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Review

Using resting state functional connectivity to unravel networks of tinnitus

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ABSTRACT

Resting state functional connectivity (rs-fc) using fMRI has become an important tool in examining differences in brain activity between patient and healthy populations. Studies employing rs-fc have successfully identified altered intrinsic neural networks in many neurological and psychiatric disorders, including Alzheimer's disease, schizophrenia, and more recently, tinnitus. The neural mechanisms of subjective tinnitus, defined as the perception of sound without an external source, are not well understood. Several inherent networks have been implicated in tinnitus; these include default mode, auditory, dorsal attention, and visual resting-state networks. Evidence from several studies has begun to suggest that tinnitus causes consistent modifications to these networks, including greater connectivity between limbic areas and cortical networks not traditionally involved with emotion processing, and increased connectivity between attention and auditory processing brain regions. Such consistent changes to these networks may allow for the identification of objective brain imaging measures of tinnitus, leading to a better understanding of the neural basis of the disorder. Further, examination of rs-fc allows us to correlate behavioral measures, such as tinnitus severity and comorbid factors including hearing loss, with specific intrinsic networks.

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1. Introduction

Resting-state functional connectivity (rs-fc) is a term used to describe interregional correlation of brain activity measured using imaging techniques. It has gained prominence in recent years not only for its usefulness in highlighting several functional neural networks of the brain, but also for identifying neuroimaging biomarkers of a condition or a disorder (Horwitz and Rowe, 2011). In this review, we focus on studies of rs-fc using functional magnetic resonance imaging (fMRI) that have underscored the neural networks subserving tinnitus and accompanying hearing loss and the use of such studies in characterizing the pathophysiological markers of the disorder. We also discuss a potential use of rs-fc as a means of identifying subtypes based on pathology rather than on symptoms and its use in assessing treatment efficacy. In this domain of identifying objective biomarkers of a disorder, much can be learned from studies of normal aging or neuropsychiatric disorders such as schizophrenia, which have a longer history of using rs-fc. We highlight challenges of using rs-fc in general and those that are unique to the study of tinnitus and end the review with suggested directions for future rs-fc studies of tinnitus.

1.1. Resting-state networks

Resting state connectivity is, by definition, spontaneous fluctuations in brain activity that can be reliably organized into coherent networks. The term 'resting state' differentiates this type of activity from that obtained as a result of some task or stimulus. Since at least the 1980s, different brain imaging tools have noted such inherent networks, including EEG, or electroencephalography (e.g.,

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Abbreviations: rs-fc, Resting state functional connectivity; EEG, electroencephalography; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; ICA, independent component analysis; RSN, resting state network; DMN, default mode network; DAN, dorsal attention network; BOLD, blood oxygen level-dependent; DTI, diffuser tensor imaging

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Giaquinto and Nolfe, 1988), MEG, or magnetoencephalography (e.g., Lu et al., 1992; Salmelin and Hari, 1994), positron emission tomography (PET) (e.g., Horwitz et al., 1987) and fMRI (e.g., Biswal et al., 1995; Lowe et al., 1998). This review is concerned primarily with fMRI studies of resting state networks (RSNs). The first fMRI study to examine RSNs discovered strong correlations between motor regions when subjects were not performing a motor task (Biswal et al., 1995). Interestingly, the characteristics of this connectivity were similar to how the network appears during a task. Other systems, including those for auditory processing (Cordes et al., 2000), visual processing (Lowe et al., 1998), or even higher-order functions such as language processing (Hampson et al., 2002), were also shown to have resting state counterparts. Exploration into the potential use of RSNs as tools to better understand the connectivity in the brain therefore began to grow in popularity. For a more detailed description of the history of studying RSNs using fMRI, see Hampson et al. (2012) and Fox and Raichle (2007).

RSNs are typically delineated via functional connectivity analyses. Here, we briefly describe three popular methods of analysis: seeding, graph connectivity analysis, and independent component analysis, or ICA. In a seeding analysis, a seed region is selected based on the question being asked by the researcher. The connectivity of the seed region can then be examined by finding correlations between the time course of voxels (a voxel is 3-D cubic element in a brain image, similar to a pixel in a 2-D image) in the seed and the rest of the voxels in the brain. Alternatively, the time course of the seed region could be correlated with those of voxels in specific regions of interest rather than with the whole brain. These correlations are then used to generate connectivity maps that can be compared across groups via standard statistical tests such as *t*-tests or tests of analysis of variance. Seeding analysis benefits from the straightforward nature of interpretation and of the analysis itself. Results using this method are, however, highly dependent upon the seed regions chosen, thereby making it vulnerable to bias. Graph connectivity analysis is similarly influenced by selecting regions of interest. Here, correlations between a set of select nodes are calculated. These correlations are represented by edges between the nodes, the strength of which is incorporated in the resulting graph. Thus, group differences can be found by comparing how nodes are connected via edges and the strength of those connections. ICA differs from the other two approaches in that it is primarily data driven and allows for the analysis of multiple whole-brain networks. There is no need for *a priori* hypotheses; instead, ICA uses the time courses of voxels in the fMRI scans to produce a specified number of components, which are optimally spatially independent (although this optimal independence does not necessarily imply that there is no overlap between components). Deciding on the number of components used is an important part of the ICA technique and can strongly influence results. The components produced by ICA should separate resting state networks from each other and noise by placing them in separate components. Unlike a seeding approach, the resulting data from group ICA may be more difficult to interpret, but its data-driven nature makes it particularly appropriate for exploratory analyses with no *a priori* hypotheses. Hampson et al. (2012) and Cole et al. (2010) both provide more detailed descriptions of these methods and the benefits and drawbacks of each.

Though spontaneous activity can engage any brain region, the default mode network, or DMN, has gained prominence as the canonical RSN. In this formulation, the DMN typically comprises of nodes in the posterior cingulate/precuneus, bilateral superior frontal gyrus, medial frontal gyrus and angular gyrus (Mantini et al., 2007). The DMN is the most active at rest and shows reduced activity when a subject enters a task-based state involving attention or goal-directed behavior (Shulman et al., 1997); an opposite pattern is seen with other RSNs, which exhibit heightened, correlated activity in the task-based state but retain connectivity (although with reduced activity) during rest. The DMN exhibits a uniform oxygen extraction fraction when examined using PET, indicating equilibrium between the energy requirements of the neurons and the blood supply to the brain (Raichle et al., 2001). When the brain is involved in a task, neurons require an increased amount of blood, and the oxygen extraction fraction reflects this. Because the fraction is uniform in the DMN, the fluctuations in activity seen are not related to a task and the brain does not need additional physiological resources to maintain them. The DMN was therefore termed a “baseline” state of the brain and may be involved in ongoing activity over longer periods of time (Raichle et al., 2001). See Raichle and Snyder (2007) for an overview of the DMN. It is also worth noting that rs-fc, including connectivity of the DMN, may be at least in part independent of ongoing cognition. The presence of the DMN has been noted in the brains of anesthetized monkeys (Vincent et al., 2007), as well as in humans, where its coherence varies with the degree of consciousness (Guldenmund et al., 2012). It would be remiss of us not to note that the value of using DMN to study brain function is not without controversy (Morcom and Fletcher, 2007), but a discussion of its merits is outside the scope of this review.

Apart from the DMN, several other RSNs are applicable in studying the neural mechanisms of tinnitus or auditory processing in general (Fox et al., 2005; Langers and Melcher, 2011; Mantini et al., 2007). Studies of task-based and resting functional connectivity in normal hearing healthy adults have shown that a diverse set of networks, including the canonical RSNs defined previously, participate in auditory processing (Langers and Melcher, 2011). For the remainder of the review, we focus primarily on the DMN, the attention networks; the visual RSN, the auditory RSN, and nodes of the limbic network (see Fig. 1 for a representative figure of these networks). The visual RSN includes the occipital cortex and temporal-occipital regions, whereas the superior temporal cortex alone defines the auditory RSN (Mantini et al., 2007). The dorsal attention network, or DAN, is comprised of the bilateral intraparietal sulci, the ventral precentral gyrus, the middle frontal gyrus,

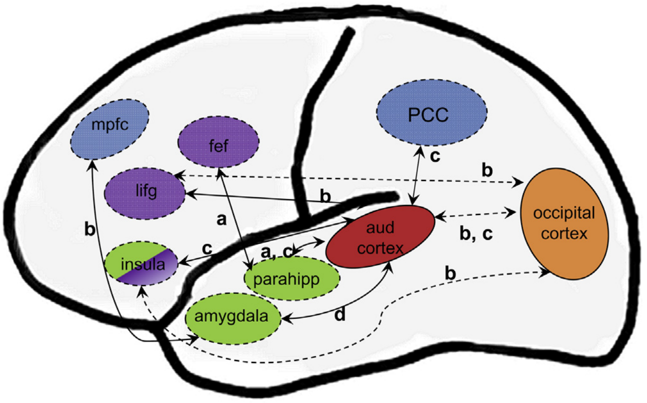

Fig. 1. Summary of main results of resting-state functional connectivity studies in tinnitus. The major networks highlighted are default-mode network (DMN, shown in blue), limbic network (green), auditory network (red), the visual network (in orange), several attention networks (specifically the dorsal attention network and the executive control of attention, shown in purple), and the visual network (in orange). Positive correlations between regions that are stronger in tinnitus patients than controls are shown in solid lines, while negative correlations are dashed lines. This figure shows modifications to the networks and does not represent the networks in their entirety. Connections are labeled with letters representing the studies in which they were reported, as follows: a) Schmidt et al., in press. b) Burton et al., 2012. c) Maudoux et al., 2012b. d) Kim et al., 2012. Abbreviations: PCC: posterior cingulate cortex; mpfc: medial prefrontal cortex; lifg: left inferior frontal gyrus; parahipp: parahippocampus; aud cortex: auditory cortex; fef: frontal eye fields.

and the frontal eye fields (Mantini et al., 2007). Other networks of attention, such as the ventral attention network (including temporoparietal junction and superior temporal sulcus) and that of the executive control of attention (including middle, inferior and medial frontal gyri and anterior insula), may also be applicable to tinnitus (Burton et al., 2012).

1.2. Tinnitus

Subjective tinnitus is the phantom perception of sound in the absence of an external source. Tinnitus is a fairly common hearing disorder, with a prevalence rate of 10–20% in the general population (Davis and Rafaie, 2000). The great majority of individuals with tinnitus are well-adjusted to it. However, 10–20% of those with tinnitus may seek medical care to alleviate symptoms associated with tinnitus and in 2–5% of the tinnitus population, the symptoms are severe and affect activities of daily living (Davis and Rafaie, 2000). About 90% of those with tinnitus have some degree of clinically-diagnosed hearing loss, but the opposite is not true; only about 40% of those with hearing loss may have tinnitus (Lockwood et al., 2002; Vernon, 1997). Therefore, hearing loss remains a major trigger and contributor to the neural changes concomitant with tinnitus. Tinnitus has also been correlated with depression and anxiety, with increased rates of co-occurrence of these conditions with tinnitus (Bartels et al., 2008). It is not surprising then that conceptual models of tinnitus have incorporated auditory processing (Bauer, 2004; Kaltenbach et al., 2005) and emotional processing networks (Jastreboff, 1990; Rauschecker et al., 2010) in their explanation of the neural mechanisms of tinnitus. Other reviews have pointed to contributions from the somatosensory system to tinnitus (Levine, 1999; Shore, 2011), and recent brain imaging studies have implicated the attention network as well (Gu et al., 2010; Husain et al., 2011b; Roberts et al., 2010). For overarching reviews of tinnitus mechanisms, see (Bauer, 2004; Eggermont and Roberts, 2004; Roberts et al., 2010).

Because of its subjective nature,[1] tinnitus may be uniquely suited to being studied using a resting-state functional connectivity paradigm; there is no task-based modulation of the tinnitus signal. Tinnitus is the perception of a phantom sound in the absence of an external source. At the same time, perception of a chronic internal noise may place the person in a task-based state and no true resting-state may be achieved by individuals with tinnitus. A better term than resting-state to denote this type of response would be steady-state or inherent functional networks. For the sake of maintaining compatibility with the broader resting-state literature and with the published studies on tinnitus, we will use the term resting-state functional connectivity in our review, but with the caveat that no true resting-state may be achieved by those with chronic tinnitus. In any case, the contrast in the spontaneous activity between individuals with tinnitus and those without should provide insights into neural bases of tinnitus.

2. Tinnitus and resting state functional connectivity

The effects of tinnitus on resting state functional connectivity have recently been explored using fMRI, although the results are variable, partly due to differences in experimental and analytical methods and partly due to the heterogeneity of the patient population. Nevertheless, two main themes have emerged in data from tinnitus patients relative to controls: an increased correlation between limbic areas and other brain regions, as well as correlation differences between attention-processing regions and other parts of the brain. A summary figure of the main findings, which place a particular emphasis on the examination of the auditory RSN, the DMN, and attention networks, is shown in Fig. 1. Major findings along with experimental and analytical details are also reported in Table 1.

2.1. Limbic system

A preliminary study (Kim et al., 2012), which examined rs-fc using fMRI in tinnitus subjects revealed findings concordant with both themes identified earlier. Increased connectivity was estimated between the auditory cortices and the amygdala in the tinnitus group when compared to age-matched normal hearing controls (see Fig. 1). This association between auditory and limbic regions in tinnitus has been suggested by numerous other brain imaging studies and conceptual models of tinnitus. The neurophysiological model of tinnitus proposed by Jastreboff (1990) describes the interaction between the limbic and auditory systems. The model emphasizes the importance of habituation to the tinnitus percept, which allows a patient to ignore the phantom sound. However, when “negative reinforcement” is present, the limbic system can cause the auditory activity to be perceived, which could then lead to a feedback loop. The correlation between the auditory RSN and limbic areas fits the framework of this hypothesis. A more recent update of the limbic-auditory interactions was proposed by Rauschecker et al. (2010) and is based on structural MRI data (Leaver et al., 2012; Muhlau et al., 2006). Task-based fMRI studies also provide evidence for the auditory-limbic link seen in the Kim et al. study. Golm et al. (2013) examined the relationship between tinnitus and emotional processing in an emotional sentences task, revealing changes in activation in limbic and frontal areas in highly distressed tinnitus patients. They suggest that the significant regions, including the anterior cingulate cortex, the medical cingulate cortex, the insula and the precuneus, are part of a general distress network and are not specific to tinnitus. The exact mechanism of and the networks involved in tinnitus distress are still being evaluated, and rs-fc studies are providing further information to suggest the importance of limbic areas in this process. We have also conducted a task-based fMRI study examining the effects of tinnitus and hearing loss on emotional processing influenced by this hypothesis (Carpenter-Thompson et al., unpublished).

A separate rs-fc study (Maudoux et al., 2012b) also found results that support the limbic-auditory link in tinnitus patients. Using a combination of independent component and graph connectivity analyses described in Soddu et al. (2011), connectivity graphs of the auditory component network were built for both tinnitus and control groups. The auditory network of the control and tinnitus groups included bilateral primary and associative auditory cortices, insula, prefrontal, sensorimotor, anterior cingulate and left occipital cortices. In addition to these regions, the tinnitus group's network comprised the brainstem, thalamus, nucleus accumbens, isthmus of cingulate gyrus, and occipital, parietal and prefrontal cortices. Increases and decreases in connectivity were seen in the tinnitus group as compared to controls; specifically, the tinnitus group showed increased connectivity in the brainstem, cerebellum, right basal ganglia/nucleus accumbens, parahippocampal areas, right frontal and parietal areas, left sensorimotor areas and left superior temporal region and decreases in the right primary auditory cortex, left fusiform gyrus, left frontal and bilateral occipital regions. In a companion study using connectivity graphs (Maudoux et al., 2012a), two connectivity patterns were found in the auditory RSN. The first involved the bilateral auditory cortices and insula. This network was positively correlated with the time course of the auditory RSN, and was found in both tinnitus and control groups. A

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[1] For the purpose of this review, we will not consider ‘objective’ tinnitus, which often results from physical or vascular reasons and can be objectively heard by the ear or by using a stethoscope.

Table 1
Summary table of the details of the various resting-state studies of tinnitus.

	Number of subjects	Age of subjects	THI scores	Hearing loss of TIN patients	Method	Networks examined	Major findings (in TIN, relative to controls)
K	6 NHC (2f), 4 TIN (1f)	45 ± 2.76 NHC, 45 ± 3.92 TIN	Not given	None to severe	Group ICA, seed-to-voxel	Aud	r AC ↔ ↑ l AC; AC ↔ ↑amyg, dmpfc
Ma	15 NHC (6f), 13 TIN (6f)	51 ± 13 NHC, 52 ± 11 TIN	16–84, mean 43.5	Mild to severe	Connectivity graph	Aud	TIN & NHC different graphs; AC ↔ ↑ l phipp
Mb	15 NHC (6f), 13 TIN (6f)	51 ± 13 NHC, 52 ± 11 TIN	16–84, mean 43.5	Mild to severe	Between group ICA	Aud	AC ↔ ↓ l pfc, l fus, occip; AC ↔ ↑ stem, bg, cereb, phipp, r pfc, pari, sm
B	17 NHC (10f), 17 TIN (6f)	50.6 ± 2.5 NHC, 53.5 ± 3.6 TIN	38–76, mean 53.5	None to severe	Seed-to-seed, seed-to-voxel	Aud, vis, Som, DAN, VAN, ECA	AC ↔ ↓ VC; VC↔ ↓ tpj, ifg, ins; Occip ↔ ↓ ins, ifg
W	23 NHC (11f), 18 TIN (6f)	Median 46 (IQR 39–54) NHC, median 54 (IQR range 52–57) TIN	0–24, mean 9.67	None to severe	Seed-to-seed, seed-to-voxel	DAN, VAN, Cog, Aud, Vis, Som, DMN	No differences
S	15 NHC (6f), 13 HLC (8f), 12 TIN (3f)	52.93 ± 8.64 NHC, 57.62 ± 9.39 HLC, 55.00 ± 6.97 TIN	0–22, mean 8.33	Mild to moderate in TIN, HLC (matched)	Seed-to-voxel	DMN, DAN, Aud	AC & fef ↔ ↑ phipp; rs-fc ↓ DMN; ips ↔ ↓ r smg

All of the major findings were found in tinnitus patients relative to controls. ↔ shows resting state functional connectivity (rs-fc) between regions, with↑ indicating increased connectivity and ↓ decreased connectivity.

Abbreviations: K: (Kim et al., 2012); Ma: (Maudoux et al., 2012a); Mb: (Maudoux et al., 2012b); B: (Burton et al., 2012); W: (Wineland et al., 2012); S: Schmidt et al., in press, NHC: normal hearing controls; HLC: hearing loss controls; TIN: tinnitus patients; THI: tinnitus handicap inventory; HL: hearing loss; Aud: auditory resting state network; Vis: visual resting state network; Som: somatosensory network; DAN: dorsal attention network; VAN: ventral attention network; ECA: executive control of attention network; Cog: cognitive network; DMN: default mode network; AC: primary auditory cortex; r: right; l: left; amyg: amygdala; dmpfc: dorsomedial prefrontal cortex; phipp: parahippocampus; pfc: prefrontal cortex; fus: fusiform gyrus; stem: brainstem; bg: basal ganglia; cereb: cerebellum; pari: partietal lobule; sm: sensorimotor; VC: visual cortex; tpj: temporoparietal junction; ifg: inferior frontal gyrus; ins: insula; Occip: occipital cortex; fef: frontal eye fields; smg: supramarginal gyrus; ips: intraparietal sulci.

second network that was anti-correlated with the auditory RSN time course was found only in control subjects. This network included the frontoparietal lobe, the anterior cingulate cortex, the amygdala, the brainstem, and the parahippocampus. Increased functional connectivity that was found between the auditory cortices and the left parahippocampus in tinnitus can therefore be explained by the loss of coherence in this anti-correlated network (Maudoux et al., 2012a). It also explains the inclusion of other brain regions in the auditory connectivity graphs created in Maudoux et al. (2012b). Of particular note in these study is the increase in connectivity in the parahippocampal areas (shown in Fig. 1), which again demonstrates a relationship between tinnitus and limbic areas in resting state analyses. There was also a trend for increased correlation between the auditory cortices and the amygdala in tinnitus patients, but it did not survive correction.

In our own study (Schmidt et al., in press) we detected increased correlations in the activity of the limbic system and inherent networks in tinnitus patients compared to controls. The study employed continuous acquisition of data for 5 min while the participants were at rest. Three groups of subjects were scanned – 12 middle-aged adults with hearing loss and tinnitus, 13 age-matched controls with hearing loss without tinnitus, and 15 normal hearing controls without tinnitus. We conducted a seed-to-voxel analysis to examine the auditory RSN, DMN and DAN in the three groups. Comparable with previous studies (Kim et al., 2012; Maudoux et al., 2012a,b), an increased correlation with the limbic network was found in tinnitus patients in the auditory network. This correlation, found in the left parahippocampus, was significant when the tinnitus group was compared to normal hearing controls, but did not reach significance when the patients were contrasted with hearing loss controls (though there was a clear trend). We also found increased connectivity between the right parahippocampus and the DAN, with seed regions located in the bilateral frontal eye fields.

2.2. Attention system

Kim et al. (2012) also found results that suggest alterations in resting state activity in brain regions associated with attention. Specifically, increased connectivity was found between the dorsal medial prefrontal cortex and the auditory RSN. The authors suggest that this aberrant functional connection may result in the tinnitus percept (Kim et al., 2012). Hypotheses that tinnitus can cause changes in the organization of sensory networks and interfere with networks of attention led (Burton et al., 2012) to examine the visual, auditory, somatosensory, DAN, ventral attention network and attention control resting state networks in 17 patients with bothersome tinnitus (with scores ranging from 38 to 76 on the Tinnitus Handicap Inventory (THI) (Newman et al., 1996)). To do so, spherical seed regions were selected within each of these networks (17 seeds in total). Temporal correlations were calculated between pairs of regions, and connectivity maps were calculated for those that had group differences with probabilities less than 0.05. T-statistics were calculated to detect significant differences between tinnitus and control groups (Burton et al., 2012). Almost all seed pairings within the DAN were not found to be significant between groups. Correlations between seeds in the auditory and visual RSNs were found to be positive in controls but negative in the tinnitus group, perhaps because the additional stimulation caused by the tinnitus percept decreases activity in the visual cortex that is irrelevant to processing the phantom sound (Burton et al., 2012). In the tinnitus group, functional connectivity in areas of attention control was greater than that in the control group (see Fig. 1). This connectivity was positively correlated with activity in the auditory cortex and negatively correlated with the occipital cortex. Increased associations with limbic areas were also found in tinnitus subjects when compared to controls, specifically between the primary auditory cortex and the insula. However, this connection was not strong enough to survive correction (Burton et al., 2012).

Alterations to attention networks were also seen in our work (Schmidt et al., in press). The DAN, with seed regions in the bilateral intraparietal sulci, showed decreased correlations with the right supramarginal gyrus in tinnitus subjects compared to hearing loss controls. This is contrary to the lack of significant results seen in the DAN seeds in Burton et al. (2012). Such differences may be accounted for by differences in analysis methods and heterogeneity of the participant groups, as discussed next. In addition, in the

DMN, our study revealed decreased correlations between seed regions (located in the posterior cingulate cortex and medial prefrontal cortex) and the precuneus in tinnitus patients when compared to both normal hearing and hearing loss controls. The precuneus is one of the main hubs of the DMN, so this decreased connectivity indicates the network is disrupted and patients are not in a true resting state. Tinnitus patients may therefore be attending to or attempting to suppress the phantom sound.

2.3. Accounting for the variability

Although the rs-fc studies to date share results with similar themes, the exact brain regions involved in the RSNs and the strength of the connections between them have been variable. This could be due to several reasons. First, the methods of analyses varied across the studies. Kim et al. (2012) used a group ICA followed by a seed analysis, whereas Burton et al. (2012) used a seed-to-seed analysis followed by a seed-to-voxel analysis. Maudoux et al. used connectivity graphs (Maudoux et al., 2012a) and between group ICA (Maudoux et al., 2012b). Each of these approaches is driven by different *a priori* hypothesis. In the case of the Kim et al. (2012) paper, the initial independent component analysis did not require any prior hypothesis, but the results are very sensitive to the number of subjects in each group and the number of components chosen during the analysis. The analysis itself can vary between replications, because there is no specific “optimal” solution to the computations. The Burton et al. (2012) seed analysis, in contrast, is highly dependent on the precise seed regions chosen. Our study (Schmidt et al., in press) is similarly influenced by seed selection, though we did not conduct a seed-to-seed analysis as Burton et al. (2012) performed as part of their analysis. It is not surprising that these different methods lead to different results.

Second, the number of subjects examined in the different studies was variable. Specifically, the Kim et al. (2011) study used a very small cohort (four tinnitus subjects and 6 controls) in their pilot study. This is quite different from the 13 patients and 15 controls used by Maudoux et al. (2012a,b), the 17 patients and 17 controls used by Burton et al. (2012), and the 15 normal hearing controls, 13 hearing loss controls, and 12 patients used in our study (Schmidt et al., in press). Especially in the case of group ICA, subject number has a large impact on the results of a study.

A third issue is variation in characteristics of the patient population. For example, the extent of hearing loss in the tinnitus patients studied is highly variable and varies greatly across subjects. In our study (Schmidt et al., in press) we included a hearing loss control group to account for the effect of this potential confound. The severity of the tinnitus experienced by the patients in each study may also have a strong impact on the results. In the Maudoux study (Maudoux et al., 2012a), severity was highly variable across patients, ranging from a THI score of 84 to a low of 16. In Burton et al. (2012), all of the patients experienced bothersome tinnitus, but the THI scores again varied quite a lot, from 38 to 76. All of the patients in our study had nonbothersome tinnitus with THI scores ranging from 0 to 18 (Schmidt et al., in press). This variation plays a key role in the affect tinnitus has on resting state connectivity and is demonstrated by Wineland et al. (2012). In the Wineland et al. study, an almost identical analysis to that used in Burton et al. was performed on a group of patients with nonbothersome tinnitus. In contrast to Burton et al. (2012), no significant results were found. This finding strongly emphasizes that alterations in the resting state are related to tinnitus severity, and variations therein could be confounds in past research. A direct comparison between bothersome and nonbothersome tinnitus groups would be highly beneficial to confirm this result. Additionally, Maudoux et al. (2012a) found that THI scores are significantly positively correlated with regression measures of correlation in the posterior cingulate cortex. Tinnitus questionnaire scores are also positively correlated with the posterior cingulate response and also those of the left parietal region; however, these correlations did not reach significance. These results further emphasize the influence of tinnitus severity on results.

RSNs have been shown to alter with age and the great majority of individuals with tinnitus are middle-aged or older (Henry et al., 2005). In the DMN, decreased connectivity in the posterior cingulate cortex, frontal gyrus and parietal regions with age has been noted. In task-based examinations, deactivations typically found in the DMN were shown to be weaker in older adults, which indicates that this population has more difficulty moving into a task-based scenario from rest (Hafkemeijer et al., 2012). Though most studies on aging and rs-fc have thus far focused on the DMN, other networks including those associated with attention have also been examined. For instance, (Ferreira and Busatto, 2013) noted heightened functional interactions between frontal and parietal cortices (Ferreira and Busatto, 2013). When using rs-fc to study tinnitus and hearing loss, both of which are associated with an older population, it is important to keep in mind the network alterations that come from aging alone. Subject groups should be carefully age-matched in order to account for this confounding variable.

3. EEG and MEG studies of resting state functional coupling

The first insights into inherent long-range cortical coupling in tinnitus were provided not by fMRI but by MEG (Lorenz et al., 2009; Schlee et al., 2009; Weisz et al., 2007a,b) and EEG (Vanneste et al., 2010a,b) resting-state studies. Weisz and colleagues (Lorenz et al., 2009; Schlee et al., 2009; Weisz et al., 2007a,b) in a series of studies have brought forth evidence that implicate alpha (8–12 Hz), delta (<4 Hz) and gamma (30–60 Hz) wave oscillations identified using MEG. We refer the reader to the article in this special issue by Weisz et al. for a review of some of these studies and their findings. EEG likewise has been used to determine long-range functional coupling in the resting state, most prominently by De Ridder and colleagues (Vanneste et al., 2011; Vanneste et al., 2010a,b). EEG and MEG do not offer the spatial resolution of fMRI, but they offer the advantage of being quiet and not interfering or masking the individual's hearing loss or tinnitus. The other advantage of these techniques is their temporal resolution of the order of a few milliseconds compared to the 1–3 s temporal resolution of most fMRI studies.

The temporal and to some extent spatial resolution differences of fMRI and EEG/MEG may mean that these tools are measuring different aspects of spontaneous brain activity (Tagliazucchi et al., 2012). For comparative studies of resting state cortical activity as measured by fMRI and EEG see (Britz et al., 2010; Laufs, 2010; Mantini et al., 2007; Musso et al., 2010; Tagliazucchi et al., 2012). The studies validate to some extent the correlation between EEG *microstates* occurring over a timescale of milliseconds with fMRI-BOLD (blood oxygen level-dependent) oscillation patterns occurring over a timescale of seconds for several RSNs. Britz et al. (2010) computed 4 RSNs from the EEG data that were the equivalent of stereotypical BOLD RSNs dedicated to auditory/phonological, visual, attention and self-referential processing. However, no EEG equivalent of the DMN was detected in the (Britz et al., 2010) study. Other studies have correlated the default-mode network with beta-2 (Laufs et al., 2003) or with delta (Mantini et al., 2007) spectral bands of EEG. Therefore, a direct comparison of EEG and fMRI studies of rs-fc is complicated by the fact that similar EEG power bands may be correlated with varying fMRI-generated spatial maps and a single RSN may be associated with different EEG spectral patterns (Laufs et al., 2008; Musso et al., 2010).

The EEG/MEG studies also point to the manner in which rs-fc studies may be used to determine efficacy of treatments for tinnitus. In one such study, (Vanneste and De Ridder, 2011) employed spontaneous electrical activity measured using EEG to dissociate the networks of responders from nonresponders. Prior to the intervention, patients who went on to become responders registered heightened functional connectivity between the frontal cortex and (a) the parahippocampus and (b) the subgenual anterior cingulate cortex, compared to the future non-responders. The responders also differed from the nonresponders with respect to connectivity of RSNs involving the auditory cortex and the parahippocampal region. Adamchic et al. (2012) verified the extent of changes in a pitch-processing network, which correlated with degree of reduction in tinnitus-related symptoms, using EEG; those with little or no change in their tinnitus pitch had the fewest changes to their pitch processing network. The therapy used in the study (Tass et al., 2012) attempted to reduce tinnitus-related symptoms by having participants listen to a series of brief tones of specific frequencies so as to induce a 'co-ordinated reset' of the tonotopic organization near the tinnitus pitch. Efficacy of repetitive transcranial magnetic stimulation for those with tinnitus is also beginning to be evaluated using rs-fc studies of MEG (Muller et al., 2013) and EEG (Fuggetta and Noh, 2012).

4. Comparisons with other disorders

Although rs-fc has not been used for subtyping of various groups and differential diagnosis and is only beginning to be used for investigating treatment efficacy, it has a long history of such usage in schizophrenia and disorders associated with aging. In this section, we briefly review the findings from rs-fc studies related to Alzheimer's disease and schizophrenia, which may provide insights into interpreting results of tinnitus rs-fc studies and illustrate uses of this tool.

Rs-fc studies have the potential to be used as diagnostic tools to predict disease onset and for classifying patients into different prognostic categories (Horwitz and Rowe, 2011). This is illustrated via Alzheimer's disease, where patients with mild cognitive impairment are differentially diagnosed as to whether they will later develop Alzheimer's disease or will remain stable (Agosta et al., 2012; Binnewijzend et al., 2012; Chen et al., 2011; Greicius et al., 2004; Koch et al., 2012). Binnewijzend et al. (2012) specifically address this possibility with a longitudinal study using 43 controls, 39 patients with Alzheimer's disease, and 23 individuals with mild cognitive impairment. The mild cognitive impairment group further separated into a group of 7 people that developed Alzheimer's disease and a larger group of 14 patients that remained stable. Changes to RSNs were assessed by calculating a functional connectivity score. Lower scores in the DMN were found in the Alzheimer's disease group when compared to normal groups. Connectivity scores for the mild cognitive impairment group were between those of the Alzheimer's disease and control groups, though not in a statistically significant manner. When the mild cognitive impairment subgroups were examined, Alzheimer's disease patients had lower scores than stable mild cognitive impairment patients, but the scores between the mild cognitive impairment patients who later developed Alzheimer's disease and the Alzheimer's disease group itself were not dissimilar. The experimenters point out that this similarity could be due to the small sample size, particularly in the converted group (Binnewijzend et al., 2012). The diagnostic capabilities of rs-fc also have potential applications in tinnitus, as there is currently no reproducible objective measure of the disorder. Further, previous studies of subtyping tinnitus has relied on the symptoms, rather than on pathophysiology (Tyler et al., 2008).

Reproducibility of rs-fc results has varied depending on the disorder being studied. For example, alterations to the DMN and attention networks in Alzheimer's disease have been relatively consistent (Agosta et al., 2012; Binnewijzend et al., 2012; Koch et al., 2012; Li et al., 2012; Zhang et al., 2010; Zhao et al., 2012). In contrast, results of schizophrenia have been variable (Greicius, 2008). Although schizophrenia is a cluster of profound neuropsychiatric symptoms, a subtype of patients experience phantom perception of sounds, although there are some fundamental differences with tinnitus, notably in the interpretation of the sound. In addition, the schizophrenic patient population is extremely variable and for both of these reasons, it may be beneficial to examine the work that has been done concerning rs-fc in schizophrenic patients (comprehensive reviews of schizophrenia rs-fc studies may be found in Greicius (2008), Karbasforoushan and Woodward (2012). In schizophrenia, connectivity within the DMN has been shown to be both increased (Zhou et al., 2007) and decreased (Bluhm et al., 2007) relative to controls. Research concerning networks anti-correlated with the DMN has also produced mixed results; Zhou et al. find increased inverse correlations between the DMN and other networks, whereas Bluhm and colleagues find no such effect. This variation could be attributed to differences in medications taken by subjects, age of participants and severity of the disease. With regards to the function of the auditory RSN in auditory/verbal hallucinations, Northoff and Qin (2011) have proposed a theory in three parts. First, there is increased activity in the auditory RSN, specifically in the secondary auditory cortex, when a patient experiences an auditory hallucination. Second, there are alterations in the activation in the DMN and an irregular relationship between the DMN and the auditory RSN, though the exact nature of this interaction is not clear. Lastly, a change in the relationship between rest and task states in the primary auditory cortex occurs. Because the auditory RSN exhibits elevated activity at rest, when a stimulus is presented there is reduced increase in activity when transitioning to a task state. This hypothesis, though it refers specifically to auditory hallucinations as a consequence of schizophrenia, may also be applicable to tinnitus patients. Of particular note is the third component of the hypothesis, which predicts that elevated level of auditory response would reduce the rest-to-task activity difference. This hypothesis has also been proposed for tinnitus by Melcher et al. (2000, 2009) with regards to elevated response in the inferior colliculus to noise stimuli in the tinnitus group compared to a control group. However, an interleaved task- and rest-based functional connectivity study that would explicitly test this hypothesis of reduced rest-to-task activity difference in tinnitus has not yet been published.

5. Challenges of rs-fc

As we write this, several new techniques of fc and rs-fc are being developed and implemented. The different tools used to study rs-fc are likely not measuring the same thing and as of yet do not index temporal interactions (Horwitz, 2003; Horwitz et al., 2005). A continuing problem of rs-fc studies is with their interpretation. Another concern when studying rs-fc using fMRI is the amount of noise produced by the MRI scanner. Though studies have attempted to minimize the amount of noise perceived by subjects during the scan with headphones and ear plugs, we cannot completely prevent participants from hearing some sound. Indeed, scanner noise has been shown to cause some suppression of the DMN (Perrachione and Ghosh, 2013). Noise is of particular concern when studying tinnitus. It is important to question subjects to verify that scanner noise does not mask their tinnitus sound. Further, the presence of the extraneous scanner noise may make the sound perceived by tinnitus subjects less salient and therefore reduce the differences in rs-fc found between tinnitus and control groups. Tinnitus subjects would not be unique in attempting to ignore an auditory stimulus at rest; all subjects are dealing with noise. An alternative is to use sparse-sampling or clustered acquisition which greatly reduces scanner noise at the expense of fewer scans (Gaab et al., 2007; Hall et al., 1999). However, switching the scanner noise on and off may remove subjects from a resting state as well. Whereas participants may habituate to the scanner noise during a continuous scan and come closer to a true resting state, such habituation would be challenging in a clustered-acquisition paradigm. In addition, sparse sampling collects fewer volumes than continuous scanning (for instance, 25 in sparse vs. 150 in continuous scan for a 5 min session) (Perrachione and Ghosh, 2013). Thus, to achieve the same statistical power, scan time would need to be significantly increased. Reconstruction of the signal from the sparse data also complicates the analysis, but likely does create an accurate portrayal of RSNs. In a functional connectivity study involving normal hearing healthy participants (Langers and van Dijk, 2011) found inherent networks to be fairly consistent whether determined through conventional continuous scanning or via sparse sampling. Nevertheless, in this same study, the signal spectra were shown to be better in continuous acquisition. It may therefore be unfavorable to employ sparse scanning given the reduction in acquired volumes. A study examining the differences in rs-fc in continuous and sparse scanning methods should be employed before any definitive conclusions can be drawn.

Other non-noise related concerns relate to variation in analysis methods and experimental design. The optimal method for analyzing resting state data is yet to be determined. Even the inclusion of different pre-processing steps is still being debated. Further, resting state data is often collected in a larger experimental paradigm that includes several tasks. How long a task can influence the resting state has not been determined. It is therefore possible that by performing a task beforehand, the resting state scan is confounded by residual activations brought about by the task. Different methods of analysis, including group independent component analysis, graph connectivity analysis, and seed-based analysis, also have their unique benefits and drawbacks that need to be kept in mind when assessing rs-fc studies, and there is currently no standardized method for obtaining and analyzing resting state data (Cole et al., 2010).

A third, but probably the most important challenge, to interpreting rs-fc studies of tinnitus is the heterogeneity of the tinnitus patient population. There are several ways rs-fc studies can minimize the heterogeneity of the subject sample. One is to restrict the sample to individuals with a particular sub-type of tinnitus (e.g., those with mild or non-bothersome tinnitus), to a specific hearing loss profile (e.g., normal hearing up to 8 kHz), and to minimize variation in age and gender. Typically, individuals are classified into sub-types based on their overall scores on standardized questionnaire, such as the Tinnitus Questionnaire (Kuk et al., 1990), the Tinnitus Handicap Inventory (Newman et al., 1996) and the Tinnitus Functional Index (Meikle et al., 2011). However, restricting to an overall score without paying attention to scores on the different subdomains may not increase homogeneity. Variability on different subdomains of these questionnaires may reflect variability of the different cortical networks, which will affect interpretation of the rs-fc data. Although it is possible to restrict heterogeneity, it is impossible to have a completely homogenous patient group. A worthwhile longer-term goal of rs-fc and task-based imaging studies is to identify subtypes via imaging paradigms, which may allow us to better interpret imaging data. This has broader implications for treatment strategies as well.

Understanding the neural bases of tinnitus using rs-fc is in an exploratory stage. Therefore it is not surprising that multiple tools have been used with different assumptions and that no coherent, integrated explanation of tinnitus has been put forward. One goal of this review was to advance a qualitative understanding of tinnitus, as determined from the rs-fc studies published so far. Another goal was to identify the challenges and gains of this tool and how it may be used in future, as described next.

6. Future directions

6.1. Combined DTI-rs-fc study

One direction that remains to be explored in studying neural correlates of tinnitus is that of combining anatomical and functional connectivity within the same framework. An anatomical link may not be functionally engaged in a task or network and a functional connection may encompass indirect anatomical links. See for instance, the (Simonyan et al., 2009) study that combined information about white matter tracts obtained using diffusion tensor imaging (DTI) with BOLD functional connectivity. DTI studies of tinnitus find altered white-matter tracts connecting inferior colliculus to the auditory cortex (Crippa et al., 2010), the amygdala and the auditory cortex (Crippa et al., 2010), and the frontal and parietal cortices with the auditory cortex (Lee et al., 2007). However, other studies do not find similar changes in the auditory processing pathways (Husain et al., 2011a). A confounding factor is hearing loss, which is accounted for in the (Husain et al., 2011a), but not in the other studies. Further, all studies suffer from low subject numbers and their results are not generalizable. A combined DTI-rs-fc study may illuminate the reason behind these differences and better inform the changes occurring along connections between regions.

6.2. Effective connectivity and modeling studies

Effective connectivity differs from functional connectivity in that it provides a framework to test both directionality and strength of functional connections within a specified anatomical model (Horwitz, 2003). To date, no effective connectivity studies of neural bases of tinnitus have been published. It is likely that some of the confusion arising from different functional connectivity studies may be allayed by employing effective connectivity models. As has been noted before, interpretation of results obtained from resting-state or task-based functional connectivity studies is not straightforward (Horwitz, 2003), especially in the context of patient groups, but neural network modeling may provide one way of interpreting the data (Kim and Horwitz, 2009). As with effective connectivity studies, they provide one more tool to supplement rs-fc investigations.

6.3. Temporal dynamics

The tinnitus and hearing loss resting-state studies reviewed here do not take into account temporal dynamics, but are rather static portraits of spontaneous activity acquired over a long period of time, ranging from 5 to 15 min. However, faster changes in the rs-fc as measured by the recently introduced dynamic BOLD functional connectivity in humans (Chang and Glover, 2010; Smith et al., 2012) and in the rodent model (Keilholz et al., 2013; Pan et al., 2010) may provide further insights into the neural bases of tinnitus and will provide greater compatibility with the published EEG and MEG results. Major findings of the dynamic functional connectivity include the fact that changes in BOLD appear to occur on a scale of a few minutes and could be correlated with changes in EEG spectra (Tagliazucchi et al., 2012). Increased alpha and beta power were correlated with decreased functional connectivity, whereas increased gamma activity was associated with increased connectivity (Tagliazucchi et al., 2012). The results of combined EEG/fMRI studies provide a means to integrate the EEG and fMRI rs-fc data obtained from separate experiments.

6.4. Future rs-fc studies of tinnitus

In the near future, there may be no standardized method of obtaining and analyzing rs-fc data. However, within the realm of tinnitus studies, a more standardized approach may be voluntarily adopted by the researchers. More than any task-based framework, a resting state paradigm lends itself to standardization in data acquisition and may be analyzed in multiple ways, at least one of which may maintain parity with other rs-fc studies of tinnitus. Of the techniques reviewed in this article, it is our opinion that seed-based rs-fc is the simplest technique and has the fewest assumptions. The major assumption made in seed-based analysis is the choice of the seed region. If several rs-fc studies chose the same seed region, it would allow for assessment of replicability and a quantitative meta-analysis of studies. We recommend that different cortical networks, apart from the auditory network (seeds in the primary auditory cortex), such as the DAN (seeds in the frontal and parietal cortices), and the DMN (seeds in the posterior cingulate cortex and medial prefrontal cortex), be routinely assessed in future studies because there is gathering evidence of the role of extra-auditory networks in tinnitus from several brain imaging studies. Additionally, it is important to account for heterogeneity by carefully choosing the test population, by controlling for variables such as degree of hearing loss, age, gender, and various aspects of tinnitus. Variability in the tinnitus profiles may relate to lateralization, age of onset, chronicity, duration of tinnitus, loudness and pitch of the percept and subjective measures of distress.

7. Conclusion

Rs-fc is in an exploratory stage in unraveling the networks subserving tinnitus. We have shown that the DMN-limbic and the auditory-limbic functional connections are altered in tinnitus and may be correlated with tinnitus-related distress. Although, the auditory-limbic link is known from task-based fMRI and structural MRI studies, the DMN-limbic link is unique to rs-fc. The third set of functional links implicated in tinnitus includes those of the attentional network. A promising avenue for further research is to focus on a particular network and to detail the specific aspects of their alteration in tinnitus, which may be invariant across sub-groups or show distinctions between sub-groups. We are optimistic about the usage of rs-fc as an objective imaging biomarker of tinnitus and its uses as a diagnostic tool. This in turn has important applications in understanding the pathophysiology of the disorder across different sub-groups, longitudinally, and also in testing the efficacy of different therapies.

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