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Emerging hubs in phantom perception connectomics

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ABSTRACT

Brain networks are small-world networks typically characterized by the presence of hubs, i.e. nodes that have significantly greater number of links in comparison to other nodes in the network. These hubs act as short cuts in the network and promote long-distance connectivity. Long-distance connections increase the efficiency of information transfer but also increase the cost of the network. Brain disorders are associated with an altered brain connectome which reflects either as a complete change in the network topology, as in, the replacement of hubs or as an alteration in the connectivity between the hubs while retaining network structure. The current study compares the network topology of binary and weighted networks in tinnitus patients and healthy controls by studying the hubs of the two networks in different oscillatory bands. The EEG of 311 tinnitus patients and 256 control subjects are recorded, pre-processed and source-localized using sLORETA. The hubs of the different binary and weighted networks are identified using different measures of network centrality. The results suggest that the tinnitus and control networks are distinct in all the frequency bands but substantially overlap in the gamma frequency band. The differences in network topology in the tinnitus and control groups in the delta, theta and the higher beta bands are driven by a change in hubs as well as network connectivity; in the alpha band by changes in hubs alone and in the gamma band by changes in network connectivity. Thus the brain seems to employ different frequency band-dependent adaptive mechanisms trying to compensate for auditory deafferentation.

1. Introduction

Brain networks analogous to protein (Maslov and Sneppen, 2002), computer, and social networks (Albert and Barabási, 2002; Strogatz, 2001) are described as small-world networks (Kaiser and Varier, 2011; Sporns and Zwi, 2004; Watts, 1999) that balance network cost with network efficiency (Achard and Bullmore, 2007; Bullmore and Sporns, 2012; Latora and Marchiori, 2003). The nodes of a small-world network are connected to other nodes through short and long-distance connections (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009; Watts and Strogatz, 1998). A small fraction of the nodes, called hubs, defined as nodes with significantly greater number of links in comparison to other nodes in the network (Barabasi and Albert, 1999), are connected directly with one another promoting long-distance connectivity thus increasing the global efficiency of information transfer (Achard and Bullmore, 2007; van den Heuvel and Sporns, 2011) and are instrumental in defining the small-world topology of the network. Different kinds of hubs exist, some predominantly connecting locally (=provincial hub) within a module and some having a large number of long range connections (=connector hub) connecting spatially distant modules (Bullmore and Sporns, 2012). Densely interconnected connector hubs are responsible for the integration of functional modules and form a core rich-club network (Bullmore and Sporns, 2012; van den Heuvel and Sporns, 2011; Zamora-López et al., 2010). Since they play a central role in information transfer, they incur high cost and are presented to be the most vulnerable centers for damage (Crossley et al., 2014; Kaiser et al., 2007; Stam, 2014). Deviation from small-world properties of functional networks has been documented in brain disorders such as Parkinson's (Olde Dubbelink et al., 2014), Alzheimer's (Stam et al., 2007, 2009), schizophrenia (Bassett et al., 2008; Fornito and Bullmore, 2015), dementia (Agosta et al., 2013), and traumatic brain injury (Stam, 2014).

Tinnitus is the perception of a continuous phantom sound that is commonly hypothesized to be caused due to sensory deafferentation (Jastreboff, 1990; Noreña and Farley, 2013). There is now converging evidence showing that, analogous to other brain disorders, tinnitus could also be the result of aberrant network connectivity (Lanting et al., 2014; Vanneste et al., 2011c). The current study thus attempts to investigate the differences in the functional network topology of a tinnitus and a healthy adult brain by observing the hubs of the network of the two groups in different oscillatory bands using graph theory. In order to do so we propose two possible hypotheses - (a) functional networks of the tinnitus and healthy brain share similar hubs but

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differ in the way they are connected and (b) functional networks of the tinnitus and healthy brain are fundamentally different networks involving different hubs with some regions overlapping with the normal functional module.

There is evidence from imaging and electrophysiological studies that tinnitus, analogous to other disorders such as neuropathic pain, major depression disorder, schizophrenia, and Alzheimer's disease shows changes in connectivity in some of the resting state networks such as the default mode network, dorsal attention network, auditory resting state network, salience network and the executive control network in healthy individuals (De Ridder et al., 2011, 2014b; Husain and Schmidt, 2014; Schlee et al., 2009). Resting-state fMRI studies show an increase in functional connectivity of the executive control network with the limbic regions (Schmidt et al., 2013) and auditory resting state network (Burton et al., 2012), limbic regions with resting state auditory network (Burton et al., 2012; Maudoux et al., 2012; Schmidt et al., 2013) and default mode network with the limbic (Burton et al., 2012) and auditory resting state network (Maudoux et al., 2012) in the tinnitus group. At the same time, a decreased connectivity was reported between the executive control network and the visual resting state network (Burton et al., 2012) in the tinnitus group. These findings allude to the idea that the tinnitus network could essentially consist of the same regions as a healthy control network but connected differently. Conceptually, this could be related to transformers or shape-shifters, which are fictional characters that can change their shape from a robot to that of a supercar by just changing the connections between different parts.

On the other hand, at the molecular level, it has been proposed that a disease network is formed by the disintegration of the normal functional network and a shift of core nodes within the same network (Barabási, 2007). Since several diseases share similar traits, it is suggested that some regions of the different disease networks overlap, but a specific disease has dedicated hubs that are different from the normal functional network (Barabási, 2007; Barabasi et al., 2011). There is also evidence from neuroimaging studies modeling damage to the normal brain connectome that show that although many neurodegenerative disorders affect the hubs of the normal connectome, different diseases result in having different central hubs (Crossley et al., 2014). Tinnitus, is a multi-symptom disorder where the different characteristics of tinnitus such as the loudness, pitch, distress, type and laterality are proposed to be the result of different functional subnetworks working in tandem (De Ridder et al., 2014b) towards bringing these different characteristics of tinnitus to consciousness by linking to consciousness supporting networks (De Ridder et al., 2014b; Dehaene et al., 2006; Schlee et al., 2009). The tinnitus loudness network has been proposed to consist of the auditory cortices and the parahippocampal areas (De Ridder et al., 2013; Husain and Schmidt, 2014), the distress network consists of the precuneus, insula, pregenual, subgenual and dorsal anterior cingulate cortex (Husain and Schmidt, 2014; Mayberg et al., 2005; Vanneste et al., 2010a; Weisz et al., 2005), the type of the tinnitus encoded by the frontopolar cortex, posterior cingulate cortex and the parahippocampus (De Ridder et al., 2014b) and the laterality of the tinnitus encoded by the gamma band activity in the contralateral parahippocampus (Vanneste et al., 2011b). Schlee et al. (2007) also showed using magnetoencephalography that the tinnitus distress was significantly correlated with the connectivity strength between pairs of regions selected in the temporal, prefrontal and parietal regions (Schlee et al., 2007). They allude to the possibility of a dedicated tinnitus distress network possibly consisting of the right parietal cortex, temporal regions and the anterior cingulum. In addition, tinnitus is viewed as the perception of a sound which is being constantly re-called from memory (De Ridder et al., 2006; Laureano et al., 2014) with the help of an active fronto-temporal memory retrieval network (Vanneste et al., 2011c) thus, alluding to tinnitus having a fundamentally different network structure compared to a control network.

In order to answer this research question, the most important nodes of both the binary and weighted functional networks in tinnitus patients and healthy controls are compared by looking at different centrality measures. A large overlap among the hubs of the two groups would allude to the transformer model of network organization and the appearance of distinct hubs would allude to a fundamentally different network topology in tinnitus and controls. The results of the current study are important in understanding the network structure of the tinnitus network and confirms the idea of several researchers about the existence of a wide spread network in tinnitus (De Ridder et al., 2014b; Schlee et al., 2007, 2009). Moreover, it could also provide a relationship between the network connectivity measures and effectiveness of a treatment procedure, especially given the volume of research now being presented in tinnitus treatment techniques. Such a study was presented by Hartmann and colleagues, where they evaluated the effectiveness of neurofeedback, rTMS and sham in increasing the alpha power thus enhancing the inhibitory mechanism (Hartmann et al., 2014). Moving forward, the results of the current study could provide more sophisticated techniques in addition to the one provided in the study mentioned above and help us evaluate different treatment measures, which are now gaining traction in the field of neuromodulation.

2. Materials and methods

2.1. Patients with an auditory phantom percept

The patient sample consisted of 311 patients ($M = 50.24$ years; $SD = 14.32$; 210 males and 101 females) with continuous tinnitus. If the onset of the tinnitus was reported to be a year or more, the patient's condition was considered chronic. The homogeneity of the sample was increased by excluding individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders from the study. Patients reported the perceived location of their tinnitus (the left ear, in both ears, and centralized in the middle of the head (bilateral), the right ear) including the type of tinnitus (pure tone-like tinnitus or noise-like tinnitus). Pure tone audiometric thresholds at .125 kHz, .25 kHz, .5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz were obtained using the British Society of Audiology procedures (Audiology, 2008). The pitch and loudness of the tinnitus were measured by performing a simple analysis on the ear contralateral to the tinnitus ear in patients with unilateral tinnitus and contralateral to the worst tinnitus ear in patients with bilateral tinnitus. A 1 kHz pure tone was presented contralateral to the (worst) tinnitus ear at 10 dB above the patient's hearing threshold in that ear. The frequency of the tone was adjusted until the pitch of the tone matched the perceived pitch of the patient's tinnitus. The intensity of this tone was then adjusted in a similar way until it corresponded to the perceived loudness of the patient's tinnitus. The tinnitus loudness (dB SL) was computed by subtracting the audiometric threshold from the absolute tinnitus loudness (dB HL) at that frequency (Meeus et al., 2009, 2011). See Table 1 for an overview of the tinnitus characteristics. This study was approved by the local ethical committee (Antwerp University Hospital) and was in accordance with the declaration of Helsinki.

2.2. Healthy control group

A healthy control group ($N = 256$; $M = 49.514$ years; $SD = 14.82$; 154 males and 102 females) was included in the study. None of these subjects reported to suffer from tinnitus. Psychiatric or neurological illness, history of psychiatric or drug/alcohol abuse, history of head injury (with loss of consciousness) or seizures, headache, or physical disability were the exclusion criteria for the study. No hearing assessment was performed for these healthy controls.