Hearing Research 307 (2014) 153–162

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review

Using resting state functional connectivity to unravel networks of tinnitus☆

Fatima T. Husain [a,b,c,*], Sara A. Schmidt [b,c]

[a] Department of Speech and Hearing Science, University of Illinois at Urbana-Champaign, Champaign, IL, USA
[b] Neuroscience Program, University of Illinois at Urbana-Champaign, Champaign, IL, USA
[c] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Champaign, IL, USA

ARTICLE INFO

Article history:
Received 4 May 2013
Received in revised form
8 July 2013
Accepted 15 July 2013
Available online 26 July 2013

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.

This article is part of a Special Issue entitled <Human Auditory Neuroimaging>.

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.,

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

* Corresponding author. 901 S. Sixth Street, Champaign, IL 61821, USA. Tel.: +1 217 333 7561; fax: +1 217 244 2235.
E-mail addresses: husainf@illinois.edu, husainf@acnlab.com (F.T. Husain).

0378-5955/$ – see front matter © 2013 The Authors. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.heares.2013.07.010

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,

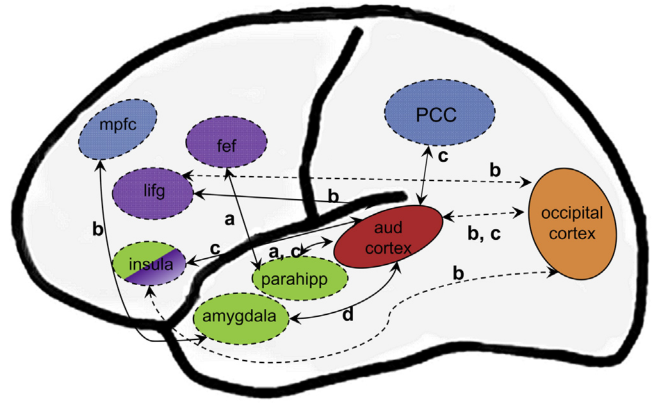

Fig. 1. Summary of main results of resting-state functional connectivity studies in tinnitus. The major networks highlighted are default-mode network (DMN, shown in blue), limbic network (green), auditory network (red), the visual network (in orange), several attention networks (specifically the dorsal 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.