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Review

An integrative model of auditory phantom perception: Tinnitus as a unified percept of interacting separable subnetworks

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ABSTRACT

Tinnitus is a considered to be an auditory phantom phenomenon, a persistent conscious percept of a salient memory trace, externally attributed, in the absence of a sound source. It is perceived as a phenomenological unified coherent percept, binding multiple separable clinical characteristics, such as its loudness, the sidedness, the type (pure tone, noise), the associated distress and so on. A theoretical pathophysiological framework capable of explaining all these aspects in one model is highly needed. The model must incorporate both the deafferentation based neurophysiological models and the dysfunctional noise canceling model, and propose a 'tinnitus core' subnetwork. The tinnitus core can be defined as the minimal set of brain areas that needs to be jointly activated (=subnetwork) for tinnitus to be consciously perceived, devoid of its affective components. The brain areas involved in the other separable characteristics of tinnitus can be retrieved by studies on spontaneous resting state magnetic and electrical activity in people with tinnitus, evaluated for the specific aspect investigated and controlled for other factors. By combining these functional imaging studies with neuromodulation techniques some of the correlations are turned into causal relationships. Thereof, a heuristic pathophysiological framework is constructed, integrating the tinnitus perceptual core with the other tinnitus related aspects. This phenomenological unified percept of tinnitus can be considered an emergent property of multiple, parallel, dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern and functional connectivity signature. Communication between these different subnetworks is proposed to occur at hubs, brain areas that are involved in multiple subnetworks simultaneously. These hubs can take part in each separable subnetwork at different frequencies. Communication between the subnetworks is proposed to occur at discrete oscillatory frequencies. As such, the brain uses multiple nonspecific networks in parallel, each with their own oscillatory signature, that adapt to the context to construct a unified percept possibly by synchronized activation integrated at hubs at discrete oscillatory frequencies.

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1. Introduction

Tinnitus is commonly defined as the perception of a sound in the absence of an external sound source. Perception is different from sensation. Whereas sensation can be defined as the detection and processing of sensory information, perception is the act of interpreting and organizing this sensory information to produce a meaningful experience of the world and of oneself (De Ridder et al., 2011a; Freeman, 1999). Auditory cortex activation evoked by an acoustic stimulus does not necessarily produce conscious auditory perception (Colder and Tanenbaum, 1999) and auditory perception is possible in the absence of auditory input: more than 80% of people with normal hearing perceive phantom sounds when placed in a soundproof room (Del Bo et al., 2008). Furthermore, some percepts do not reach the level of consciousness. Thus, in non-conscious perception or perception without awareness, the meaning of a stimulus is extracted while the subject cannot consciously identify it or even detect its presence (Dehaene et al., 1998). In addition, deafferentation of auditory input can result in an auditory phantom phenomenon called tinnitus. It is important to understand that some forms of auditory deafferentation are not discovered by behavioral measures such as audiometry (Weisz et al., 2006). Indeed, partial cochlear nerve sections can be performed without detectable changes in hearing thresholds (Dandy, 1941; Schuknecht and Woellner, 1953). This could explain why tinnitus can also occur in the absence of audiometrical hearing loss (Barnea et al., 1990; Lee et al., 2007; Weisz et al., 2006), as this does not preclude auditory deafferentation.

Whereas some people just perceive the phantom sound without being bothered, others suffer emotionally severely from their tinnitus (Axelsson and Ringdahl, 1989), with or without associated cognitive deficits (Hallam et al., 2004). Thus the unified tinnitus percept includes not just a sound percept but also affective components intimately linked to the sound percept.

Tinnitus is a symptom of high prevalence: 10 to 15% of the population in Europe and the USA have prolonged tinnitus requiring medical evaluation (Axelsson and Ringdahl, 1989; Hoffman and Reed, 2004). The prevalence increases with age (Axelsson and Ringdahl, 1989; Hoffman and Reed, 2004) and in noise-exposure, whether occupational (Axelsson and Prasher, 2000; Phoon et al., 1993) or leisure induced (Axelsson and Prasher, 2000; Gilles et al., 2012).

Tinnitus can be subdivided in two entirely different entities, one type in which an internal sound source can be objectivized by an external observer, also known as objective tinnitus, and one in which no perceivable sound source is present, also known as subjective tinnitus (Moller, 2000). Subjective tinnitus is commonly considered to represent an auditory phantom phenomenon (De Ridder et al., 2011a; Jastreboff, 1990). Other classifications describe pulsatile, non-pulsatile and pseudopulsatile tinnitus (De Ridder, 2011). Subjective non-pulsatile tinnitus is the scope of this review. Tinnitus can possibly be caused by different pathophysiological mechanisms (De Ridder et al., 2012c) and it can present itself in multiple forms. The tinnitus type can be different, it can be perceived as a pure tone, a noise-like percept, or polyphonic sound or a combination of these types, with different brain areas involved in the different percepts (Vanneste et al., 2010d), or hypothetically different pathways (De Ridder et al., 2007c). The tinnitus can be perceived unilaterally, bilaterally or holocranially. In bilateral tinnitus it can be perceived as one sound, or it can be perceived as two different sounds in the two ears, all likely to be associated with a different pathophysiology (De Ridder et al., 2007b; De Ridder et al., 2012b) and involving different brain areas (Vanneste et al., 2011a; Vanneste et al., 2011d). There are gender differences in the emotional aspects of tinnitus: in men and women with the same tinnitus intensity, the same tinnitus type and the same amount of distress, there are still differences in mood associated with differences in brain activation (Vanneste et al., 2012a). But most importantly tinnitus can be perceived as a sound with or without distress, with different brain areas involved in tinnitus distress (De Ridder et al., 2011c; Langguth et al., 2012; Schlee et al., 2009b; Schlee et al., 2008; van der Loo et al., 2011; Vanneste et al., 2010a; Weisz et al., 2011; Weisz et al., 2005a; Weisz et al., 2004; Weisz et al., 2005b).

2. Integrating different existing tinnitus models

The first conceptual tinnitus model that was proposed the neurophysiological model, considered tinnitus as an auditory phantom percept (Jastreboff, 1990). It explained the process by which tinnitus emerges, and divided it into three stages; (i) generation; (ii) detection, and (iii) perception and evaluation (Jastreboff, 1990; Jastreboff and Hazell, 1993). The generation could be attributed to many different causes, such as (1) discordant damage of outer (OHC) and inner (IHC) hair cell systems; (2) crosstalk between the VIII nerve fibers; (3) ionic imbalance in the cochlea; (4) dysfunction of cochlear neurotransmitter systems; (5) heterogeneous activation of the efferent system; (6) heterogeneous activation of Type I and II cochlear afferents. The detection was proposed to be based on a pattern recognition principle of decoding auditory information by neural network mechanisms (Jastreboff, 1990; Jastreboff and Hazell, 1993).The perception and evaluation process was proposed to involve different cortical as well as memory and limbic areas. (Jastreboff, 1990; Jastreboff and Hazell, 1993). The model suggests that the abnormal neural activity that causes tinnitus will be typically generated at the periphery of the auditory system, possibly in the dorsal cochlear nucleus (Jastreboff and Hazell, 2004; Kaltenbach, 2006) (see Fig. 1). This signal may then be detected and further processed in the subconscious part of the brain. Finally, it reaches the high cortical levels of the auditory system where it can

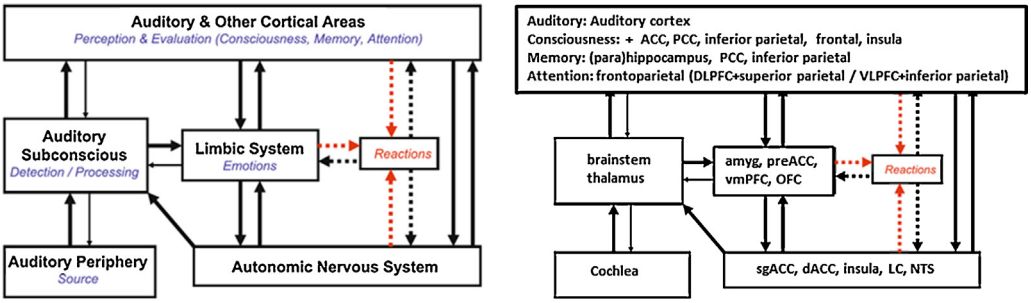

Fig. 1. Left image: the blackbox neurophysiological model proposed by Jastreboff (Jastreboff, 2011). Right image: the boxes filled in with the brain structures associated with the box's respective correlates. Some brain areas are represented in multiple boxes, suggesting the boxes actually are anatomically correlated with overlapping networks. ACC: Anterior Cingulate Cortex, PCC: Posterior Cingulate Cortex, DLPFC: Dorsolateral Prefrontal Cortex, VLPFC: Ventrolateral Prefrontal Cortex, Amyg:amygdala, PreACC: pregenual Anterior Cingulate Cortex, vmPFC:ventromedial Prefrontal Cortex, OFC: Orbitofrontal Cortex, LC: Locus Coeruleus, NTS: Nucleus Tractus Solitarius.

become perceived. If the abnormal activity that causes tinnitus is classified by the conscious and the subconscious brain as a neutral stimulus, then it is subsequently blocked from reaching conscious perception (habituation of perception) and it is not spreading to other systems in the brain, as there is no need for any action in response to its presence. Specifically, the limbic and autonomic nervous systems are not activated by such neural activity. This scenario happens spontaneously in the majority of persons with tinnitus. However when the abnormal activity is classified as important it will spread to other brain systems (Jastreboff and Hazell, 2004) (see Fig. 1).

Subsequent deafferentation based models modified some aspects of the neurophysiological model. The thalamocortical cortical dysrhythmia model explained the spectral changes seen associated with deafferentation (Llinas et al., 2005; Llinas et al., 1999), the central gain model focused on deafferentation based maladaptive gain processes (Norena, 2011) as an explanation for tinnitus and hyperacusis, and another model focused on deafferentation based homeostatic plasticity changes (Schaette and Kempter, 2006, 2012; Yang et al., 2011). Other modifications focused on neuronal synchrony (Eggermont, 2007; Tass et al., 2012) or map plasticity (Muhlnickel et al., 1998; Norena and Eggermont, 2005, 2006), but all had in common that the maladaptive brain changes (Moller, 2007) were based on deafferentation. Further refinements stressed the importance of multiple separable networks being involved in tinnitus, such as the salience network, memory network, distress network, loudness network etc. (De Ridder et al., 2011a) basically specifying the parallel networks already proposed in the neurophysiological model (Jastreboff, 1990).

The above-mentioned models have in common that they consider the brain as an adaptive system, adjusting to a lack of auditory input. Recently a new approach was proposed, suggesting the brain actively fills in the missing information. This is based on the view that the brain actively searches for auditory information in the environment in order to reduce environmental (auditory) uncertainty. The brain thus makes predictions about what it is likely to encounter next, and updates the prediction in a Bayesian way by sampling the environment (De Ridder et al., 2012c). Thereby the brain minimizes Shannonian (=informational) free energy, which has been proposed as a universal principle governing adaptive brain function and structure (Friston, 2010). Bayesian inference can be summarized as using sensory information from the environment to update (memory based) prior beliefs about the state of the world (that are held before acquiring sensory inputs) to produce posterior beliefs (that emerge after acquiring inputs). Auditory deafferentation, limits the amount of information the brain can acquire to make sense of the world. In other words, it increases the uncertainty inherently present in the environment. In order to minimize the Shannonian free-energy, i.e. to decrease topographically selective auditory uncertainty, the topographically deafferented brain area will attempt to obtain the missing information or fill in the missing information. The topographically specific deafferentation induces a topographically specific prediction error hypothetically based on temporal incongruity (De Ridder et al., 2011a), in other words it is inconsistent with what is stored in memory and should be updated. It has been proposed that this can be achieved using different mechanisms, depending on the bandwidth of the deafferentation. In a very limited amount of receptor loss, a selective increase of cortical excitability, either via increased excitatory tone or via reduced inhibitory tone will suffice (Rajan, 1998), and the missing information can be obtained via access of overlapping tuning curves of the neighboring cortical cells. If the deafferentation is somewhat larger a widening of auditory receptive fields (Chen et al., 1996) will permit to pull the missing information from the auditory cortical neighborhood. If this is insufficient, due to a still larger deafferentation, dendritic and axonal rewiring can occur (Hsieh et al., 2007), and if that doesn't work the missing auditory information can be pulled from (para)hippocampal memory. But in principle also this model is deafferentation based.

However, a very different approach was recently proposed, not focusing on the deafferentation causing tinnitus but on a lack of noise canceling (Leaver et al., 2011; Rauschecker et al., 2010). This concept is analogous to what has been described in the pain system, in which the presence of pain depends on a balance of afferent nociceptive pathways and descending anti-nociceptive pathways (Bingel and Tracey, 2008; De Ridder et al., 2012d). This model proposes that the loudness percept is generated as a consequence of a dysfunctional noise suppressing mechanism, which could be limbically driven (Leaver et al., 2011; Rauschecker et al., 2010). Based on structural and functional changes in the subgenual/vmPFC it has been postulated that tinnitus is the result of a deficient sensory attentional gating mechanism, originating in the subgenual cingulate cortex/nucleus accumbens area and acting on the reticular thalamic nucleus (Leaver et al., 2011; Muhlau et al., 2006; Rauschecker et al., 2010), thereby interfering with reverberating thalamocortical activity. However, not only the loudness perception is modulated by the subgenual anterior cingulate cortex. The amount of distress perceived by tinnitus patients is related to alpha activity in a network encompassing the subgenual anterior cingulate cortex and insula, extending to the amygdala-hippocampus and parahippocampus (De Ridder et al., 2011c; Vanneste et al., 2010a). Thus it is likely that the emotional state influences the loudness perception and/or vice versa. The exact anatomical noise canceling pathway hasn't been elucidated yet, but it has been proposed to involve the vmPFC/ACC (Leaver et al., 2011; Rauschecker et al., 2010), the reticular nucleus of the thalamus (Leaver et al., 2011; Rauschecker et al., 2010) and the tectal longitudinal column

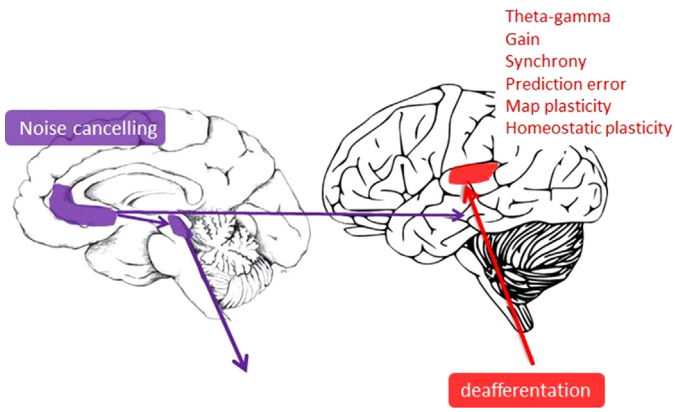

Fig. 2. Deafferentation based pathophysiological changes (red) and noise canceling mechanism (purple). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(De Ridder et al., 2012d). The tectal longitudinal column can be considered the auditory equivalent of the periaqueductal gray, which is part of the descending anti-nociceptive system (Saldana et al., 2007). It is a recently discovered auditory structure present in all mammals investigated, adjacent to the periaqueductal gray, connected to the auditory cortex (Saldana et al., 2007), and based on its electrophysiological properties considered part of an descending auditory system (Marshall et al., 2008).

The current integrative model wants to unify the abovementioned models (see Fig. 2) and to describe putative neural correlates of a tinnitus core, related to the phantom sound percept per se, and to integrate the different brain areas and networks that have been associated to the other aspects of tinnitus, such as spatial localization, tinnitus type, tinnitus related distress, tinnitus related depression etc. in one model. In other words, this paper basically attempts to fill in the boxes of the 'blackbox' neurophysiological model (see Fig. 1) and extends it by proposing the hypothetical neural core of conscious phantom sound perception per se, which is more extensive than the initially proposed auditory system (Jastreboff and Hazell, 2004). The integrative model proposes mechanisms that can physiologically explain how the different parallel (Jastreboff, 1990) and overlapping (De Ridder et al., 2011a; Vanneste and De Ridder, 2012a) networks interact via oscillatory mechanisms (Palva and Palva, 2012). It furthermore attempts to explain the electrophysiological spectral oscillatory changes seen in tinnitus from a Bayesian point of view and to combine the deafferentation based and dysfunctional noise canceling mechanism in one integrative model (see Fig. 2).

Historically the ear was considered the sole cause of tinnitus, and later the auditory cortex was proposed as the seed of the neural code of tinnitus (Jastreboff, 1990; Muhlnickel et al., 1998; Weisz et al., 2007). Anatomically (Schneider et al., 2009) and functionally (Muhlnickel et al., 1998) the auditory cortex in people suffering from tinnitus seems to be altered. People with tinnitus exhibit significantly smaller gray matter volumes in the medial part of Heschl's gyrus than controls (Schneider et al., 2009): in unilateral tinnitus, in the hemisphere ipsilaterally to the affected ear, in bilateral tinnitus in both hemispheres (Schneider et al., 2009). The tinnitus-related volume reduction was found across the full extent of Heschl's gyrus, and not tonotopically restricted (Schneider et al., 2009). However, there was also evidence for a relationship between volume reduction and hearing loss, which has been confirmed by another study (Husain et al., 2011). Since this study found only correlations with hearing loss and not with tinnitus it is likely that the structural changes possibly reflect the hearing loss rather than the tinnitus. This could be related to the deafferentation seen in the lemniscal pathway in deafferentation, as demonstrated by changes in parvalbumin staining (Cervera-Paz et al., 2007).

Not only the structural anatomy is altered, also the functional anatomy is altered. It has been shown that the auditory cortex is reorganized: a marked shift of the cortical representation of the tinnitus frequency into an area adjacent to the expected tonotopic location has been observed. In addition, a strong positive correlation was found between the subjective strength of the tinnitus and the amount of cortical reorganization (Muhlnickel et al., 1998). In view of the Bayesian brain model as described above it has been proposed that tinnitus can exist without this map plasticity (De Ridder et al., 2012c), a hypothesis which has been recently confirmed by an fMRI study in patients without hearing loss (Langers et al., 2012), as predicted by the Bayesian brain model.

Non-auditory brain areas have also shown altered structure in people with tinnitus (Vanneste and De Ridder, 2012a). Voxel based morphometry studies have demonstrated changes in the ventromedial prefrontal cortex (Muhlau et al., 2006) and hippocampus (Landgrebe et al., 2009). However another study could not find VBM changes related to tinnitus (Husain et al., 2011). Functional imaging studies also showed activity in non-auditory brain areas such as the frontal lobe (Mirz et al., 1999), anterior (Plewnia et al., 2007b) and posterior cingulate cortex (Mirz et al., 2000; Plewnia et al., 2007a), precuneus and inferior lateral parietal cortex as well as the cerebellum (Lanting et al., 2009). These changes cannot be accounted for if the pathophysiology of tinnitus is limited to the auditory cortex.

Severe tinnitus can lead to distress (Budd and Pugh, 1996), anxiety (Bartels et al., 2008), depression (Dobie, 2003; Langguth et al., 2011a), cognitive dysfunction (Hallam et al., 2004), insomnia (Cronlein et al., 2007) and to an important decrease in the quality of life (Bartels et al., 2008). Thus–in contrast to the narrow definition given above, namely that tinnitus is the perception of a sound in the absence of an external sound source – a person's unified tinnitus percept is a complex percept encompassing multiple separable clinical cognitive and emotional aspects. It therefore becomes clear that an exclusive focus on the auditory cortex is not sufficient to understand tinnitus in a clinically relevant sense and that researchers in this area will also need to consider the importance of distributed networks (Elgoyhen et al., 2012). The question is whether the aforementioned separate aspects of tinnitus are all represented by alternative subnetworks, working in parallel, possibly partially overlapping and dynamically changing depending on the evolving severity of each aspect, the duration or other modulating factors such as context (e.g. stress, fatigue, etc.).

A theoretical pathophysiological framework capable of explaining all these aspects in one model is highly needed. By operationally defining tinnitus as a problem of persisting auditory awareness of a sound in the absence of an external auditory stimulus, tinnitus can be tackled from studies focusing on auditory consciousness. Two separate approaches can be followed: one neurophysiological approach looking at oscillatory characteristics of auditory conscious perception and tinnitus, and another approach that tries to delineate the neuroanatomy of auditory conscious perception and tinnitus. These latter studies are principally investigating brain activity in vegetative state patients and sleep states, and have demonstrated that auditory cortical activity is a prerequisite but is not sufficient for auditory consciousness (Boly et al., 2005; Laureys et al., 2000a). The activity has to be linked to the consciousness supporting brain networks (Demertzi et al., 2012) of a global workspace in order to gain access to consciousness (Bekinschtein et al., 2009; Dehaene et al., 2006). The global workspace has not been anatomically specified, and might involve multiple subnetworks in order to bring stimulus related sensory cortex activity to consciousness. This could be related to the fact that a stimulus only has relevance, irrespectively of whether it is externally triggered or pulled

from memory, if this stimulus is referenced to the self and if it is salient. It should be specified that salience has two meanings in neuroscience, which might be interrelated but are clearly separable (Serences and Yantis, 2006). In visual research salience refers to the physical, bottom up distinctiveness of a stimulus, i.e. the ability of a stimulus to stand out of his neighbors (Yantis, 2005), whereas in network science salience refers to the top-down intentionality driven behavioral relevance of the stimulus (Fecteau and Munoz, 2006).

The model must incorporate a 'tinnitus core' subnetwork, the minimal assembly of brain areas required for the auditory phantom perception per se, in other words the neural correlates of the tinnitus sound percept, following the definition of the neural correlates of consciousness by Crick and Koch (Crick and Koch, 1995, 2003). This would reflect the minimal brain network activity required to perceive tinnitus, but without being distressed or bothered by its presence.

As the person with tinnitus perceives a sound which is externally attributed but not present in the environment, a proposal for the tinnitus core can be distilled from studies investigating the neural correlates for auditory pitch awareness, combined with neural correlates of auditory pitch memory. The common brain areas associated with pitch awareness, both memory derived and by externally presented auditory stimuli might represent the tinnitus core. It can be hypothesized that areas that change activity when 'someone returns from oblivion' (Langsjo et al., 2012) hold the key to delineating the tinnitus core network.

The studies on spontaneous resting state magnetic and electrical activity of specific aspects of tinnitus (e.g. loudness, side etc.) while controlling for all other aspects can be used as a first attempt to delineate the subnetworks involved in the characteristics of tinnitus and by combining these functional imaging studies with neuromodulation techniques some of the correlations can be turned into causal relationships (Langguth et al., 2012).

Therefore, a heuristic pathophysiological framework is constructed, integrating the tinnitus perceptual core with the other tinnitus related aspects.

The phenomenologically unified tinnitus percept can be considered an emergent property of multiple, parallel, dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern and functional connectivity signature. These subnetworks (e.g. lateralization, mood, distress) can be nonspecific and similar to those of other pathologies. For example the network involved in tinnitus distress is similar to the distress network described in pain (Moisset and Bouhassira, 2007), social rejection (Masten et al., 2009), dyspnea in asthma (von Leupoldt et al., 2009) and functional somatic syndromes (Landgrebe et al., 2008). Communication between these different subnetworks is proposed to occur at hubs, i.e. brain areas that are involved in multiple subnetworks simultaneously. These hubs can take part in each separable subnetwork at different frequencies. Communication between the subnetworks most likely occurs at discrete frequencies.

3. Tinnitus is a problem of persistent auditory consciousness

Tinnitus can be seen as a problem of persistent auditory consciousness in the absence of an external auditory stimulus. When trying to unravel the mechanisms that generate tinnitus from this approach, consciousness and specifically auditory consciousness have to be investigated.

Consciousness is ill defined, and multiple different definitions exist, some of which, such as the dualist definition of consciousness as an immaterial entity distinct from matter (brain) are not amenable to scientific research (Tassi and Muzet, 2001). Consciousness has been defined as being aware of things, and things may be objects outside ourselves, or in our own memories, thoughts and feelings (Niedermeyer, 1994). This suggests that consciousness is a multifaceted concept that has at least two major components: awareness of environment and of the self (e.g. the content of consciousness) and wakefulness (e.g. the level of consciousness) (Laureys, 2005) (see Fig. 3).

In view of this multifaceted approach to consciousness, tinnitus can be defined as a pathological awareness of a non-existing sound in the environment, as a kind of hyperconsciousness. In this sense consciousness can be seen as a spectrum with on one hand a decrease in auditory consciousness, such as in sleep, coma, anesthesia, vegetative and minimally conscious states, and on the other side of the spectrum increases in auditory consciousness such as in tinnitus or auditory hallucinations. This has to be differentiated from hearing loss or hyperacusis, where auditory consciousness is intrinsically not changed, but only the sensitivity to acoustic stimuli is changed.

3.1. Neuroanatomy of auditory consciousness

Wakefulness is driven by activity from the dorsal raphe, nucleus coeruleus and pedunculopontine nucleus in the posterior pontomesencephalic area, under control of the hypocretin system in the dorsolateral hypothalamus (Sutcliffe and de Lecea, 2002; Zhang et al., 2010). This has been confirmed by PET studies in sleep (Braun et al., 1997; Maquet et al., 2005) and patients in vegetative state (Boly et al., 2005; Boly et al., 2004; Laureys, 2007), in other words in patients without awareness. Normally wakefulness and awareness are linked, one has to be awake to be aware (Laureys, 2005). In states of coma, anesthesia and deep sleep there is little or no wakefulness and hence no awareness. In light sleep (drowsiness) there is more awareness. But some dissociations between wakefulness and awareness exist, such as in the dream state there is awareness with decreased wakefulness and in the vegetative state there is wakefulness presumably without awareness (Laureys, 2005).

It is impossible to dissociate awareness from the self. A stimulus that leads to a conscious percept only makes sense if it is related to and incorporated to the person's self-percept. In David Hume's words: "The self is nothing but a bundle of interconnected perceptions" (Hume, 1740). Therefore, the self-perception network, consisting of the anterior cingulate cortex, ventromedial prefrontal cortex, posterior cingulate cortex, precuneus, superior frontal-parietal area, and superior temporal sulcus (Svoboda et al., 2006) most likely has to be activated for the tinnitus to be consciously perceived (see Fig. 4). The fact that "I" hear a stimulus as coming from externally can only be accounted for if the external stimulus is attributed to a source distinct from the self. Some of the areas that are visualized in tinnitus studies, especially studies related to spatial localization (e.g. unilateral versus bilateral tinnitus (Vanneste et al., 2011d), left versus right sided tinnitus (Vanneste et al., 2011a)) might therefore be related to the self-perception network, rather than to the phantom sound percept.

Furthermore, based on neural Darwinism (Edelman, 1993), especially (but not exclusively) those stimuli that are salient (behaviorally relevant) will gain access to consciousness. Salience is a mechanism involved in prioritizing among the large amount of ongoing competing internal and external stimuli. Thus, a network which unites conflict monitoring, interoceptive-autonomic, and reward-processing centers has been delineated as the 'salience network' (Seeley et al., 2007). This salience network consists of the dorsal anterior cingulate cortex, anterior insula, amygdala as well as the dorsomedial thalamus, putamen, pregenual anterior cingulate cortex, periaqueductal grey, hypothalamus and ventral tegmental area (Seeley et al., 2007). Commonly the core of this network, the

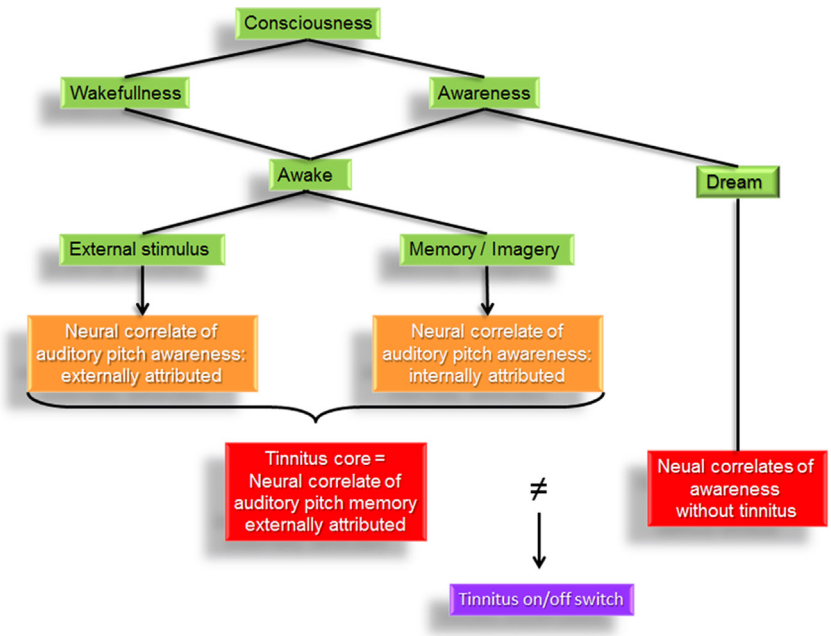

Fig. 3. Rationale for distilling the neural correlates of tinnitus (tinnitus core) and on/off switch in tinnitus based on studies of auditory consciousness. Consciousness is a multifaceted concept that has at least two major components: awareness of environment and of the self (e.g. the content of consciousness) and wakefulness (e.g. the level of consciousness). Awareness is present both in the awake and dream state. In the awake state an external stimulus can trigger awareness, or one can be aware of an internally generated idea, song etc. The tinnitus core, meaning the neural correlates of the phantom sound without its affective components, can theoretically be distilled from a comparison of auditory pitch memory and auditory pitch awareness by external stimuli. In auditory pitch memory the person does not attribute the sound as coming from externally, whereas in pitch awareness the sound is not spontaneously internally generated. In dreams there is awareness but no tinnitus perception. Thus when comparing the neural correlates of dream awareness with the neural correlates of the tinnitus core (while awake), the putative on/off switch could theoretically be retrieved.

dorsal anterior cingulate cortex and anterior insula, are defined as regions of interest in functional imaging studies that evaluate salience (Sadaghiani et al., 2009; Taylor et al., 2008; van Marle et al., 2010) (see Fig. 3).

Functional imaging studies have illustrated the relevance of the salience network in conscious perception by demonstrating that fluctuations in the dorsal anterior cingulate cortex and anterior insula activity determine whether an auditory stimulus becomes detected or not (Sadaghiani et al., 2009), identical to what has been described for the somatosensory system (Boly et al., 2007). Thus, activity elicited in the auditory cortex by an external sound only reaches awareness when there is co-activation of the salience network comprised of the dorsal anterior cingulate cortex and the anterior insula. This does not imply that the salience network is part of the neural correlates of auditory consciousness, it might be a prerequisite (Aru et al., 2012; de Graaf et al., 2012). And indeed, when remembering a pitch these same areas are deactivated (Rinne et al., 2009), suggesting they are involved in auditory awareness, but differentially activated when auditory awareness is triggered by an external stimulus or is pulled from memory.

3.2. The neural correlate of auditory consciousness

As stated in the definition (Niedermeyer, 1994) one can be aware of things from the environment or from our memory. The neural correlates of (auditory) consciousness have been defined as the minimal neuronal mechanisms jointly sufficient for any (auditory) conscious percept (Crick and Koch, 2003). Thus when looking for the neural correlates of auditory awareness both the neural correlates of auditory pitch perception evoked by external auditory

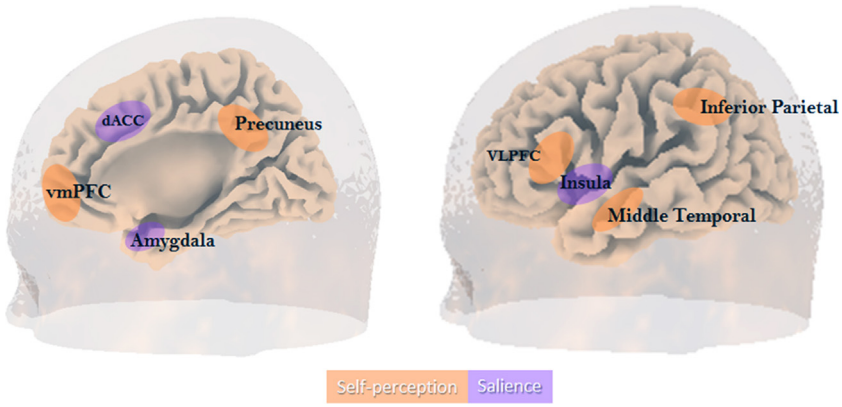

Fig. 4. Salience and self-perceptual networks. When the dorsal anterior cingulate cortex and anterior insula are active, an external auditory stimulus is consciously perceived (Sadaghiani et al., 2009), when the dACC and insula are deactivated, auditory information is pulled from memory (Rinne et al., 2009). Tinnitus chronification might be critically linked to a persisting abnormal salience attached to the phantom sound. Tinnitus is perceived as coming from an external sound source. This is only possible if the sound is related to self-perceptual network activity. dACC: dorsal anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex, VLPFC, ventrolateral prefrontal cortex.

stimuli have to be described as well as the neural correlates of auditory pitch memory (see Figs. 2 and 4).

It has been suggested by Crick and Koch that in the visual system V1 activation is necessary but insufficient for visual awareness (Crick and Koch, 1990; Crick and Koch, 1995), and similar claims are made for the other primary sensory cortices, including the primary auditory cortex (Meyer, 2011). It has further been proposed that only activity induced in the primary sensory cortices through cortico-cortical top-down signals can become consciously accessible, whereas activity induced by bottom-up signals from the thalamus cannot (Boly et al., 2011; Meyer, 2011). This is consistent with the brain as a prediction machine, where based on intentionality the external and internal environment is sampled for salient information (De Ridder et al., 2012c). This requires top-down attentional selection to behaviorally relevant information in the environment worthwhile of further conscious processing (De Ridder et al., 2012c). Thus, isolated activity in the primary auditory cortex is most likely not sufficient to generate the conscious percept of tinnitus. Indeed, it has been shown that the activation associated with auditory stimuli is restricted to the primary auditory cortex bilaterally in patients in a persisting vegetative state without functional connectivity between the secondary auditory cortex and temporal and prefrontal association cortices (Boly et al., 2004), similarly to what has been shown for pain processing (Boly et al., 2005). Based on these data, it can be proposed that activity restricted to the primary auditory cortex does not lead to auditory conscious perception, similarly to the somatosensory and visual system, but that this auditory activity becomes conscious when functionally connected to consciousness supporting networks (Demertzi et al., 2012) such as the anterior cingulate cortex/ventromedial prefrontal cortex and frontopolar cortex (Laureys et al., 2000b; Meyer, 2011).

A recent study looking for the neural correlates of auditory awareness of pitch indicated that it is related to a bilateral network, including Heschl's gyrus, the middle temporal gyrus, the right inferior, and the frontopolar gyri (Brancucci et al., 2011) (see Fig. 5). The conscious experience of perceived side is instead accompanied by later activity observed bilaterally in the inferior parietal lobe and in the superior frontal gyrus (Brancucci et al., 2011) (see Fig. 5). However conscious detection or identification of pitch is still different from discriminating a pitch, which is performed by an integrated action between the anterior cingulate cortex and the hippocampus (Schwenzer and Mathiak, 2011).

Auditory memory for pitch involves the superior temporal gyrus, supramarginal gyrus (= inferior parietal gyrus), posterior dorsolateral frontal regions, superior parietal regions, and dorsolateral cerebellar regions bilaterally as well as the left inferior frontal gyrus (Gaab et al., 2003; Grimault et al., 2009; Koelsch et al., 2009) (see Fig. 5). When training pitch memory, good learners suffice with increased activity in the left Heschl's gyrus as well as in the left posterior superior temporal and supramarginal gyrus, while those who have more difficulty memorizing pitch, increase activity in the left Heschl's gyrus and anterior insular cortex as well as in a lingual–orbitofrontal–parahippocampal network (Gaab et al., 2006).

Even though there is activation of the auditory cortex in auditory memory, it is very limited, only marginally bigger than auditory cortex activation in visual memory and less than in visual imagery (Huijbers et al., 2011). This could be related to the fact that auditory memory at the level of the auditory cortex involves only map plasticity (Weinberger, 2004) or synchronization measures which do not require extra energy consumption (Buzsaki and Draguhn, 2004) and thus do not activate on fMRI or PET scan.

In summary, retrieving a sound from memory minimally involves the inferior parietal area and likely also the auditory cortex (Gaab et al., 2003; Rinne et al., 2009). Cathodal (i.e. suppressive) tDCS of the inferior parietal (supramarginal) cortex can indeed disrupt auditory pitch memory (Vines et al., 2006). Other areas such as the ventrolateral prefrontal cortex, orbitofrontal cortex, orbitofrontal cortex, dorsolateral prefrontal, superior parietal area, parahippocampal area might also be involved (see Fig. 5).

The neural correlate of auditory pitch can be considered the common activity of the exteroceptive auditory awareness and auditory pitch memory, and consists of the auditory cortex–ventrolateral prefrontal cortex/frontopolar cortex, i.e. the auditory cortex and those areas that are functionally disconnected from the auditory cortex in the vegetative state.

3.3. The neuroanatomy of tinnitus

Based on the neural correlate of auditory awareness, a core tinnitus subnetwork can be described, consisting of the minimal amount of brain areas that jointly suffice to generate the phantom sound, irrespective of its perceived location, loudness, and emotional and cognitive aspects.

The neural correlate of tinnitus, the tinnitus core, as an internally generated conscious auditory percept in the absence of a sound stimulus should consist of areas that are involved in both the neural correlates of auditory pitch awareness and the neural correlates of auditory pitch memory. These are the auditory cortex, inferior parietal area and ventrolateral prefrontal/frontopolar cortex. Thus the combination of these neural correlates is expected to encompass the neural correlates of tinnitus but does not equal them.

However, tinnitus is characterized by the perception that the phantom sound comes from an external sound source, even though the sound might be pulled from memory (De Ridder et al., 2006b; Shulman, 1995). This is reminiscent of a dream state, when there is awareness, with stimuli attributed to the external world but generated internally (Hobson, 2009).

People with tinnitus do not perceive tinnitus in their dreams (Klaps & De Ridder, unpublished data: in a questionnaire in 80 members of the VLATI, the Flemish Tinnitus association and 100 patients on consultations, only 4 of 100 people perceived tinnitus in their dreams), analogous to what is reported for many phantom limb perceptions (Alessandria et al., 2011; Mulder et al., 2008). Dreams and wakefulness are both associated with awareness, but in one state of awareness there is no tinnitus (sleep), whereas in the other (wakefulness) there is tinnitus.

The reason why patients with tinnitus do not perceive tinnitus in their dream state can be theoretically explained by the Bayesian brain model which has been used as an explanation for the development of tinnitus in relation to auditory deafferentation (De Ridder et al., 2012c). When we dream, we create an image of the world entirely within our own brains that is detached from sensory feedback (Hobson and Friston, 2012). This is mediated via aminergic decline in REM sleep: aminergic activity is highest during waking, declines during NREM sleep and is lowest during REM sleep; whereas cholinergic activity shows the reverse pattern (Hobson and Friston, 2012). As the precision of sensory prediction errors is suppressed by aminergic gating during sleep, there are no sensory surprises (Hobson and Friston, 2012). This means that the discrepancy between top-down predictions and (the absence of) sensory signals received will not be registered, and the auditory deafferentation will not be filled in, resulting in the absence of tinnitus in the dream state.

In the dream state, characterized by Rapid Eye Movement (REM) sleep, the ventrolateral prefrontal cortex and inferior parietal area, as well as the medial parietal area (left parahippocampus, posterior cingulate cortex extending to precuneus) and the cerebellum are less active than in the awake state (Braun et al., 1997; Maquet et al., 1996; Maquet et al., 2005).

As the inferior parietal area is strongly related to auditory pitch memory, and is less active in dream state, this possibly suggests the

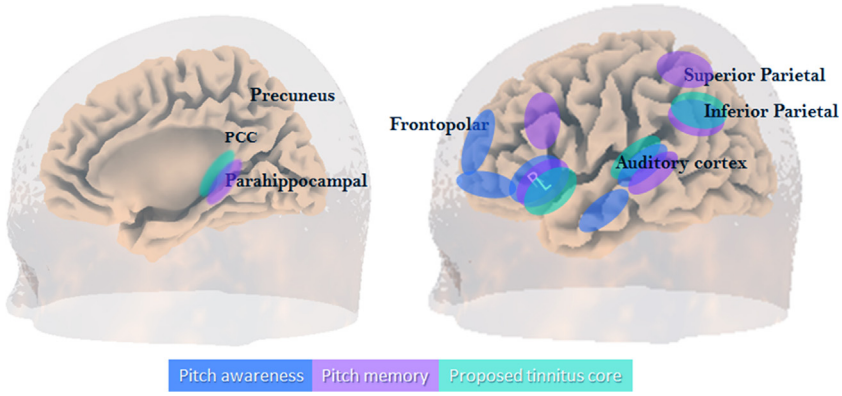

Fig. 5. Brain areas involved in auditory pitch awareness (blue) and pitch memory (lila). The putative neural correlates of tinnitus are superposed (green), in other words the minimal joint brain activity required for tinnitus perception. PCC: posterior cingulate cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

phantom sound is not pulled from memory any more, and therefore not perceived in dreams. The ventrolateral prefrontal cortex, which is also less active in dream state than in wakefulness, is involved in external auditory stimulus awareness and might thus also be involved in the tinnitus core. The putative on/off switch for tinnitus is to be found in these areas (see Fig. 2).

The parahippocampal area has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas. A dysfunction of this mechanism resulting in a gating dysfunction for irrelevant or redundant auditory input (Boutros et al., 2008) has been proposed as an explanation for complex auditory phantom percepts such as auditory hallucinations (Diederen et al., 2010). This is most likely mediated via its sensory gating function for irrelevant or redundant auditory input (Boutros et al., 2008). As the parahippocampal area is involved in tinnitus and tinnitus distress (Vanneste et al., 2010a), a similar mechanism could be relevant for tinnitus.

In summary, the core tinnitus network likely consists of the VLPFC–inferior parietal area – parahippocampal and auditory cortices (see Figs. 5 and 6). This is confirmed by an ALE meta-analysis of PET studies of tinnitus (Song et al., 2012). The most consistently activated regions in a recent meta-analysis of PET studies in tinnitus subjects in comparison to controls do involve the tinnitus core areas such as the left primary- and bilateral secondary auditory cortices (A2), the left parahippocampal area, the right middle- and inferior frontal gyri, and the right angular gyrus, as well as other areas such as the left geniculate body, the left middle- and bilateral inferior temporal gyri, the left precuneus, the right anterior cingulate cortex, as well as the right claustrum (Song et al., 2012). Further support for the causal involvement of the VLPFC and parietal area comes from 2 recent TMS studies targeting the VLPFC (Vanneste and De Ridder, 2012b) and parietal area (Vanneste et al., 2012b) which results in a transient improvement of the tinnitus.

3.4. Neurophysiological correlates of auditory consciousness

The emergence of a unified percept relies on the coordination of scattered mosaics of functionally specialized brain regions (Varela et al., 2001). Large-scale integration has been proposed to bind the distributed anatomical and functional organization of brain activity enabling the emergence of coherent behavior and cognition. Although the mechanisms involved in large-scale integration are still largely unknown, it has been convincingly argued that the most plausible candidate is the formation of dynamic links mediated by synchrony over multiple frequency bands (Varela et al., 2001). Although within-frequency phase synchronization may support the binding of anatomically distributed processing, it cannot coordinate neuronal processing distributed into distinct time windows or frequency bands (Palva and Palva, 2012). The binding of anatomically, spectrally and temporally distributed processing could, however, be carried out by nested oscillations (phase–amplitude interactions) or by phase–phase interactions, such as n:m phase synchrony, at discrete frequencies (Palva and Palva, 2012), as shown in both invasive human recordings (Canolty et al., 2006) and with M/EEG recordings related to sensory awareness (Monto et al., 2008).

3.4.1. Gamma band activity and consciousness

The EEG power spectrum (of the oscillation rate) and the level of wakefulness are correlated (Zeman, 2002). Slow delta frequencies (0.5–4 Hz) are recorded in patients under deep sleep, anesthesia, and coma. Somewhat higher frequencies, called theta waves (4–7 Hz), are noted in light sleep, and alpha waves (8–12 Hz) are recorded from all sensory areas in a resting state. Frontal beta waves (13–30 Hz) are recorded predominantly when people pay attention to external or internal stimuli. Beta band activity is associated with a continuation of the cognitive set and the dominance of endogenous top-down influences that override the effect of potentially novel, or unexpected, external events, which would be reflected by gamma band activity. Thus, beta activity is related to imposing a maintenance of the sensorimotor set during the next processing step or in other words to signaling the status quo (Engel and Fries, 2010). Synchronization of separate gamma-band activities (30–80 Hz), present in different thalamocortical columns (Steriade, 2000), is proposed to bind (Gray et al., 1989; Gray and Singer, 1989) distributed neural gamma activity into one coherent auditory percept (Crone et al., 2001; Joliot et al., 1994; Llinas et al., 1998; Llinas et al., 1994; Ribary et al., 1991; Tiitinen et al., 1993). Sound intensity is also reflected by the amount of gamma band activity (Schadow et al., 2007). In general, coherent gamma band activity is present only in locally restricted areas of the cortex for short periods of time (Buzsaki and Draguhn, 2004; Canolty et al., 2006; von Stein and Sarnthein, 2000). Whereas normally gamma activity waxes and wanes, related to the presence of a novel external stimulus, persisting gamma activity localized in one brain area can be considered pathological. Recent data from the visual system suggest that stimuli that reach consciousness and those which do not reach consciousness are characterized by a similar increase of local gamma oscillations in the EEG (Gaillard et al., 2009; Melloni et al., 2007). Thus, gamma band activity, per se, is not related to conscious perception, but could be a condition sine qua non, an essential prerequisite, for conscious perception.

3.4.2. Nested activity and awareness

It has been proposed that transient coupling between low and high frequency brain rhythms coordinates activity in distributed cortical areas, providing a mechanism for effective communication during cognitive (Canolty et al., 2006), memory (Buzsaki and Draguhn, 2004; Lisman and Buzsaki, 2008), and auditory processing (Doesburg et al., 2012). This is based on the concept that gamma oscillations integrate local information whereas theta activity integrates information over long distances (von Stein and Sarnthein, 2000). Thus theta-gamma coupling permits synchronization of different spatially distant local areas if the gamma power is coupled to the theta phase (Canolty et al., 2006).

In auditory attention the theta phase determines gamma power in the superior temporal gyrus, inferior and superior parietal area and the inferior frontal area (Doesburg et al., 2012). Learning furthermore alters the theta-gamma coupling, producing potentiation in neural networks simply through altering the temporal pattern of their inputs (Kendrick et al., 2011). Thus theta activity can indeed be a carrier wave synchronizing multiple areas of locally restricted gamma band activity into one widespread gamma network.

Based on the free energy principle as an explanation for the emergence of tinnitus related to auditory deafferentation, auditory prediction and Bayesian updating should be linked to theta-gamma activity as well. According to the free-energy principle the brain must minimize its prediction errors about its environment. As mentioned, the topographically specific deafferentation induces a topographically specific prediction error hypothetically based on temporal incongruity (De Ridder et al., 2011a), in other words it is inconsistent with what is stored in memory and should be updated. The auditory prediction that tries to reduce environmental uncertainty relates both to 'when' and 'what' auditory stimulus is likely going to arrive, and it has been proposed that auditory (and other sensory) predictions are related to specific oscillatory activity. Whereas predicting 'when' predominantly involves low-frequency delta and theta oscillations, predicting 'what' points to a combined role of gamma and beta oscillations (Arnal and Giraud, 2012). Beta and gamma oscillations could underlie the flow of information in opposite directions, that is, forward vs. backward. Along the lines of predictive coding, this suggests that prediction errors could be propagated in a feed-forward manner, mainly using the gamma frequency band, whereas predictions (and their revisions) could be transmitted 'backward' using mainly the beta band (Arnal 2012). Thus, beta oscillations may synchronize neuronal populations that encode expected sensory inputs: if the input is correctly anticipated, evoked gamma activity could be limited to the population 'pre-synchronized' by beta oscillations, and conversely, if the neuronal population recruited by sensory stimulation differs from the pre-activated one, gamma activity would be proportional to prediction error (e.g., a spatial mismatch) (Arnal and Giraud, 2012). Thus the increased gamma activity in tinnitus would be related to a deafferentation related (thalamocortical column specific spatial mismatch) prediction error, and the nesting on theta or delta related to its temporal prediction.

Whether theta or top-down beta activity could also be an electrophysiological representation of the noise canceling mechanism is unknown. But the prediction is that in a normally functioning noise canceling mechanism alpha activity would predominate in the vmPFC/ACC, whereas in a dysfunctional noise canceling mechanism delta/theta and beta would predominate.

3.4.3. Gamma band activity and nested activity in tinnitus

Based on the principle that gamma band activity is associated with the conscious percept of auditory stimuli (Crone et al., 2001; Gurtubay et al., 2004; Joliot et al., 1994), Llinas proposed that tinnitus, as a conscious percept, should be associated with gamma band activity (Llinas et al., 1999). It has indeed been shown both by EEG (van der Loo et al., 2009), MEG (Llinas et al., 1999; Weisz et al., 2007) and intracranial recordings (De Ridder et al., 2011b) that tinnitus is related to gamma band activity in the (contralateral) auditory cortex and nested on theta activity (De Ridder et al., 2011b; Llinas et al., 1999; Weisz et al., 2007). An explanation for the occurrence of this theta-gamma coupled activity in sensory deafferentation has been developed in the concept of thalamocortical dysrhythmia (Llinas et al., 1999). This model states that in the deafferented tinnitus state, the dominant resting state alpha rhythm (8–12 Hz) decreases to theta (4–7 Hz) (Llinas et al., 1999) band activity. As a result, $GABA_A$ mediated lateral inhibition is reduced (Llinas et al., 2005), inducing gamma (>30 Hz) band activity (Llinas et al., 1999). Gamma band activity in the auditory cortex is a prerequisite for auditory conscious perception and therefore, likely also contributes to the perception of a phantom sound. As theta-gamma coupling also exists in physiological auditory processing (Canolty et al., 2006; Doesburg et al., 2012), the thalamocortical dysrhythmia state can be considered a pathological persistence of normally waxing and waning theta-gamma band coupled activity in specific topographic thalamocortical columns, resulting from sensory deafferentation. It can be conceived that the theta activity is the carrier wave connecting widespread areas (von Stein and Sarnthein, 2000), and that focal gamma band activity in geographically separated brain areas is synchronized by nesting on the theta phase, as exemplified in auditory attention (Doesburg et al., 2012). However this has not been investigated yet in tinnitus. Surgical neuromodulation treatments such as thalamic lesioning (Jeanmonod et al., 1996; Jeanmonod et al., 2003) and auditory cortex stimulation via implanted electrodes (De Ridder et al., 2011b; Ramirez et al., 2009) have shown to alter electrophysiological signatures of tinnitus-related thalamocortical dysrhythmia (De Ridder et al., 2011b; Jeanmonod et al., 2003; Ramirez et al., 2009), supporting the claims that thalamocortical dysrhythmia is involved in tinnitus.

In people with unilateral tinnitus, source analysis of resting state electroencephalographic beta3 and gamma band oscillations in the contralateral auditory cortex show a strong positive correlation with Visual Analogue Scale loudness scores (van der Loo et al., 2009). Whether the perceived loudness is only encoded by the auditory cortex beta3 and gamma band activity or by a larger yet to be determined network has not been investigated yet.

Neuromodulation studies targeting the auditory cortex can decrease the perceived tinnitus intensity or loudness. Both transcanial magnetic stimulation (TMS) (De Ridder et al., 2005; Khedr et al., 2010; Plewnia et al., 2006a; Vanneste et al., 2010b), transcranial direct current stimulation (tDCS) (Garin et al., 2011) and electrical implants in and on the primary and secondary auditory cortex (De Ridder et al., 2006a; De Ridder et al., 2007a; De Ridder et al., 2004; De Ridder et al., 2011e; Friedland et al., 2007; Seidman et al., 2008) have been shown to decrease tinnitus intensity or loudness transiently or permanently, suggesting the auditory cortex is indeed involved in processing of tinnitus intensity.

Based on the network principle that auditory cortex activity related to loudness has to be linked to a larger consciousness network, and based on the fact that TMS and tDCS can modulate activity in brain areas functionally connected to the stimulated area, it should be possible to modulate tinnitus loudness by TMS and tDCS of the frontal cortex, if and only if the frontal cortex is functionally connected to the auditory cortex. And indeed both frontal cortex TMS (De Ridder et al., 2012a) and tDCS (Vanneste et al., 2011b) can modulate auditory cortex related tinnitus loudness in those people who present with functional connectivity between frontal cortex and auditory cortex, either via the anterior cingulate or parahippocampal area (De Ridder et al., 2012a; Vanneste et al., 2011b).

3.4.4. Subnetworks representing tinnitus aspects

It has been proposed that tinnitus is the result of multiple dynamically active overlapping subnetworks (De Ridder et al., 2011a; Vanneste and De Ridder, 2012a). We now propose that each subnetwork represents a specific aspect of the tinnitus. These clinically separable aspects (e.g. loudness, type, laterality, distress, mood etc.) can be generated by neurophysiologically separable networks. These networks are not fixed, but seem to change in time, at least with respect to the relative activity and functional connectivity within the tinnitus network (Schlee et al., 2009a; Vanneste et al., 2011e). It is thus also possible they might change contextually: many patients describe their tinnitus worsens when they are tired or stressed. It has not been unequivocally demonstrated yet whether the brain areas of the network remain the same and only the strength of connectivity changes or whether the amount of brain areas involved also changes when tinnitus becomes chronic.

3.4.5. Tinnitus related distress

Whereas about 80% of people who perceive tinnitus are not distressed by it, about 20% are bothered by it (Axelsson and Ringdahl, 1989).

The areas that are part of the salience network (amygdala, anterior cingulate, anterior insula) overlap with areas involved in the distress (De Ridder et al., 2011c; Vanneste et al., 2010a) and mood component (Joos et al., 2012)in tinnitus. The same network (dorsal anterior cingulate cortex and insula) is also involved in filling-in as a repair mechanism for missing auditory input (Shahin et al., 2009).

These areas also overlap with brain areas involved in central control of the autonomic system which include subgenual anterior cingulate cortex, dorsal anterior cingulate cortex, insula, hypothalamus and amygdala (Critchley et al., 2000; Critchley et al., 2002; Nicotra et al., 2006; Ter Horst et al., 1996; Wong et al., 2007), supporting the hypothesisthat the autonomic system, and especially the sympathetic component (van der Loo et al., 2011) is involved in bringing the phantom percepts to consciousness, flavored by an emotional component, as described in the neurophysiological model for tinnitus (Jastreboff, 1990, 2007). Memory retrieval is enhanced under influence of the sympathetic system (Murchison et al., 2011), possibly explaining why stress, which activates the sympathetic system, is associated with the persistence of tinnitus (Fagelson, 2007; Hinton et al., 2006).

Furthermore, when tinnitus becomes chronic, the anterior cingulate and insula are more active (Vanneste et al., 2011e), and potentially as a corollary attributes a salience to the phantom sound resulting in a persistence of the awareness of the phantom sound (Sadaghiani et al., 2009).

Tinnitus distress as characterized by independent component analysis is related to two anterior cingulate based EEG components. Spectral analysis of these components demonstrates that distress in tinnitus is related to alpha and beta changes in a network consisting of the subgenual anterior cingulate cortex extending to the pregenual and dorsal anterior cingulate cortex as well as the ventromedial prefrontal cortex/orbitofrontal cortex, insula, and parahippocampus (De Ridder et al., 2011c). In comparison to non-tinnitus controls increased synchronized alpha and beta activity and less synchronized delta and theta activity in the dorsal anterior cingulate cortex is seen in people with tinnitus with distress (Vanneste et al., 2010a). The amount of distress correlates with alpha activity in a network including the subcallosal anterior cingulate cortex, the insula, parahippocampal area and amygdala. In addition, less alpha activity is found in the posterior cingulate cortex, precuneus and dorsolateral prefrontal cortex (Vanneste et al., 2010a). The distress is related to sympathetic activity, controlled by delta and gamma band activity in the right insula (van der Loo et al., 2011). This suggests that tinnitus distress might be a reflection of sympathetic hyperactivity, or in other words a reflection of autonomic nervous system involvement in tinnitus (Datzov et al., 1999), compatible with the neurophysiological model of tinnitus (Jastreboff, 1990). The involvement of the sgACC/vmPFC area suggests that distress might influence tinnitus loudness perception and vice versa. This area, which is involved in the recently proposed noise canceling mechanism, could influence thalamocortical (dysrhythmic) activity via its connectivity with the reticular nucleus of the thalamus, which exerts a topographic, frequency selective thalamic inhibition(Crabtree, 1998).

Magnetoencephalography studies have shown that distress is associated with alpha and delta changes in the right temporal and left frontal areas (Weisz et al., 2005a). Due to the low spatial resolution of the study it cannot be excluded that the right temporal activity is or is not derived from the right insula. The amount of input to the temporal cortex, as measured by partial directed coherence is related to the amount of perceived distress (Schlee et al., 2009b), suggesting that it is not only the activity that changes but also the connectivity in distress. Indeed, the distress is related to network activity and phase couplings between the anterior cingulum and the right frontal lobe as well as between the anterior cingulum and the right parietal lobe show significant correlations with the perceived distress (Schlee et al., 2008).

A series of resting state fMRI studies has been performed comparing healthy controls to patients with tinnitus (Burton et al., 2012; Kim et al., 2012; Maudoux et al., 2012a, b; Wineland et al., 2012). In an initial study increased functional connectivity was noted predominantly in the left amygdala and in the dorsomedial prefrontal cortex in 4 unilateral left sided tinnitus patients in comparison to controls (Kim et al., 2012). But chronic tinnitus patients, as compared to controls, showed more increased connectivity than in the amygdala and frontal cortex. Increased functional connectivity was also shown in the brainstem, cerebellum, right basal ganglia/NAc, parahippocampal areas, right frontal and parietal areas, left sensorimotor areas and left superior temporal region (Maudoux et al., 2012a). Tinnitus patients showed decreased connectivity in right primary auditory cortex, left fusiform gyrus, left frontal and bilateral occipital regions (Maudoux et al., 2012a). However this was a mixed group of patients, some of whom were distressed, some who were not. In non-bothersome tinnitus no abnormal resting state fMRI functional connectivity is detected in comparison to controls (Wineland et al., 2012). In contrast, in bothersome tinnitus there is an abnormal resting state functional connectivity (Burton et al., 2012). In comparison to controls, patients with bothersome tinnitus had less functional connectivity to the insula and cingulate, which was proposed to be related to a dissociation between auditory networks and control networks (Burton et al., 2012). This is in contrast to the abovementioned MEG data that show increased functional connectivity between the cingulate and right frontal cortex (Schlee et al., 2008). Using graph analysis techniques on resting state fMRI data increased connectivity was shown related to distress in the posterior cingulate cortex/precuneus region (Maudoux et al., 2012b). It is of interest that tinnitus distress is associated with altered activity in the posterior cingulate cortex/precuneus region as demonstrated by resting state EEG data (Vanneste et al., 2010a). Neuromodulation studies targeting the anterior cingulate, either with a double cone coil TMS (Vanneste et al., 2011c) or with bifrontal tDCS (Frank et al., 2011; Vanneste and De Ridder, 2011; Vanneste et al., 2011b) can improve tinnitus related distress, suggesting these areas are indeed correlated with the tinnitus distress. For tDCS electrophysiological data do indeed show that the distress improvement is associated with changes in the anterior cingulate (Vanneste and De Ridder, 2011). For double cone coil TMS only indirect evidence (De Ridder et al., 2011d; Hayward et al., 2007) is available. The involvement of the anterior cingulate in tinnitus related distress is furthermore suggested by a PET study demonstrating that the amount

of improvement in tinnitus distress obtained by temporoparietal rTMS is correlated to the PET activity in the anterior cingulate (Plewnia et al., 2006b).

3.4.6. Tinnitus related depression

Tinnitus is associated with depression in about 15% of the people with tinnitus as measured by an internet questionnaire (Andersson et al., 2003; Crocetti et al., 2009). In the population who seeks medical help the prevalence is higher, up to 48%.(Harrop-Griffiths et al., 1987), whereas in population based studies the prevalence of depression among people with tinnitus is only slightly increased (Krog et al., 2010). In contrast to former theories, which assumed that depression occurs as a reaction to tinnitus (Jastreboff, 1990), more recent theories assume that the increased prevalence of depression among tinnitus reflects an overlap in pathophysiological mechanisms (Langguth et al., 2011b; Rauschecker et al., 2010).

Tinnitus related distress and more chronic changes in mood are associated with specific alterations in brain activity of separate neural pathways. Both aspects have their own specific neural circuit embedded within a larger common network. The continuous awareness of tinnitus accompanied by distress can induce more long-term changes in mood. This more constant emotional disturbance, assessed by the BDI-II, can be linked to alpha 2 (10–12 Hz) synchronized activity in the left frontopolar and orbitofrontal cortex, whereas the distress component is lateralized to the same areas on the right (Joos et al., 2012). A recent TMS neuromodulation study demonstrates that right frontal TMS + left temporal TMS can improve tinnitus severity scores and depressive symptoms in comparison to baseline, albeit not significantly different from temporal cortex stimulation alone (Kreuzer et al., 2011). Furthermore, no electrophysiological data exist to demonstrate the abovementioned networks change associated with an improvement of the depression in tinnitus.

3.4.7. Tinnitus lateralization

Tinnitus can be perceived in the left ear, the right ear, sometimes alternating between the left and right ear or it can be perceived in both ears with the same or a different sound. In some people tinnitus is perceived somewhere in the middle of the head or more to one side, and sometimes even outside of the head. In other words, there is no typical presentation of where the phantom sound is perceptually localized in people with tinnitus. For study purposes usually people are selected who can clearly distinct the spatial localization of their phantom sound.

3.4.7.1. Left versus right sided tinnitus. It has been shown both by EEG (van der Loo et al., 2009), MEG (Llinas et al., 1999; Weisz et al., 2007) and intracranial recordings (De Ridder et al., 2011b) that tinnitus is related to gamma band activity in the (contralateral) auditory cortex and nested on theta activity (De Ridder et al., 2011b; Llinas et al., 1999; Weisz et al., 2007). However, it has also been shown that gamma band activity is increased in both primary and secondary auditory cortices of both sides irrespective of whether the tinnitus is perceived unilaterally on the left side, unilaterally on the right side or bilaterally (Vanneste et al., 2011a), clearly demonstrating that the gamma band activity is not determining on which side the tinnitus is perceived. The side, in narrow band noise tinnitus, on which the tinnitus is perceived relates to gamma-band activity in the contralateral parahippocampal area (Vanneste et al., 2011a). This is associated with increased functional connectivity between the auditory cortex and the parahippocampal area which is also retrieved by graph analysis techniques used on resting state fMRI data of tinnitus patients in comparison to a control group (Maudoux et al., 2012b).

No neuromodulation studies have been performed to directly stimulate the parahippocampal area. However, some indirect evidence exists that suggests the parahippocampal area might be involved in lateralizing tinnitus. Supraselective amobarbital injections in the anterior choroidal artery which transiently suppress amygydalohippocampal activity can transiently (10 minutes) suppress the pure tone component in chronic tinnitus on the contralateral side to the amytal (De Ridder et al., 2006b). This is in agreement with the electrophysiological findings.

3.4.7.2. Uni- versus bilateral tinnitus. Unilateral tinnitus is characterized by contralateral beta2 (18.5–21 Hz) activity in the superior prefrontal gyrus in comparison to bilateral tinnitus, but gamma band activity in comparison to non-tinnitus subjects (Vanneste et al., 2011a; Vanneste et al., 2010c). The difference between unilateral and bilateral tinnitus is reflected by high frequency activity (beta and gamma) in the superior prefrontal gurus, right parahippocampus, right angular gyrus and right auditory cortex. Bilateral tinnitus has delta activity in the ventrolateral prefrontal cortex in comparison to unilateral tinnitus, and bilateral beta1 (12.5–18 Hz) in comparison to non-tinnitus subjects. Bilateral tinnitus is also characterized by bilateral frontopolar beta1 activity (Vanneste et al., 2010c). Thus, the difference between uni-and bilateral tinnitus is reflected by oscillatory changes in a network of brain areas, and not by one single hub.

Neuromodulation studies specifically evaluating this network has not been published but some indirect data support the findings. Electrodes implanted extradurally over the posterior part of the superior temporal gyrus for tinnitus suppression can, in very high amplitudes alter the side on which the tinnitus is perceived (De Ridder et al., 2007a; De Ridder et al., 2011e). As higher amplitudes of electrical current modulate more brain cells influencing a larger area of brain (Kringelbach et al., 2007), it is conceivable that the current spreads to the contiguous angular gyrus area thereby changing the spatial localization of the tinnitus, analogous to the mechanism of other reported side effects (De Ridder et al., 2007e). This stimulation-induced spatial localization changes were only found in patients with electrodes implanted on the right superior temporal gyrus (De Ridder et al., 2011e).

3.4.7.3. Tinnitus type (noise versus tone). Not only can people perceive their tinnitus uni-or bilaterally, but also the characteristic of their sound can be different. One distinction often used is the difference between pure tone tinnitus and noise-like tinnitus. Based on the differences between the two parallel auditory pathways, the lemniscal being tonotopic and the extralemniscal being less tonotopic, and the fact that the extralemniscal auditory thalamus fires predominantly in burst mode and the lemniscal auditory thalamus in tonic mode (He and Hu, 2002), it has been hypothesized that white noise tinnitus may be caused by synchronous hyperactivity of burst firing in the non-tonotopic extralemniscal system, whereas pure tone tinnitus may be the result of increased synchronous tonic firing in the tonotopic (lemniscal) system (De Ridder et al., 2007c). Narrow band tinnitus could be the result of a co-activation of the lemniscal and extralemniscal pathways (De Ridder et al., 2007c).

That the extralemniscal system can be involved in tinnitus in some patients has been demonstrated by use of TENS stimulation of the median nerve, changing the tinnitus percept in certain people (Moller et al., 1992).

Resting state brain activity in people with narrow band noise tinnitus differs from pure tone people with pure tone tinnitus in the lateral frontopolar, PCC and the parahippocampal area for delta, beta and gamma frequency bands, respectively. The parahippocampal-PCC current density differences might be load dependent, as noise-like tinnitus constitutes multiple frequencies in contrast to pure tone tinnitus. The lateral frontopolar differences might be related to pitch-specific memory retrieval (Vanneste et al., 2010d).

Neuromodulation studies of the auditory cortex have shown that noise-like tinnitus and pure tone tinnitus respond differentially to tonic and burst stimulation, both for TMS (De Ridder et al., 2007c,d; Vanneste et al., 2010b) and implanted electrodes (De Ridder et al., 2011e; De Ridder et al., 2009), as theoretically predicted. It has been shown that burst firing is a stronger activator of the postsynaptic cell (Sherman, 2001; Swadlow and Gusev, 2001), and that burst TMS (Huang et al., 2005) and burst electrical stimulation (De Ridder et al., 2011e) are stronger modulators than tonic TMS and tonic electrical stimulation. Thus it was hypothesized that only burst TMS and burst electrical stimulation on implanted electrodes would be strong enough to modulate noise-like tinnitus associated burst firing, but that burst and tonic TMS and electrical stimulation would be equally effective in modulating tonal tinnitus. And this was indeed demonstrated both for TMS (De Ridder et al., 2007c,d) and electrical stimulation on implanted electrodes (De Ridder et al., 2011e; De Ridder et al., 2010). A further argument is related to the fact that burst stimulation preferentially modulates activity in the extralemniscal auditory thalamus (Xiong et al., 2004), which fires in burst, in contrast to tonic stimulation.

3.4.8. Chronification

The generators involved in tinnitus of recent onset seem to change over time with increased activity in several brain areas (auditory cortex, supplementary motor area and dorsal anterior cingulate cortex plus insula), associated with a changes in connectivity between the different auditory and non-auditory brain structures (Vanneste et al., 2011e) This is so both for EEG recordings (Vanneste et al., 2011e) and MEG recordings (Schlee et al., 2009a), even if the direction of the changes differs slightly between these two studies. In the MEG study the temporal cortex as center of the network in people with short tinnitus duration is replaced by a more widespread distribution of the gamma network in longer lasting tinnitus (Schlee et al., 2009a). The EEG study demonstrates a decrease of overall connectivity with increasing tinnitus duration (Vanneste et al., 2011e). An exception to this general connectivity decrease in long-standing tinnitus in comparison to tinnitus of recent onset is an increase in gamma-band connectivity between the left primary and secondary auditory cortex and the left insula, and also between the auditory cortices and the right dorsal lateral prefrontal cortex. These networks are both connected to the left parahippocampal area. Thus, both studies find that acute and chronic tinnitus are related to differential activity and connectivity in a network comprising the auditory cortices, insula, dorsal anterior cingulate cortex and premotor cortex, linked to the parahippocampal area.

Whereas the long-range gamma coupling of the temporal cortex decreased with longer tinnitus duration, similarly to what is seen in EEG (Vanneste et al., 2011e), the long-range gamma coupling of the other regions increases with longer duration of tinnitus symptoms (Schlee et al., 2009a), in contrast to what is seen in EEG (Vanneste et al., 2011e). Whether this difference is due to different connectivity measures used, or because of the differences between the spatial resolution of the source analysis technique used is still has to be resolved.

Most (De Ridder et al., 2011e; De Ridder et al., 2005; Frank et al., 2011; Khedr et al., 2008; Kleinjung et al., 2007) but not all (Burger et al., 2011) neuromodulation studies have shown that chronic tinnitus is more difficult to suppress by TMS than tinnitus of recent onset. Only one study looked at the stimulation parameters in relation to the tinnitus duration (De Ridder et al., 2005). The amount of tinnitus suppression that was obtained was frequency-dependent: in long-standing tinnitus maximal suppression could be obtained by low frequencies, whereas in tinnitus of recent onset high TMS frequencies yielded better results (De Ridder et al., 2005). It is unclear whether this is related to the increase noted in gamma band activity in the auditory cortex in chronic tinnitus in comparison to tinnitus of recent onset, as transient tinnitus is also correlated with an important transient increase in gamma band activity (Ortmann et al., 2011). Furthermore, another study demonstrated that 1, 10 and 25 Hz are equally suppressive in tinnitus at a group level (Khedr et al., 2008), but in this study tinnitus duration was not incorporated as a variable that can determine which TMS frequency would be optimal. Surprisingly, when TMS and electrical stimulation of implanted electrodes on the auditory cortex are compared in the same group of patients, the amount of obtained tinnitus suppression with TMS is duration dependent, whereas for electrical stimulation the response is independent from tinnitus duration (De Ridder et al., 2011e). This further suggests that TMS and electrical stimulation differ in their mechanism of action (De Ridder et al., 2011e).

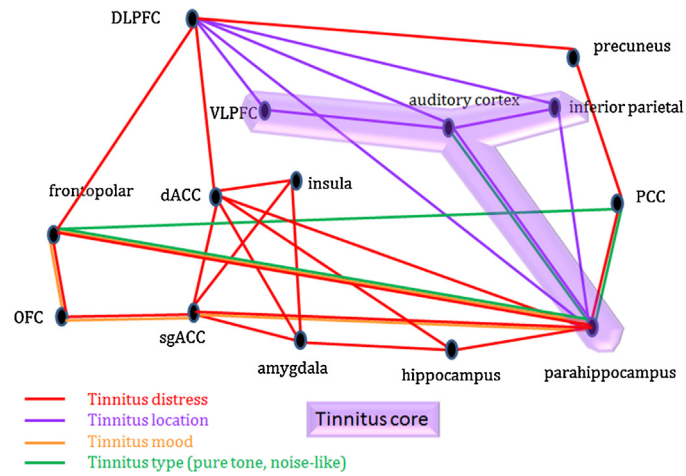

Fig. 6. Tinnitus working model of distinct parallel overlapping subnetworks each representing a specific aspect of tinnitus based on EEG and MEG literature. Some brain areas are involved in multiple subnetworks, and can be considered hubs. The tinnitus core is superposed (lila T). Note that the lines are not based on connectivity studies but merely connect brain areas that have shown to be involved in the depicted tinnitus aspects. It is proposed that each subnetwork has a signature oscillation frequency and that different subnetworks communicate at discrete oscillatory frequencies at the hubs. dACC: dorsal anterior cingulate cortex, sgACC: subgenual anterior cingulate cortex, PCC: posterior cingulate cortex, DLPFC: dorsolateral prefrontal cortex, vmPFC: ventromedial prefrontal cortex, VLPFC, ventrolateral prefrontal cortex, OFC: orbitofrontal cortex.

4. A working model for tinnitus

The brain areas involved in the tinnitus percept overlap largely with areas described for pitch memory and auditory memory retrieval (see Fig. 5), combined with subgenual anterior cingulate cortex and precuneus involvement (see Figs. 5 and 6), suggesting that the missing information triggers the brain to pull it from the auditory cortical neighborhood or from (para)hippocampal memory and integrates it in a self-perceptual network (see Fig. 4). This self-reference is essential to attribute the tinnitus to an external sound source. Retrieving a sound from memory involves the (para)hippocampus, inferior parietal area, posterior cingulate cortex as well as auditory cortex, but the minimal activity related to successful auditory memory retrieval consists of the auditory cortex and inferior parietal area (see Fig. 5). As people who dream do not perceive tinnitus, even though they are aware without wakefulness, this suggests the tinnitus on/off switch should be located in one or more areas that differ between waking and REM state, i.e. the ventrolateral prefrontal cortex/frontopolar-inferior parietal-cerebellar-parahippocampal network. The inferior parietal- ventrolateral prefrontal cortex -auditory cortex areas are essential for auditory awareness (see Fig. 5).

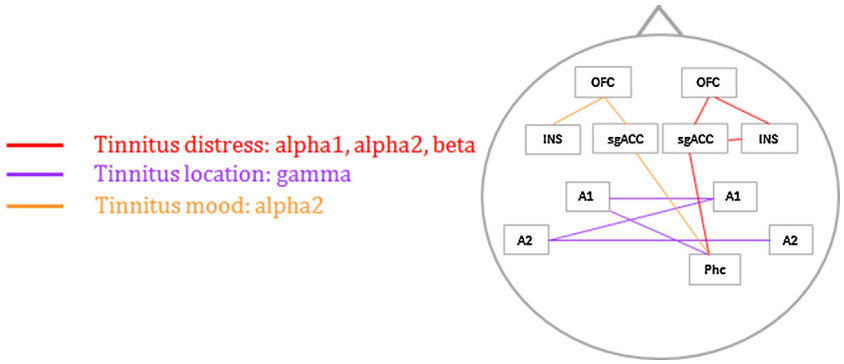

Fig. 7. The parahippocampus is involved in multiple networks. Lateralization can be one way of separating its involvement in different networks oscillating at similar frequencies, e.g. mood and distress, which both oscillate at alpha2 frequencies. The parahippocampus can however oscillate both at alpha1, alph2 and gamma frequencies, and its alpha1, alpha2 and beta activity and connectivity is related to distress network activity, whereas its alpha2 is more related to mood networks and its gamma oscillatory signature is involved in lateralization effects. Thus one hub oscillating at multiple different frequencies simultaneously can be involved in multiple overlapping networks oscillating at different frequencies.

Thus, the neural correlate of tinnitus, or the tinnitus core, probably consists of the minimal areas involved in auditory awareness and auditory memory retrieval, but they have to include areas that differ between REM sleep and being awake. This limits the tinnitus core to the auditory cortex–parahippocampus- ventrolateral prefrontal cortex -inferior parietal area (see Figs. 5 and 6), compatible with consciousness studies (Langsjo et al., 2012), and confirmed by an ALE meta-analysis of PET studies of tinnitus (Song et al., 2012). The phenomenologically unified tinnitus percept, meaning the perception of a phantom sound with its tonal or noise-like character, associated with or without distress, with or without mood or cognitive changes etc. seems to be built up of multiple subnetworks, each subnetwork representing a specific aspect of the tinnitus (see Figs. 5 and 6).

Whereas deafferentation can trigger these responses, the conscious maintenance of the abnormal activity might also be linked to an insufficient noise canceling mechanism, emotionally driven, and triggered by the ACC/vmPFC and influencing thalamocortical activity via the reticular nucleus of the thalamus. This fits with a homeostatic plasticity concept at a network level, analogous to what has been described computationally at a cellular level (Schaette and Kempter, 2006, 2012).

Different separable resting state networks that run in parallel can communicate with each other by using multiple discrete oscillatory frequencies simultaneously (Palva and Palva, 2012). And indeed, distress and emotional (mood) networks share parahippocampal activity, as well as subgenual anterior cingulate and amygdala activity, but at different oscillations: alpha1(8–10 Hz) (Vanneste et al., 2010a), alpha2 (Joos et al., 2012) and beta (De Ridder et al., 2011c), alpha2 (10–12 Hz) for mood (Joos et al., 2012), and gamma for lateralization (Vanneste et al., 2011a; Vanneste et al., 2011d) aspects (see Fig. 7).

The interaction between the different subnetworks, each encoding a specific tinnitus aspect, and each active at their signature frequency, can be brought about by phase-amplitude (=nested activity) or phase-phase (n:m phase) interactions (Palva and Palva, 2012). This has been shown in an independent component analysis study looking at different separable networks (= independent components) in healthy humans (Congedo et al., 2009). In animals 4 Hz seems to be a discrete frequency that connects and synchronizes the hippocampus to ventral tegmental area and the frontal lobes (Fujisawa and Buzsaki, 2011), suggesting that the use of discrete frequencies might not be exclusive for humans. A study using independent component analysis on resting state activity in people with tinnitus and looking at lagged phase synchronization between those components, demonstrates that whether or not a person with tinnitus is distressed depends on a single highly frequency specific functional connection between the distress and loudness specific independent components (Vanneste, in press). This model is dynamic, in that depending on the context some subnetworks might persist and others not. For example, in a moment of distraction, when the phantom sound is not perceived, the tinnitus core subnetwork might become detached from the global network, whereas the affective networks might persist. An alternative mechanism could involve the interplay between the noise generating deafferentation and the noise canceling networks. Or both these proposed mechanisms could be involved and influence each other.

The clinical implications of this integrated model of the brain using multiple nonspecific networks in parallel, each with their own oscillatory signature, that adapt to the context to construct a unified percept possibly by synchronized activation integrated at hubs at discrete oscillatory frequencies are enormous (see Fig. 7). It would theoretically predict that selectively interfering with one frequency of a specific subnetwork, for example by applying this same frequency to jam or disrupt synchronous signal transmission would be possible without interfering with the other subnetworks, that oscillate at other frequencies, thereby preventing collateral network disruptions and clinically preventing complications. Thus, depending at what frequency one hub would be stimulated, for example the parahippocampal area, either sound lateralization (by gamma band stimulation) or distress (by alpha stimulation) could theoretically be modulated.

5. Conclusion

The unified percept of tinnitus can be considered an emergent property of multiple, parallel, dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern and functional connectivity signature. These subnetworks encode specific aspects of the tinnitus percept, e.g. lateralization, mood, distress can be similar to other pathologies. Communication between these different subnetworks is proposed to occur at hubs, brain areas that are involved in multiple subnetworks simultaneously. These hubs can take part in each separable subnetwork at different frequencies. Communication between the subnetworks is proposed to occur at discrete oscillatory frequencies. As such, the brain uses multiple nonspecific networks in parallel, each with their own oscillatory signature, that adapt to the context to construct a unified percept possibly by synchronized activation integrated at hubs at discrete frequencies.

The context dependent perceptual changes might involve a noise canceling mechanism.

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