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Research paper

Left hemisphere fractional anisotropy increase in noise-induced tinnitus: A diffusion tensor imaging (DTI) study of white matter tracts in the brain

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ABSTRACT

Diffusion tensor imaging (DTI) is a contemporary neuroimaging modality used to study connectivity patterns and microstructure of white matter tracts in the brain. The use of DTI in the study of tinnitus is a relatively unexplored methodology with no studies focusing specifically on tinnitus induced by noise exposure. In this investigation, participants were two groups of adults matched for etiology, age, and degree of peripheral hearing loss, but differed by the presence or absence (+/−) of tinnitus. It is assumed that matching individuals on the basis of peripheral hearing loss, allows for differentiating changes in white matter microstructure due to hearing loss from changes due to the effects of chronic tinnitus. Alterations in white matter tracts, using the fractional anisotropy (FA) metric, which measures directional diffusion of water, were quantified using tract-based spatial statistics (TBSS) with additional details provided by *in vivo* probabilistic tractography. Our results indicate that 10 voxel clusters differentiated the two groups, including 9 with higher FA in the group with tinnitus. A decrease in FA was found for a single cluster in the group with tinnitus. However, seven of the 9 clusters with higher FA were in left hemisphere thalamic, frontal, and parietal white matter. These foci were localized to the anterior thalamic radiations and the inferior and superior longitudinal fasciculi. The two right-sided clusters with increased FA were located in the inferior fronto-occipital fasciculus and superior longitudinal fasciculus. The only decrease in FA for the tinnitus-positive group was found in the superior longitudinal fasciculus of the left parietal lobe.

1. Introduction

Noise-induced hearing loss (NIHL) is a ubiquitous phenomenon observed in modern society (Clark and Bohne, 1999). It is also a prominent concern for individuals serving in the military (Humes et al., 2006) and represents a known risk factor for developing tinnitus (e.g., Dong et al., 2010; Henderson et al., 2011; Yankaskas, 2012). Epidemiological studies indicate that as hearing thresholds exceed the mild range of severity in the better ear at 4.0 kHz, the odds ratio for expressing moderate to severely annoying tinnitus increases from 5 to 27 (Coles, 2000). Other studies support this observation by documenting that over 83% of individuals with NIHL have tinnitus (Mazurek et al., 2010). While mechanisms underlying tinnitus expression are not completely known, available evidence suggests that temporary or permanent damage to sensory cells in the inner ear is a known trigger of this phenomenon, resulting in temporary or permanent elevations in auditory thresholds, physiological changes in auditory nerve discharge properties (e.g., Liberman and Kiang, 1978; Henderson et al., 2011; Kujawa and Liberman, 2009) and secondary anatomical and physiological effects in the central auditory nervous system (e.g., Morest et al., 1998; Salvi et al., 2000; Syka, 2002; Schreiner and Cheung, 2004). These observations suggest that reduced afferent drive from the periphery leads to an imbalance between inhibitory and excitatory input to auditory neurons at various levels in central auditory pathways (e.g., Middleton et al., 2011; Wang et al., 2011; Brozoski et al., 2012; Browne et al., 2012; Godfrey et al., 2012). This altered

Abbreviations: ATR, anterior thalamic radiations; dB, decibels; DTI, diffusion tensor imaging; FA, fractional anisotropy; FMRIB, functional magnetic resonance imaging of the brain; FSL, functional software library; GABA, gamma-aminobutyric acid; ICBM, International Consortium of Brain Imaging; MRI, magnetic resonance imaging; NIHL, noise induced hearing loss; ROI, region-of-interest; SLF, superior longitudinal fasciculus; TBSS, tract based spatial statistics; TE, echo time; TR, repetition time

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pattern of activity is thought to destabilize circuits in the brainstem and cortex resulting in plastic readjustments attempting to compensate for this disparity (e.g., Eggermont and Roberts, 2004; Roberts et al., 2010). Either alone or in combination, neuronal hyperactivity, bursting discharges, and increased cortical or brainstem/thalamic neural synchrony are thought to be the neurophysiological substrates that result in the perception of tinnitus (e.g., Dong et al., 2010; Henderson et al., 2011; Kaltenbach, 2011; Brozoski et al., 2012). Interestingly, while excessive noise exposure can produce anatomical, physiological, and biochemical changes in peripheral and central auditory pathways, not all individuals with NIHL or other otopathologies develop tinnitus (e.g., Lockwood et al., 2002). Indeed, the precise reasons for this discrepancy remain unknown.

To better understand the neurobiology of noise-induced tinnitus and evaluate its relationship, if any, to white matter changes in the brain, diffusion-tensor imaging (DTI) was used as a platform for discovery. Diffusion-tensor imaging represents a neuroimaging modality that can provide insight into plastic/reactive changes in white matter microstructure and connectivity associated with tinnitus that cannot be detected by conventional magnetic resonance imaging (MRI). Specifically, this imaging modality measures the displacement of water molecules (diffusion) within white matter tracts, providing information on the microstructure of cerebral white matter and thus serves as a biomarker of tissue integrity (e.g., Ling et al., 2012). For each voxel, DTI estimates diffusion in three orthogonal axes (eigenvectors) of an ellipsoid, defining the principal (major), intermediate, and minor axes. The most commonly used metric to quantify the relationship between eigenvalues is fractional anisotropy (FA), a normalized scalar that represents the fraction of the diffusion tensor which is anisotropic. Herein, we focus on FA, because it reveals information regarding fiber integrity and network reorganization, i.e., activity dependent neuroplasticity (Yu et al., 2007; Scholz et al., 2009; Steele et al., 2013).

The FA metric ranges between 0 and 1, where 0 represents perfectly "isotropic" diffusion, such as is found in the cerebrospinal fluid where diffusion is equivalent in all directions, and where 1 is the extrema for "anisotropic" diffusion, indicating maximum difference between directional components, such as is found in coherent white matter tracts which consist of long tubes.

Prior use of DTI in tinnitus research is limited to a small number of studies with mixed results (e.g., Lee et al., 2007; Crippa et al., 2010; Husain et al., 2011; Aldhafeeri et al., 2012). These studies are reviewed below.

Lee et al. (2007) used DTI to study adults with mild-to-severe hearing loss and tinnitus ($n = 28$; 11 female, 17 males; age range 22–70 years) and compared results to a group of "normal hearing" younger controls ($n = 12$; 6 males, 6 females; age range 22–34 years). While they indicated that 12 had left-sided tinnitus for a duration of 1–8 years (mean duration 3 years), details regarding etiology were not provided. In comparison to the control group, Lee et al. (2007) found significant *reductions* in FA in the left frontal and right parietal arcuate fasciculus. However, because the control group was not matched for hearing loss or age, it would be difficult to differentiate white matter changes due to tinnitus from changes due to hearing loss or age effects. Thus, these findings are indeterminate with respect to tinnitus-related dysfunction.

Crippa et al. (2010) used region-of-interest (ROI) analysis and probabilistic tractography as methods to study DTI changes in tinnitus in 15 healthy subjects and 10 subjects with tinnitus which were matched for age but not explicitly for hearing thresholds. In theory, probabilistic tractography is of interest because it allows investigators to resolve voxels with multiple fiber directions that cross in a voxel. This ROI analysis scheme helps to isolate white matter fiber connections in classical (inferior colliculus to auditory cortex) and non-classical (auditory cortex to amygdala) auditory pathways. Their approach was partially successful in that the tinnitus group showed a right lateralization of increased FA values which they describe as "an increased patency of the white matter tracts between the auditory cortex and the amygdala in tinnitus patients as compared to healthy controls, p. 16." This difference in the non-classical pathway, however, may be a consequence of chronic exposure to an unpleasant or distressing perception rather than a clue to the generation mechanism of the tinnitus perception.

Husain et al. (2011) were unable to detect differences in FA in adults with tinnitus ($n = 8$) in comparison to age and hearing loss matched controls without tinnitus ($n = 7$) and normal hearing controls ($n = 11$). Possible reasons for their negative results include: a small sample size, heterogeneity of etiology of hearing loss and/or tinnitus, and the fact that the average severity rating of tinnitus in their sample was in the "mild" range.

Aldhafeeri et al. (2012) studied cortical and white matter FA and diffusivity in healthy volunteers with no tinnitus and normal hearing ($n = 14$; 9 males, 5 females; age range 30–60 years, mean age 46.5 years) and participants with tinnitus and hearing loss, described as no worse than 40 dB HL at 2.0 kHz and 60 dB HL at 4.0 kHz ($n = 14$), 8 males, 6 females, 30–60 years of age, mean age 49.5 years. Whereas cortical thickness was found to negatively correlate with hearing thresholds, in comparison to controls, the participants with tinnitus and hearing loss showed reduced white matter FA values in the right prefrontal cortex, right auditory cortex, and corpus callosum. However, this study was also limited by the fact that comparisons of FA were made between a tinnitus positive group *with* hearing loss to a control group *without* hearing loss.

In summary, out of 4 studies using DTI to study tinnitus, 1 had negative results (Husain et al.), 2 had inadequate control groups (Lee et al., 2007; Aldhafferi et al., 2012) and 1 showed positive results (Crippa et al., 2010) but their novel quantification methodology requires further development in order to be successfully applied to all participants. Nevertheless, both whole brain (voxel-wise) and ROI DTI analyses have proven successful in identifying brainstem and cortical pathway anomalies in tinnitus positive groups. While there are both strengths and weaknesses to each type of analysis methodology (e.g., Snook et al., 2007), combining both procedures may be the most comprehensive approach to be applied in future endeavors in this area.

Therefore, to enhance understanding in this area, improve the specificity of results and to help distinguish white matter changes due to pathologic plasticity associated with noise-induced tinnitus from white matter changes due to hearing loss, we studied two groups of individuals, using whole brain and ROI approaches, matched for NIHL but differing in presence or absence of tinnitus.

2. Materials

2.1. Subjects

Two groups of adults with a common history of occupational, recreational, or military noise exposure, *with* and *without* tinnitus, matched for degree/severity of hearing loss and age were evaluated. Participants were recruited from newspaper ads, referrals from medical and/or allied health professionals in the greater Detroit metropolitan area (i.e., otolaryngologists, neurologists, audiologists) and by word-of-mouth. Group 1 consisted of adults with NIHL *without* tinnitus ($n = 13$, mean age 58 years, range 22–88 years); Group 2 consisted of adults with NIHL *with* tinnitus ($n = 13$, mean age 54 years, range 28–80 years). The selection criteria utilized was based on the assumption that homogeneous groups of individuals with similar etiologies will improve biomarker