with ASSR amplitude lower in the tinnitus subjects than controls ( $p = 0.044$ ; interaction of frequency with  $p = 0.015$ ; see supplementary information). It was suggested that increased ASSR amplitude at 500 Hz may have reflected a bottom-up effect of auditory attention in tinnitus, which may be frequency nonspecific (the whole auditory cortex appears to be activated by auditory attention; see Gander et al.,



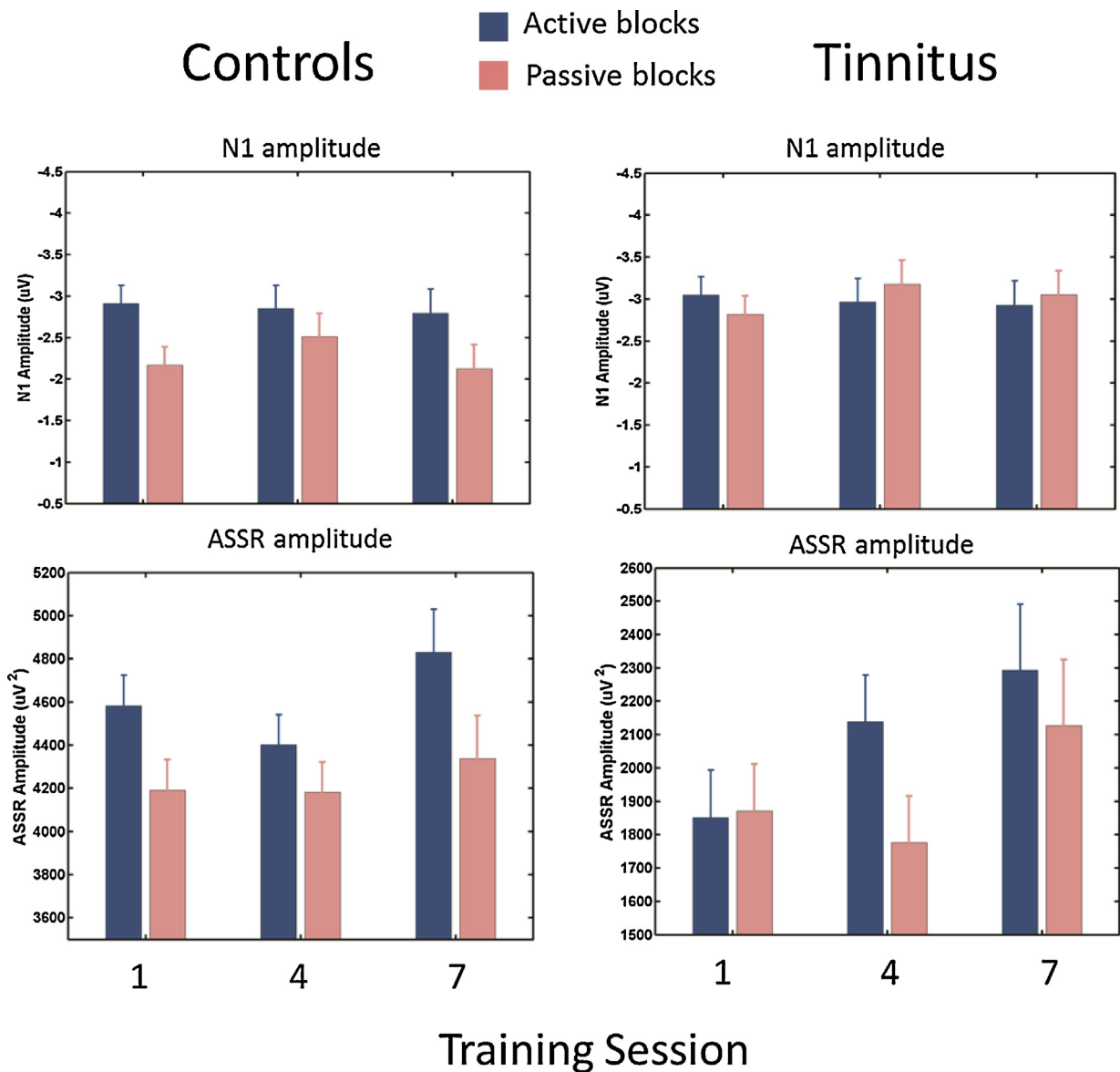
**Fig. 4.** Electrophysiological responses in tinnitus. Transient (N1, left panel) and steady-state (ASSR, right panel) responses are shown for individuals with tinnitus and for age and hearing-level matched controls. 14–16 subjects were tested in each of four independent groups (tinnitus and control subjects probed at either 500 Hz or 5 kHz). The four groups were matched for age and degree of audiometric threshold shift. The 5 kHz probe was in the tinnitus spectrum and 500 Hz below the tinnitus spectrum of the tinnitus subjects. Probe intensity was matched by each subject to a 1 kHz sound in the range of normal hearing to control for variation in loudness perception related to carrier frequency or hyperacusis. Because ASSR and N1 amplitude are known to decrease with carrier frequency ( $p < 0.001$  in this data set), the results are aligned to amplitude in the control groups for each frequency. N1 amplitude (left panel) was larger in the tinnitus groups than in the control groups at both probe frequencies ( $p = 0.023$ ). Frequency dependence was observed for ASSR amplitude (right panel). Here ASSR amplitude was larger in the tinnitus group than in the control group where 500 Hz was probed ( $p = 0.004$ ), but smaller in tinnitus subjects than controls in groups where 5000 Hz was probed ( $p = 0.045$ ). The group by probe interaction was also significant ( $p = 0.014$ ). Only N1 and ASSR amplitude distinguished between the tinnitus and control groups; P1, P2, and N2 transient responses did not (results not shown).

2010a, experiment 2). ASSR amplitude at 5 kHz, on the other hand, may have been reduced in the tinnitus group by neural changes underlying the tinnitus percept. The possibilities include a busy line effect (neurons forged into synchronous networks are not available for recruitment by the AM envelope), depression of thalamocortical synapses on cortical neurons by uncorrelated inputs from the damaged ear (Roberts and Bosnyak, 2010), or hyperpolarization of thalamic sources following deafferentation (Llinas et al., 2005). The diminished ASSR response at 5 kHz in the tinnitus group is consistent with a recent fMRI study that found reduced functional connectivity between primary auditory cortex and the thalamus in tinnitus patients compared to hearing-level matched controls (van Dijk et al., 2013). However, the frequency profile of the reduced connectivity could not be determined from the procedure used.

Persisting activation of a mechanism for auditory attention in tinnitus might be expected to affect the ability of an attention manipulation to modulate ASSR and N1 responses in individuals with tinnitus, compared to age and hearing-level match control subjects without tinnitus. Roberts et al. (2012) trained a tinnitus group and a group of age and hearing-level matched controls to detect an auditory target embedded in a 5 kHz 40-Hz AM sound (this sound in the tinnitus frequency region of the tinnitus subjects). EEG was measured in the first, middle, and last session of a training series consisting of seven sessions delivered over 2 weeks. Within each session, active blocks requiring auditory attention and behavioral performance alternated with passive blocks on which subjects were instructed to ignore the sounds and rest. In control subjects N1 and ASSR amplitude increased on active compared to passive blocks in each EEG session (Fig. 5, left panels), in accordance with prior evidence revealing an effect specifically of auditory attention on these responses under conditions in which behavioral response requirements were controlled (Gander et al., 2010a). Neither response changed over training sessions in the control subjects, in agreement with previous evidence obtained with this procedure showing N1 and ASSR amplitude to be resistant to plastic change in normal hearing individuals (Bosnyak et al., 2004; Gander et al., 2010b). The results in the tinnitus group were different (Fig. 5, right panels). Unlike the findings in controls, N1 amplitude did not differ between active and passive blocks in any session in the tinnitus group, suggesting reduced modulation by attention in tinnitus subjects. ASSR amplitude did not modulate between active and passive blocks on the first day of training, either, in the tinnitus group. However, this response increased on active

blocks with continued training in the tinnitus group, such that overall a main effect of active/passive blocks, and an interaction of blocks with sessions, were obtained in this group. It was suggested that reduced inhibition in the TFR of the tinnitus subjects fostered a training-directed, neuroplastic expansion of the 5 kHz representation in these subjects, and that attention while not modulated at the outset of training came to exert a degree of control over this process. An additional finding was that the amplitude of the long latency N2 transient response (latency 326 ms) and the auditory sustained response (400–900 ms) was also larger on active than on passive blocks in the tinnitus group, and equally so in control subjects, suggesting an influence of attention in both groups. Although the long latency of these responses allows that behavioral response preparation could have been a contributing factor, the hypothesis is raised that reduced modulation of N1 responses between active and passive blocks in tinnitus subjects, and reduced modulation of ASSR amplitude early in training, may have reflected aberrant neural changes taking place in the tinnitus frequency region of the tinnitus subjects, rather than a frequency nonspecific disturbance of auditory attention in these subjects. Weisz et al. (2004) found abnormal MMN responses in tinnitus compared to control subjects for sound frequencies near the tinnitus frequency region but not for sound frequencies well below this region.

Thus, while these electrophysiological results raise the question of possible changes in auditory attention in tinnitus, it must be acknowledged that this literature does not speak with a clear voice on the topic. The results of Fig. 4 are congruent with those of Wienbruch et al. (2006) who found for bilateral cases of tinnitus larger ASSR responses than in controls for sound frequencies below 2 kHz, which is below the tinnitus frequency region. In that study the group difference was not significant above this frequency. It may further be noted that the results of Fig. 4, where smaller ASSR responses were evoked by a 5 kHz 40-Hz AM sound in tinnitus subjects compared to controls while N1 amplitude was increased in tinnitus, are congruent with those of Fig. 5, where N1 amplitude evoked by the same sound again tended to be larger ( $p = 0.077$ ) and ASSR amplitude smaller ( $p = 0.22$ ) in tinnitus than in controls on passive blocks where attention was not required. However, different N1 findings were reported by Diesch et al. (2012). These investigators presented three carrier frequencies, each AM at a different AM rate, either singly or in various combinations to tinnitus and control subjects, and observed no group differences in N1 amplitude when this response was extracted from the



**Fig. 5.** Effects of auditory training and attended performance on N1 and ASSR responses in tinnitus. Tinnitus subjects ( $n = 11$ , right panels) and controls ( $n = 11$ , left panels) were trained for seven sessions to detect a target (a single amplitude enhanced 40-AM pulse of variable magnitude, in a 5 kHz 40-Hz AM stimulus of 1 s duration) present on 2/3 of the trials in each session. The 5 kHz carrier frequency was in the TFR of the tinnitus subjects. In each session (given at 2-day intervals) active blocks (blue) on which subjects attended to the trained sounds and performed the task were interleaved with passive trials (red) on which subjects ignored the sounds and rested. EEG (128 channels) was measured during sessions 1, 4, and 7. N1 amplitude (top panels) is reported for electrode Fz and the ASSR (bottom panels) as global field power (this response dipolar, peaking near Fz and Oz). In controls N1 amplitude ( $p = 0.03$ ) and ASSR amplitude ( $p = 0.05$ ) were larger when the training stimulus was attended than when it was not, with no significant effect of training sessions on either response. In the tinnitus group N1 amplitude did not differ between active and passive blocks in any session and did not change over the training series. ASSR amplitude did not differ between active and passive blocks on day 1 of training in the tinnitus group (congruent with their N1 results on this day), but this response increased in amplitude over the training sessions preferentially on active blocks, yielding a significant overall main effect of active/passive blocks ( $p = 0.033$ ) and an interaction of blocks with sessions ( $p = 0.021$ ). It may also be noted that on passive blocks (red) where attention was not required, N1 amplitude tended overall to be larger in the tinnitus group than in controls ( $p = 0.077$ ) and ASSR smaller in tinnitus than controls ( $p = 0.22$ ; note the different ordinates for ASSR amplitude), in qualitative agreement with results presented in Fig. 4 for independent groups tested with a 5 kHz 40-Hz AM sound. Error bars are 1 SE of the difference between active and passive blocks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Results from Roberts et al. (2012).

steady-state waveform. On this basis Diesch et al. (2012) concluded that attention was not responsible for increases in ASSR amplitude reported previously in tinnitus. Overall, prior research comparing N1 responses between tinnitus and normal hearing subjects have produced an inconsistent picture with some studies reporting increases in N1 amplitude or N1 loudness growth functions in tinnitus subjects compared to controls for tones presented near the edge of the tinnitus frequency region compared to other frequencies (Dietrich et al., 2001; Noreña et al., 1999; Hoke et al., 1989), and other studies reporting either decreases in these variables at

frequencies below or near the edge of the putative tinnitus pitch (Kadner et al., 2002; Lee et al., 2007) or no changes at all in N1 amplitude in tinnitus compared to controls (Jacobson et al., 1991; Jacobson and McCaslin, 2003; Diesch et al., 2012; Sereda et al., 2013). Most electromagnetic imaging studies of tinnitus have been guided by the hypothesis that expansion of the cortical representation for frequencies at the edge of hearing loss should enhance brain responses evoked by edge frequency sounds compared to frequencies below the hearing loss region. However, there are numerous neural changes occurring in tinnitus that may express variably in

different evoked brain responses, with some changes (for example, in central gain) favoring augmented responding and other changes (for example, reduced connectivity) not, with different degrees of frequency dependence. A further limiting factor is that most evoked potentials, even when the 3-D location of their generators is known, do not map onto discrete underlying neural processes. Current experience suggests that considerable effort may be needed to achieve corroborating and meaningful results in this literature.

#### 4.3. fMRI and PET imaging

Metabolic imaging by PET or fMRI has been used to identify brain regions in which neural activity is elevated or suppressed in individuals with tinnitus compared to control subjects without tinnitus (see Lanting et al., 2009 and Adjamian et al., 2009 for reviews). An advantage of PET is that intrinsic neural activations can be assessed in the absence of external sound stimulation, whereas the majority of studies employing fMRI have compared sound-evoked activations to resting baselines between these groups. While there is variability among the studies with respect to the specific brain regions that differentiate tinnitus and control subjects, most studies concur that intrinsic or evoked neural activity in primary auditory cortex and auditory association areas (areas that are known to be attention sensitive) is also elevated in tinnitus (Lanting et al., 2009). Gu et al. (2010) contrasted sound-evoked brain activity between four groups of individuals, targeting specific regions of interest in auditory pathways. All subjects had pure tone thresholds <25 dB HL to 8 kHz. One of the four groups experienced tinnitus and abnormal sound level tolerance (the latter measured by two methods), two groups experienced one but not the other of these conditions, and a fourth group did not experience either condition. Each group was probed with an identical broadband noise presented at three sound levels in an fMRI scanner, using a sparse sample protocol that measured sound-evoked responses in the absence of scanner noise. Abnormal sound level tolerance (hyperacusis) was accompanied by increased sound-evoked activity (BOLD responses) in the auditory midbrain, thalamus, and medial and lateral Heschl's gyrus (regions of primary auditory cortex), whereas tinnitus was associated with increased activity only in regions of primary auditory cortex. It was suggested that hyperacusis reflected changes in central gain in distributed auditory structures whereas tinnitus may reflect activity in the auditory core regions facilitated by persistent auditory attention.

In another recent study Langers et al. (2012) compared stimulus driven BOLD responses between individuals with tinnitus and age matched controls, with both groups having hearing thresholds in the normal range to 8 kHz and some degree of hearing loss above this frequency. Pure tone stimuli varying between 0.25 and 8 kHz were used, which permitted frequency-specific responses to be spatially resolved and macroscopic tonotopic organization in medial and lateral Heschl's gyrus to be mapped to 8 kHz. Macroscopic map structure did not differ between the two groups over these frequencies, although the possibility of more fine-grained map differences could not be excluded by this analysis. However, sound-evoked BOLD responses were significantly larger in tinnitus than control subjects in left lateral Heschl's gyrus, where voxels were preferentially tuned to sound frequencies below about 1 kHz. It may be noteworthy that this result is similar to group differences in the ASSR reported by Wienbruch et al. (2006) including the hemispheric trend. In normal hearing subjects modulation of the 40-Hz ASSR (Ross et al., 2004) and of BOLD responses (Jäncke et al., 1999) by auditory attention has been reported to be larger in the left hemisphere than in the right hemisphere, raising the possibility that larger BOLD responses in the left hemisphere observed by Langers et al. (2012) for low frequency sounds in tinnitus may have had an attentional origin.

Although it cannot be considered a novel insight (Jastreboff, 1995; Rauschecker et al., 2010; De Ridder et al., 2011), one implication of the viewpoint described here, in which neuromodulatory systems activated by attention distribute widely to cortical and subcortical targets, is that brain activity distinguishing individuals with and without tinnitus should not be confined to the auditory cortices but should extend to non-auditory brain regions as well, depending on the task procedure that is used for scanning and on whether correlated tinnitus attributes such as emotion and behaviors of distress are present. There is now extensive evidence indicating that brain activity in non-auditory regions is enhanced in individuals with tinnitus compared to nontinnitus controls (Lanting et al., 2009; Adjamian et al., 2009; Husain et al., 2011), including the middle and superior frontal gyri (Mirz et al., 1999, 2000), cingulate gyrus (Mirz et al., 1999; Plewnia et al., 2007a), amygdala (Mirz et al., 2000), the precuneus (Mirz et al., 1999), and the parietal cortices (Mirz et al., 1999). Elevated activity in the hippocampal and parahippocampal gyri has also been reported (Lockwood et al., 1998; Vanneste and De Ridder, 2012), which are regions important in memory storage and retrieval. These brain regions have been identified as components of the Global Neuronal Workspace described by Dehaene and Changeux (2011), which is engaged when subjects are required to consciously process task stimuli and make discriminated behavioral responses to achieve task goals.

More recently, fMRI has been used to examine functional network connectivity in individuals with tinnitus under baseline conditions. Maudoux et al. (2012) examined functional connectivity patterns among auditory and non-auditory regions in patients with chronic tinnitus and normal hearing controls. Two distinct anticorrelated networks were identified in controls, the first network encompassing the auditory cortices and the insula and the second network including the frontoparietal and anterior cingulate cortices, brainstem, amygdala, basal ganglia/nucleus accumbens and parahippocampal regions. In tinnitus only the first network was observed, and when contrasted to controls only increased functional connectivity between the auditory cortices in both hemispheres (A1 and A2) and now the left parahippocampal region survived statistical filtering. This increase in functional connectivity between auditory and parahippocampal regions in tinnitus is in accordance with Vanneste et al. (2011a,b) who reported an increase in electrical brain activity in the gamma frequency band in the parahippocampal area and an increase in connectivity between parahippocampal regions and auditory cortices in tinnitus patients compared to control subjects. On the other hand, as discussed above, van Dijk et al. (2013) found evidence of reduced functional connectivity between the thalamus and the auditory cortex in tinnitus compared to a control group with similar audiometric profiles, although an earlier study by this group found larger stimulus driven BOLD responses for low frequency sounds in the left Heschl's gyrus of tinnitus patients compared to control subjects (Langers et al., 2012). Overall these findings suggest that at least two mechanisms, one modulating attention in the auditory cortices and its functionally coupled regions, and the other accounting for reduced stimulus efficacy in the tinnitus frequency region of A1, may be needed to explain current findings. In bothersome tinnitus correlations depicting functional connectivity were positive within auditory cortical regions but negative between auditory and visual regions compared to normal hearing controls, suggesting suppression of communication between the latter regions by auditory attention in tinnitus (Burton et al., 2012).

#### 4.4. Oscillatory brain dynamics in tinnitus

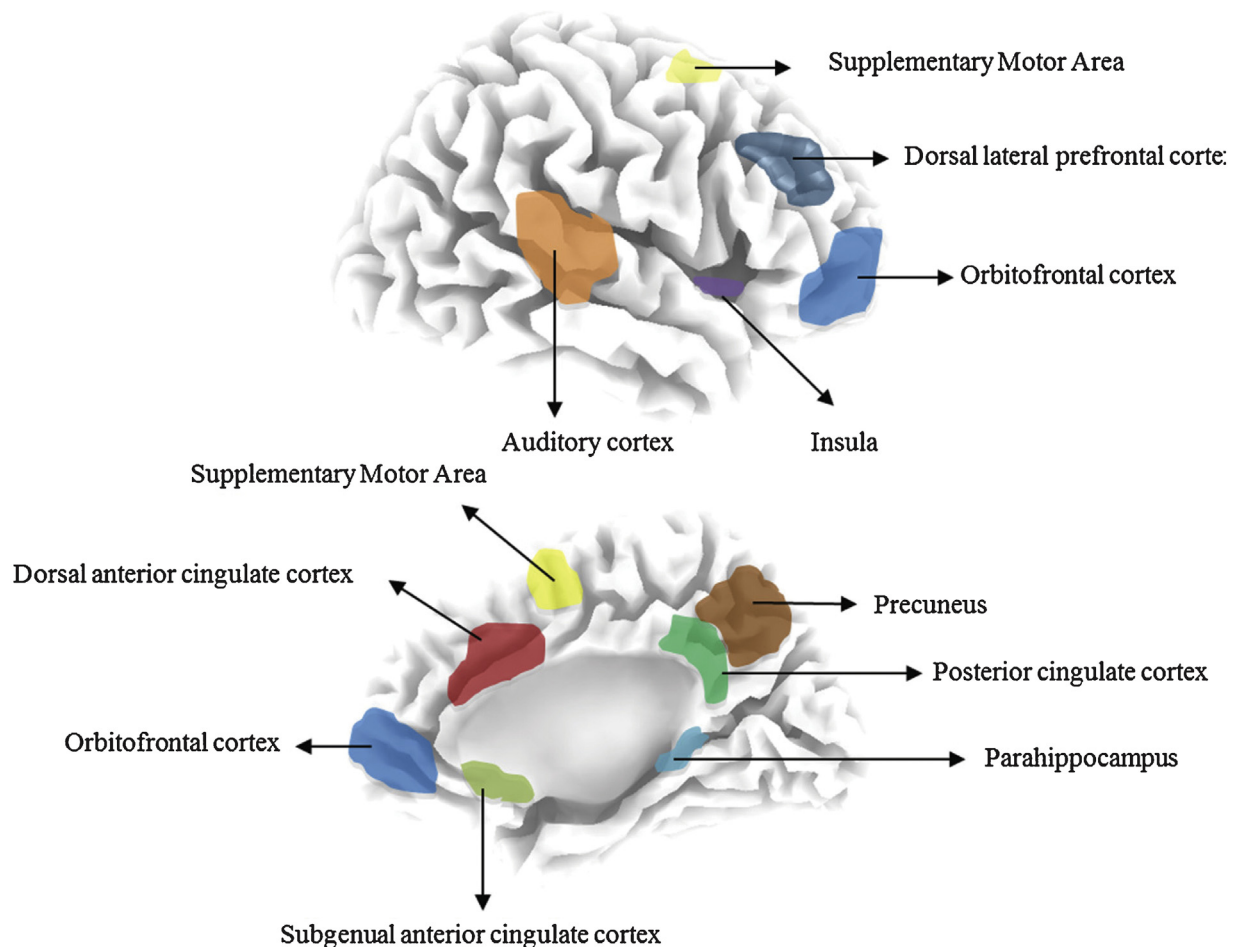
Functional connectivity in baseline fMRI recordings depicts correlated or anticorrelated fluctuations in BOLD activity among



voxels in different brain regions, which may be a signature for the exchange of information among the regions. Notwithstanding limits on spatial resolution, such exchange should also be reflected in the phase locked activity of neural networks in the regions which can be recorded with fine grain temporal resolution in different frequency bands using EEG and MEG. There are now several reports of resting-state oscillatory brain changes recorded electromagnetically in tinnitus patients compared to controls including decreased auditory alpha (10–14 Hz) (Weisz et al., 2005), increased slow wave delta activity (1.5–4 Hz) (Weisz et al., 2005; Adjajian et al., 2012), increased gamma activity coupled to slow oscillations in auditory cortex (Weisz et al., 2007a,b), and increased gamma oscillations that track the laterality of the tinnitus percept (Weisz et al., 2007a,b; Van der Loo et al., 2009), although, unlike changes in slow wave activity, reports of changes in gamma have not been consistent (Adjajian et al., 2012). Slow wave oscillations have been attributed to hyperpolarization of thalamic nuclei consequent on deafferentation, which may disinhibit thalamocortical oscillations in the 40-Hz range giving rise or contributing to synchronous activity underlying the tinnitus percept (Llinas et al., 2005). Increased phase locking of oscillatory responses among the frontoparietal, temporal, and cingulate cortices has been reported in tinnitus patients compared to controls (Schlee et al., 2008) with greater involvement of frontal and parietal regions in longer term compared to acute cases of tinnitus (Schlee et al., 2009a). These connectivities were expressed predominantly in the alpha (9–12 Hz) and gamma

(48–54 Hz) bands (Schlee et al., 2009b). Stronger top-down inflow to temporal cortex from prefrontal, orbitofrontal, and parieto-occipital regions was also found to correlate positively with tinnitus distress (Schlee et al., 2009b). Notwithstanding that inverse modeling of EEG and MEG sources is subject to limitations (see Palva and Palva, 2012, for a discussion), low-resolution electromagnetic tomography (LORETA) of EEG data has been used to describe resting-state oscillatory activities in coarsely imaged brain regions in individuals with tinnitus compared to various control conditions (Vanneste et al., 2010). Results reviewed by Vanneste and De Ridder (2012) point to tinnitus-related oscillatory changes occurring in several regions including auditory cortex, the dorsal anterior and posterior cingulate cortex, dorsolateral prefrontal cortex, regions of frontal cortex, and the parahippocampus (see Fig. 6). While the functional roles of oscillatory activities in these regions and their precise localizations are not well established, they could relate to different aspects of tinnitus including the retrieval of its encoding from memory, its attended conscious experience, or distress behavior associated with a persistent annoying phantom sound (Vanneste and De Ridder, 2012). Of the areas identified in Fig. 6 regions of the auditory cortex (Paltoglou et al., 2009), anterior cingulate (Sadaghiani et al., 2009), and prefrontal cortex (Voisin et al., 2006) are activated when normal hearing subjects attend to anticipated sound stimuli on cognitive tasks.

Oscillatory responses measured by EEG/MEG reflect intra- and inter-regional communication (phase coupling) between brain



**Fig. 6.** Brain areas showing altered resting-state EEG oscillatory activity in tinnitus patients compared to controls. Localizations were described using standardized low-resolution brain electromagnetic tomography (LORETA). Regions of auditory cortex, cingulate cortex, and frontal cortex are activated by auditory attention when normal hearing subjects anticipate sound delivery on auditory tasks.

From Vanneste and De Ridder (2012), with permission.

networks and in principle provide distinctive information not contained in hemodynamic changes imaged by fMRI and PET. The frequency signatures of these couplings likely express communication between modules that perform specific functions in perception and cognitive processing (Doesburg et al., 2012). For example, selective attention to one of two competing continuous speech patterns enhanced the power of 4–8 Hz oscillations arising from auditory cortex for the perceived speech pattern, possibly reflecting a brain response to the speech envelope which has significant power in the 2–20 Hz range (Kerlin et al., 2010; Purcell et al., 2004). In contrast, hemispheric lateralization of parietal alpha power (8–12 Hz) predicted the direction of selective attention to the auditory streams (Kerlin et al., 2010). Presently it is not known how these modulations arise. However, auditory attention has been associated with desynchronization of oscillatory activity in the alpha band (Hartmann et al., 2012; Weisz et al., 2011), which may set the stage for couplings driven by correlated stimulus attributes. Reduced alpha in temporal regions has also been reported in individuals with tinnitus compared to normal hearing controls (Weisz et al., 2005), which is in line with increased auditory attention in tinnitus. At present there is no evidence bearing on the question of whether top-down activation of the BF cholinergic system or another modulatory system is involved in these oscillatory phenomena. However, cortical desynchronization by such a mechanism could modulate the sensitivity of the affected neurons to correlated features of an auditory speech pattern as well as bind that pattern to ongoing activity in distributed brain regions depending on the content of input signals and the performance requirements of the task (Obleser and Weisz, 2012). Persisting activity in neuromodulatory systems may also underlie the increased functional connectivity between auditory cortex and brain regions important for memory, emotion, and perceptual processing that has been reported in individuals with tinnitus.

## 5. Summary, limitations, and looking ahead

Most cases of persistent tinnitus are associated with hearing impairments expressed in the audiogram (Noreña et al., 2002; Roberts et al., 2008) or in more sensitive measures (Weisz et al., 2006; Schaette and McAlpine, 2011; Gu et al., 2012). Research has identified several neurophysiological changes that occur in tinnitus associated with hearing loss, and revealed brain regions and networks where functional activity is modified in human tinnitus sufferers. This paper has raised the question of whether mechanisms for auditory attention are involved in the development and maintenance of the neural changes that underlie tinnitus, and if so, what the triggering signal for attention may be.

Here we propose that in tinnitus there is a disparity between what the brain predicts it should be hearing (this representation incorporating aberrant neural activity underlying the tinnitus percept) and the acoustic information that is delivered to the brain by the damaged cochlea. In normal auditory perception such disparities activate a system for auditory attention and are resolved as the brain builds a more accurate central representation of the auditory scene. In tinnitus, however, the disparity persists owing to aberrant neural activity occurring in cortical regions affected by hearing loss that is not corroborated by sensory input arriving from the damaged auditory periphery. Auditory attention may remain active and facilitate (through basal forebrain or other neuromodulatory mechanisms) forms of neural plasticity that entrench aberrant neural changes underlying tinnitus sound. Looking ahead we consider questions raised by this hypothesis and implications in four areas of tinnitus research and treatment.

### 5.1. Is a concept of attention needed?

The viewpoint advanced here assumes that most cases of tinnitus are associated with hearing impairment detected by the audiogram (Roberts et al., 2008) or by more sensitive measures such as ABRs (Schaette and McAlpine, 2011; Gu et al., 2012) or abnormal loudness growth functions (Hébert et al., 2013) that reflect undetected damage to noise-sensitive high threshold auditory nerve fibers (Kujawa and Liberman, 2009). The resulting deafferentation is accompanied by changes in the response properties of auditory neurons and in network behavior expressed at several levels of the auditory projection pathway. However, one can question whether it is necessary to invoke a mechanism of auditory attention in this process, in order to understand the neural correlates and other properties of tinnitus. Could not persisting neural changes consequent on deafferentation be sufficient by themselves to explain phenomena such as (1) the privileged access of tinnitus-related neural activity to mechanisms for conscious awareness, (2) altered processing of sounds presented to the normal hearing ear of individuals with unilateral tinnitus (Cuny et al., 2004), (3) electrophysiological correlates of tinnitus expressed in attention-sensitive N1 and ASSR evoked potentials and the frequency dependence of the latter (Fig. 4), or (4) altered modulation of these responses by attended processing when evoked by sounds in the tinnitus frequency region of tinnitus subjects (Fig. 5)?

One answer to this question appeals to the fact that tinnitus is an audible conscious percept the awareness of which can be dynamically modulated by task involvement. Mutually suppressive interactions are known to exist among different sensory modalities (Johnson and Zatorre, 2005), which may contribute to modulation of tinnitus awareness when other sensory or top-down inputs are processed (Burton et al., 2012). Suppression of neural activity in a brain network supporting auditory attention might thus occur when awareness of tinnitus lapses. Alternatively, a gate to the global workspace in prefrontal or cingulate cortex may determine access of tinnitus-related neural activity to a system for conscious processing (De Ridder et al., 2011) while tinnitus-related activity remains unaffected. This hypothesis is better able to account for the subjective report of tinnitus sufferers that fluctuations in tinnitus awareness can be near-instantaneous. At present, the fate of tinnitus-related neural activity during modulation of its awareness by task involvement is unknown. Either way a modulatory mechanism of some type is implied, although it is not necessarily a neural mechanism supporting auditory attention.

It is known, however, that metabolic activity in brain regions involved in auditory attention is increased in individuals with tinnitus. Regions showing enhanced activity in tinnitus compared to individuals without tinnitus (particularly auditory core, belt, parabelt, and regions and auditory association cortex) are also areas that show increased metabolic activity in normal hearing individuals when auditory attention is experimentally manipulated with sensory input held constant (Paltoglou et al., 2009; Johnson and Zatorre, 2005, 2006; Voisin et al., 2006). The overlap of attention-related brain regions and those of tinnitus while not precisely co-extensive (Lanting et al., 2009; Plewnia et al., 2007b) invites an attention hypothesis. Variability between imaging studies of attention and tinnitus with respect to the specific auditory regions activated may relate to the auditory stimuli that are presented (Johnson and Zatorre, 2005) and the specific experiment procedures applied.

In future research other evidence for involvement of auditory attention in tinnitus may come from study of whether neural changes related to tinnitus are confined to the frequency regions of the tinnitus (these typically also the region of hearing

impairment) or extend beyond this frequency region in central auditory structures. If it is accepted that one role of a mechanism for auditory attention is to facilitate coding of novel sounds that are not predicted by the prevailing context, one would expect that the effects of this mechanism should be broadly tuned so as to be sensitive to the features of unknown inputs. Because cholinergic projections from the BF to the auditory cortex, while functionally and anatomically distinct from projections to other cortical sensory regions (Mesulam et al., 1983), do not appear to be selective for specific frequency bands, some of the neural changes associated with tinnitus (such as shifts in the balance of excitation and inhibition in central auditory structures, increased spontaneous activity, and increased central gain) could reflect engagement of this or other neuromodulatory mechanisms. Although present data are limited, animal studies suggest that while these particular changes are prominent in hearing loss regions, they may not be confined to this region (although changes in neural synchrony appear to be expressed at the hearing loss frequencies; Noreña and Eggermont, 2003). Similarly, hyperacusis putatively reflecting changes in central gain does not appear to be restricted to the tinnitus or hearing loss frequencies in humans reporting tinnitus (Noreña and Chéry-Croze, 2007; Hébert et al., 2013).

### 5.2. Role of the BF cholinergic and other neuromodulatory systems

We have suggested that neuromodulatory systems may play an important role in forging the neural changes that underlie tinnitus percepts. While the BF cholinergic system is a likely candidate for this role, little research to date has considered a role for this system in the generation and maintenance of tinnitus. This picture, however, may be changing. Stimulation of vagal afferents that project to the BF has been found to modify tonotopic organization when paired with sounds in the normal range of hearing, in an animal model of tinnitus (Engineer et al., 2011). Recently such stimulation has been shown to modulate cortical activity via afferent pathways that are sensitive to cholinergic blockade (Nichols et al., 2011). It would be of interest to learn whether prior lesioning of BF cholinergic system by immunotoxin (Ramanathan et al., 2009) or manipulation of it by other methods can modify or prevent the development of tinnitus in noise-exposed animals or reduce it if induced after noise exposure within a sufficient (therapeutic) time window. The most direct evidence for a role of attention in tinnitus could be provided by experiments that assess whether this system (or others known to support attention-like functions) contributes to or is necessary for the development or maintenance of tinnitus following hearing impairment.

We have highlighted a possible role for the BF cholinergic system in the model discussed here, because there is strong evidence that this system is involved in gating neural plasticity and other attention-like functions believed to be involved in tinnitus. A role for cholinergic pathways in the PMT as discussed earlier is also possible. This midbrain structure, which sends cholinergic projections to the medial geniculate body, inferior colliculus, and dorsal cochlear nucleus (Motts and Schofield, 2010), receives direct projections from layer V pyramidal neurons in primary auditory cortex that could exert a top-down influence on neural processing in subcortical auditory pathways (Fig. 1b). Other neuromodulatory systems that are associated with cognitive and behavioral functions and sensitive to perceptual disparity (Schultz and Dickinson, 2000) include noradrenergic projections from the locus coeruleus that modulate arousal and behavioral orienting (Sara and Bouret, 2012), dopaminergic neurons in the ventral tegmental area (VTA) which participate in motor control and reward-directed behavior (Tritsch and Sabatini, 2012), and serotonergic neurons

in the Raphe nucleus that affect brain functions associated most prominently with emotional processing (Lesch and Waider, 2012). The organization of these neuromodulatory systems is similar in the sense that their cell bodies are found in compact subcortical nuclei and send axonal projections to several forebrain regions including the striatum and cortex (Sara and Bouret, 2012). Because the systems act cooperatively to support behavioral adaptation, it is not surprising that there are numerous interactions among them at the neuronal and synaptic levels (Pawlak et al., 2010). In one example (Fig. 1a), dopaminergic neurons in the VTA project to the BF cholinergic system, the PFC, and the NAc, and are in turn contacted by projections from PFC, a circuitry that allows interactions between cholinergically mediated attention and the effects of dopamine which can change the properties of synapses in many brain areas by several mechanisms (Tritsch and Sabatini, 2012). The locus coeruleus (the sole source of noradrenergic input to higher centers) projects to other neuromodulatory nuclei and in turn receives input from cholinergic and serotonergic neurons as well as from the PFC enabling top-down communication among these systems. Yu and Dayan (2005) have proposed that noradrenergic pathways are particularly sensitive to gross violations of top-down expectancies, which might be considered to be the case when auditory representations predicted by the tinnitus brain do not correspond with sound information conveyed from the environment. Functional connections from the lateral hypothalamus to noradrenergic and other neuromodulatory subcortical nuclei by orexin-expressing neurons provide a further pathway for activation of modulatory systems by triggers for stress (Carter et al., 2013), which is acknowledged by patients to exacerbate their tinnitus. Interactions among neuromodulatory systems is an area of increasing neuroscience study using optogenetic and other new methods (Lee and Dan, 2012) that if applied to animal models of tinnitus may open uncharted territory yielding important advances.

Early concepts of the role of neuromodulatory systems in brain function emphasized their tonic, nonspecific effects on cortical processing, putatively achieved by volume release of neuromodulators at the synapse. However, while this view is supported by several lines of evidence (see Picciotto et al., 2012), it has been challenged by evidence for wired, function-specific effects and is evolving (Sarter et al., 2009). Using choline-sensitive microelectrodes in rats, Parikh et al. (2007) observed transient increases in acetylcholine in prefrontal cortex (putatively initiated from the BF) that lasted a few seconds and correlated with successful detection of a visual cue signaling reward; during trials where cues were missed, cholinergic transients did not occur. Tonic changes in cholinergic activity lasting minutes were also observed, which predicted stronger phasic signals. Tonic and phasic modes of release ranging from seconds to steady state have been described as well for other neuromodulatory systems (Goto et al., 2007), including time locked dopamine responses to reward-predicting stimuli (reviewed by Schultz, 2007). On the basis of such evidence Sarter et al. (2009) suggested that, although the projections of neuromodulatory systems exhibit a diffuse structured organization, neuromodulator release may act on heteroreceptors in local circuits to achieve highly specific functional effects. Clearly, the timing and mode of action of cholinergic and other putative neuromodulators is relevant to their possible role in the generation and maintenance of tinnitus. Understanding these roles, the specific receptors involved, and how neuromodulatory systems are affected by hearing loss could provide insight into whether pharmacological blockade during therapeutic windows might prevent neuroplastic changes leading to tinnitus or to its centralization in auditory pathways (Robertson et al., 2013). Elgoyhen et al. (2012) have described how brain pathologies dependent on brain network activity might better be treated by therapeutic “shotguns” aimed at

neurochemically diverse networks than by drugs targeting specific receptors.

### 5.3. Tinnitus and peripheral hearing function

While the question of whether chronic tinnitus is invariably associated with hearing impairment is currently debated (Weisz et al., 2006; Schaette and McAlpine, 2011; Gu et al., 2012), the existence of high frequency hearing impairment without tinnitus is beyond dispute (Roberts et al., 2008). The control groups reported in Figs. 4 and 5 are examples of such individuals (their ages and hearing thresholds in the range of 30–60 dB HL above 3 kHz were matched to those of the tinnitus subjects). One of the most important questions to be tackled going forward is to understand cases of hearing loss without tinnitus. One recent hypothesis has proposed that such cases may be explained by a pathology or neural trait affecting non-auditory brain regions that is independent of hearing loss but necessary for tinnitus when hearing loss is present (Rauschecker et al., 2010; Leaver et al., 2012). Alternatively, variable trajectories between individuals in age-related changes in intracortical inhibition may contribute to the expression of tinnitus when hearing loss is present (Caspary et al., 2008; Frisina, 2010). A third possibility concerns the nature and degree of peripheral cochlear pathology in cases where tinnitus is absent despite threshold shift. Threshold shift in the moderate range is generally thought to reflect mainly (although not exclusively) damage to outer hair cells. If inner hair cells surviving with intact ribbon synapses innervating high threshold ANFs generate a degree of driven or spontaneous ANF activity sufficient to preserve feed-forward inhibition and normal tonotopy (notwithstanding their low firing rates), aberrant neural synchrony may not develop, perceptual disparity will not be experienced, and mechanisms for change detection such as that described in Fig. 3 may not be activated. Evaluation of these and other hypotheses will require further study comparing hearing loss groups with and without tinnitus on more detailed measures of cochlear pathology that are sensitive to cochlear pathology not expressed in the audiogram (Tan et al., 2013). Group comparisons on measures of central auditory function and on markers for intracortical inhibition that are sensitive to aging could also be informative.

The model described here emphasizes the role of hearing loss in tinnitus and the maladaptive changes that occur in central auditory structures as a consequence of damage to the cochlea. However the specific pattern of damage that is present in the cochlea may be important in the generation of tinnitus in addition to any contribution arising from central adaptations (Noreña, 2011; Tan et al., 2013). The recent shift to central mechanisms in theorizing about tinnitus derived in part from evidence that sectioning the auditory nerve does not eliminate tinnitus in the majority of pre-existing cases (House and Brackmann, 1981), whereas sectioning the auditory nerve during surgery for acoustic neuromas causes tinnitus where it did not exist previously. However, while it is not a recommended procedure (Soleymani et al., 2011), section of the cochlear nerve has been reported to reduce tinnitus in a number of cases of tinnitus (Pulec, 1995), implying that processes taking place in the cochlea remain relevant to its generation (specific etiologies such as Meniere's disease may be relevant to this result). Frequency-specific hyperactivity in the inferior colliculus (IC) induced by noise trauma in guinea pigs is abolished by cochlear resection up to 6 weeks of trauma although not afterwards (Mulders and Robertson, 2009, 2011), suggesting that output from the damaged cochlea may contribute within this window to centralization of tinnitus percepts. It would be unfortunate if the current emphasis on central mechanisms dissuaded inquiry into the possible role of pathophysiological changes in the cochlea in contributing to the development of tinnitus percepts.

### 5.4. Tinnitus management

As noted previously, clinical experience and laboratory data tell us that one's conscious awareness of tinnitus sounds can be suppressed when individuals engage in cognitively demanding tasks, particularly of a non-auditory nature. Although its effects are fleeting, involvement in such tasks is one of the few procedures that can substantially modulate tinnitus awareness. Whether such experience has cumulative effects in tinnitus is not known, although recent treatment innovations are exploring the possibility (Searchfield et al., 2007, 2012a). The mechanisms underlying tinnitus suppression by task involvement are also largely unknown and may include inhibition of auditory regions by top-down structures in the global workspace as well as inhibitory interactions between sensory modalities that may be engaged by a task. One cannot say what benefits basic research into these mechanisms may yield for tinnitus management and treatment, but the question is significant given their ability to modulate tinnitus awareness for brief periods.

Understanding the role of attention in tinnitus may also be relevant to designing sound therapies for tinnitus. In normal hearing adult animals, it has been shown that continuous passive exposure to spectrally complex background sound can greatly reduce cortical representations for the exposure frequencies and modify the response properties of auditory neurons for these frequencies and for nearby frequencies (Noreña et al., 2006; Pienkowski and Eggermont, 2010, 2012; Pienkowski et al., 2013; Zhou and Merzenich, 2012). The question of whether neural representations are similarly modified when the background signals are given behavioral significance (that is, are attended to) is largely unknown but could be relevant to the treatment of tinnitus. In this connection it has been reported that auditory training procedures that require focused attention on the tinnitus frequencies appear to be less beneficial (Herraiz et al., 2010; Sereda et al., 2013) or not beneficial (Roberts et al., 2012) for tinnitus patients. However, when these frequencies are presented instead as passive background signals, evidence for a therapeutic effect has been reported in tinnitus patients (Davis et al., 2007, 2008; Tass et al., 2012) and in an animal model of hearing loss (Noreña and Eggermont, 2006), although not all findings are consistent (Vanneste et al., 2013). It is possible that background sounds presented passively suppress the call to attention and enable suppression of their cortical representations by providing tinnitus-corroborating input to auditory pathways. However, it is not presently known whether exposure to passive sound will reduce cortical representations when delivered to an animal model where hearing loss is present for the exposed frequencies. Inhibitory deficits consequent on reduced input from the damaged cochlea might enhance the cortical representations for these frequencies to the detriment of tinnitus, just as attended training in human tinnitus patients with hearing loss appears to do (Roberts et al., 2012). Research into whether modulation of cortical representations by passive sound is affected by hearing status and/or attention to the exposure frequencies in an animal model would be of value in guiding sensory therapies for tinnitus.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neubiorev.2013.07.007>.

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