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Research Report

Cluster analysis for identifying sub-types of tinnitus: A positron emission tomography and voxel-based morphometry study

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ABSTRACT

Tinnitus is a heterogeneous disorder with respect to its etiology and phenotype. Thus, the identification of sub-types implicates high relevance for treatment recommendations. For this aim, we used cluster analysis of patients for which clinical data, positron-emission tomography (PET) data and voxel-based morphometry (VBM) data were available. 44 patients with chronic tinnitus were included in this analysis. On a phenotypical level, we used tinnitus distress, duration, and laterality for clustering. To correct PET and VBM data for age, gender, and hearing, we built up a design matrix including these variables as regressors and extracted the residuals. We applied Ward's clustering method and forced cluster analysis to divide the data into two groups for both imaging and phenotypical data. On a phenotypical level the clustered groups differed only in tinnitus laterality (uni- vs. bilateral tinnitus), but not in tinnitus duration, distress, age, gender, and hearing. For grey matter volume, groups differed mainly in frontal, cingulate, temporal, and thalamic areas. For glucose metabolism, groups differed in temporal and parietal areas. The correspondence of classification was near chance level for the interrelationship of all three data set clusters. Thus, we showed that clustering according to imaging data is feasible and might depict a new approach for identifying tinnitus sub-types. However, it remains an open question to what extent the phenotypical and imaging levels may be interrelated.

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1. Introduction

Tinnitus, the perception of sound in the absence of an external auditory stimulus, is experienced by 5–15% of the general population (Shargorodsky et al., 2010). Tinnitus can be perceived as a pure tone or as a more complex sound and can be perceived in one ear, both ears, or in the head. Frequency, loudness, and the capability to mask tinnitus by external sounds vary also from patient to patient (Tyler and Conrad-Armes, 1984; Tyler et al., 1984). The clinical manifestation of tinnitus ranges from

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intermittent tinnitus perception with little impact on daily life to very bothersome tinnitus preventing the ability to perform intellectual work and leading to social isolation (Stouffer and Tyler, 1990). It is estimated that the condition severely affects quality of life in approximately 1% of the population (Axelsson and Ringdahl, 1989; Khedr et al., 2010). In these patients tinnitus is often accompanied by comorbid symptoms such as anxiety, depression, irritability, agitation, stress, depression and/or insomnia (Langguth, 2011; Malouff et al., 2011). In the light of this high diversity of the phenotype, heterogeneous pathophysiological mechanisms are to be expected. For example, pulsatile tinnitus synchronous to heart beat is often caused by malformations of blood vessels in the brain (Madani and Connor, 2009). In these cases of objectively measurable tinnitus an internal sound source can often be identified and causally treated in contrast to subjective tinnitus, where no sound source can be identified (De Ridder et al., 2007).

Various criteria for sub-typing of subjective tinnitus have been proposed based both on clinical experience (Levine et al., 2008; Lindblad et al., 2011) and on empirical data (Kleinjung et al., 2007; Vielsmeier et al., 2011). However, it still remains a major challenge to identify useful criteria for identifying clinically relevant subtypes.

One approach for identification of tinnitus sub-types is based on cluster analysis procedures. Using this data-driven statistical technique subjects can be classified to particular sub-groups. Subjects within the sub-groups are more similar to each other than subjects between the groups based on the variables included in the analysis. There are three studies which used phenotypical variables to establish tinnitus sub-groups. Andersson and McKenna (1998) found in a sample of 30 patients three sub-groups which differed in depressivity and tinnitus characteristics. Rizzardo et al. (1998) extracted two groups out of 83 patients which differed in depressivity, anxiety, and neuroticism, indicating the existence of a distressed sub-group. Recently, Tyler et al. (2008) found four subgroups in 153 patients with one group depicting again a distressed group. Tinnitus distress is uni-dimensionally classified in severity grades as elicited by the tinnitus questionnaires THI and TQ (Göbel and Hiller, 1994; Hallam et al., 1988; Newman et al., 1996).

With respect to tinnitus distress, it could be shown that high levels of tinnitus distress are related to altered alpha, beta and theta activity in the frontal, temporal, cingulate, insular, and parahippocampal areas as well as the amygdala as indicated by altered resting state electroencephalography (EEG) or magnetoencephalography in contrast to low levels of distress (De Ridder et al., 2011a; van der Loo et al., 2011; Vanneste et al., 2010; Weisz et al., 2005). Resting state positron emission tomography (PET) showed an association of tinnitus distress with metabolic activity of bilateral (para-) hippocampal and posterior temporal areas (Schecklmann et al., 2011). Thus, tinnitus sub-groups as elicited by cluster analysis of phenotypical variables (i.e., tinnitus variables such as distress) are related to alterations on a neurobiological level. However, correlation coefficients of these studies are low.

Besides distress, a small number of studies also showed a relationship of other tinnitus variables such as tinnitus duration and laterality with neural activity. A magnetoencephalographic (MEG) study explored the changes of neuronal network activity occurring with increasing tinnitus duration (Schlee et al., 2009). This analysis demonstrated that tinnitus with a duration of more than 4 years is related to a more widespread and distributed network activity as compared to shorter lasting tinnitus. Resting state PET showed an association of duration with metabolic activity of right frontal areas and the posterior cingulate cortex (Schecklmann et al., 2011). Findings in relation to laterality are heterogeneous. Resting state EEG power showed relationships of contralateral auditory gamma activity with unilateral tinnitus (van der Loo et al., 2009). Uni- and bilateral tinnitus differed in beta and gamma activity in premotor, parahippocampal and parietal areas (Vanneste et al., 2011).

These papers exemplarily stand for a recently proceeding paradigm shift in tinnitus research broadening the scientific focus from periphery to neural structures—although there is long standing evidence that retrocochlear processes might also be involved (Tyler and Conrad-Armes, 1984). Earlier assumptions of tinnitus as being a problem of the ear have been replaced by pathophysiological models of neuroplastic changes in the auditory pathways and recently complemented by the identification of multiple parallel networks, involving auditory and non-auditory brain areas (for an overview see Adjamian et al., 2009; De Ridder et al., 2011a; Lanting et al., 2009). A recent working model indicates several neural tinnitus networks for conscious perception, attention allocation, distress, and memory processes (De Ridder et al., 2011a). However, direct relationships of these areas with the attributed functions in tinnitus still remain to be shown in future studies.

In conclusion, cluster analysis of tinnitus characteristics revealed tinnitus sub-groups on a phenotypical level. Thus, the aim of our study was to show the feasibility of cluster analysis for structural (voxel-based morphometry, VBM) and functional imaging (PET) data. Furthermore, there are some hints for a relationship between neural activity and structure and the clinical phenotype. However, these associations are weak. Thus, we aimed to investigate the interrelationship and classification correspondence of clustering approaches based on neuroimaging and phenotypical variables. The goal of these analyses is to shed light on the question whether clustering of imaging data can contribute additional information to tinnitus sub-typing.

2. Results

Results of cluster analyses are shown in Tables 1 and 2 and Fig. 1. Cluster analysis of phenotypical data resulted in groups that were different with respect to tinnitus laterality, but not to tinnitus duration and distress (Table 1). In addition, groups were comparable for age, gender, and hearing (Table 1). Cluster analysis of VBM data showed that groups differed in grey matter volume in medial frontal, cingulate, temporal, insular, pre- and postcentral, and thalamic areas (Table 2, Fig. 1). One group showed higher grey matter volume in contrast to the other group. Again, groups were comparable for age, gender, and hearing, and also for tinnitus duration, laterality, and distress (Table 1). Cluster analysis of PET data showed that groups differed in medial and superior temporal, superior parietal, and precuneus areas (Table 2, Fig. 1). Again one group had higher glucose metabolism in contrast to the