

Cortical auditory evoked potentials, brain signal variability and cognition as biomarkers to detect the presence of chronic tinnitus

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ABSTRACT

The current limited understanding of tinnitus neurophysiology is one of the major obstacles in developing effective treatments for chronic tinnitus. As such, there is an urgent need for knowledge on underlying neural and/or neurobehavioral correlates that might function as potential biomarkers for tinnitus. We aimed to develop a model for the detection of tinnitus cases based on such potential biomarkers. In a first step, data from twenty patients suffering from chronic tinnitus, but no concurrent hearing loss or psychological complaints, were compared to data from twenty matched controls. Cortical auditory evoked potentials (CAEP) were elicited using a standard oddball paradigm. Source estimation and brain signal variability were analyzed to investigate putative differences between tinnitus patients and controls. Other examinations included standard audiometry, speech understanding in quiet and noisy conditions, and cognitive testing using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The P300 component, a response to unexpected but relevant stimuli, was significantly reduced in the tinnitus group. Source estimation revealed that the response of tinnitus patients was characterized by a decreased activity in temporal cortex, parahippocampus and insula. Brain signal variability on fine time scales was significantly higher in the tinnitus group, suggesting that tinnitus patients rely more strongly on local information processing. Furthermore, tinnitus was associated with a decreased cognitive performance, especially on tasks measuring delayed memory. In a second step, a logistic regression model was constructed based on CAEP activity, brain signal variability and RBANS scores. This model performed significantly above chance level when detecting tinnitus cases in an unseen dataset (accuracy of 75%, area under the ROC curve of 0.86). The successful classification between tinnitus cases and controls demonstrates the potential value of the proposed combination of biomarkers. Moreover, the identified associations between tinnitus, auditory evoked activity and cognitive performance point towards a significant contribution of top-down information processing in the perception of tinnitus.

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1. Introduction

Tinnitus, the conscious awareness of a sound in the absence of a corresponding external sound source, is estimated to occur in 12 to 30% of the worldwide adult population (Bhatt et al., 2016;

McCormack et al., 2016). The term 'Tinnitus Disorder' has recently been introduced to describe those cases when tinnitus becomes associated with emotional distress, cognitive dysfunction and/or autonomic arousal (De Ridder et al., 2021). Patients suffering from Tinnitus Disorder may experience one or several accompanying symptoms such as anxiety, depression, hyperacusis, insomnia, concentration difficulties and hearing problems, all of which can contribute to a substantial decrease in quality of life (Bhatt et al., 2017; Schecklmann et al., 2014; Tegg-Quinn et al., 2016). The extent of tinnitus and its accompanying symptoms varies severely within the patient population, and this heterogeneity has proven

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to be one of the most challenging hurdles in the search for an evidence-based treatment for tinnitus (McFerran et al., 2019). For a subgroup of patients with concurrent hearing loss, hearing aids or implantable devices such as cochlear implants and auditory brainstem implants can provide significant tinnitus relief (Gilles et al., 2020; Mertens et al., 2016; Zarenoue et al., 2017). However, a large group of tinnitus patients is not eligible for this type of treatment, and there is an urgent need for personalization in tinnitus treatment (Van de Heyning et al., 2015). Counseling-based treatment options, such as cognitive behavioral therapy, have a well-documented beneficial effect on quality of life in tinnitus patients. However, these interventions sometimes have only modest effects on tinnitus severity, and evidence for long-term effects is currently lacking (Fuller et al., 2020).

The exact pathophysiological mechanisms underlying tinnitus emergence and maintenance remain elusive. Undoubtedly, there is a strong link between tinnitus and hearing loss. As such, hearing loss is considered the main risk factor for tinnitus. However, it has proven particularly challenging to explain why not all tinnitus patients have hearing loss as measured via an audiogram. Cochlear damage seems to be a critical condition for the development of tinnitus, but this damage may not necessarily be expressed in elevated hearing thresholds. Rather, if hair cells are still intact but the synapses connecting them to auditory nerve fibers are affected, only suprathreshold hearing may be reduced (Gilles et al., 2016; Roberts, 2018). How this so-called 'hidden hearing loss' eventually leads to tinnitus is formalized in the theory of central gain (Schaette and Kempster, 2006; Sedley, 2019). As cochlear damage deprives auditory neurons from their usual somatosensory input, they maintain homeostasis by increasing their firing rate in response to auditory stimuli and amplifying spontaneous firing. This amplified activity is then relayed to higher order nuclei and, ultimately, the auditory cortex, leading to the perception of tinnitus.

Increased spontaneous activity in central auditory pathways and increased synchronous activity have indeed been shown in animal models of tinnitus (Engineer et al., 2011; Norena and Eggermont, 2003, 2006; Wu et al., 2016), but direct evidence for this bottom-up central gain hypothesis in humans is sparse. Moreover, recent findings offer some arguments against central gain as the sole cause of tinnitus perception. For instance, lasting effects of these proposed alterations in central auditory pathways would include a re-tuning of auditory cortex neurons and a reorganization of its tonotopy. However, cortical tonotopic map changes were recently shown to be more extensive in patients with hearing loss than in those with additional tinnitus (Koops et al., 2020). Thus, recent research in the tinnitus field is characterized by a turn away from the central gain hypothesis towards additional or alternative explanatory models, often offering a more top-down perspective (Knipper et al., 2020). For instance, the predictive coding hypothesis stipulates that the perception of tinnitus is not determined by spontaneous synchronous activity, but relies on higher perceptual networks switching to recognizing spontaneous auditory activity as an auditory entity instead of noise (Sedley et al., 2016). Additional mechanisms via which the perception of tinnitus is maintained could also include focused attention or the formation of pervasive memory traces (De Ridder et al., 2014a).

Overall, there is a large, albeit diffuse, body of evidence of higher-order cortical network malfunctioning in tinnitus. Different neuroimaging techniques have been used to chart cortical function and connectivity in tinnitus patients (for an overview: see Elgoyhen et al., 2015). Resting-state EEG and MEG studies have shown hyperactivity in the auditory cortex, mostly expressed as a reduction of alpha power and increase in slow-wave (delta and theta) and gamma power (Adamchic et al., 2014; Moazami-Goudarzi et al., 2010; Weisz et al., 2007). These abnormal oscillatory

patterns are often associated with tinnitus loudness (van der Loo et al., 2009). Overall, these studies point towards a heightened involvement and altered connectivity among auditory and non-auditory cortical areas (De Ridder et al., 2014b), most notably the prefrontal cortex, parahippocampus, anterior cingulate and insula (Song et al., 2015; Vanneste et al., 2010, 2011). Particularly ubiquitous in tinnitus research are cortical auditory evoked potentials (CAEP), voltage fluctuations in response to auditory stimuli that can be extracted from the ongoing EEG (Alain et al., 2013; Picton, 2011). CAEPs can broadly be divided into exogenous components, occurring largely regardless of subject state, and endogenous components reflecting task-dependent neural processes (Linden, 2005). A recent meta-analysis revealed the P300, an endogenous CAEP component indicating the detection of an informative task-relevant stimulus, as a potential biomarker for tinnitus (Cardon et al., 2020). This specific deficit in evoked cortical response has been suggested to reflect an impairment in top-down attentional processing in tinnitus patients (Gabr et al., 2011; Hong et al., 2016).

As a possible manifestation of these cortical deficits, tinnitus is often accompanied by some degree of cognitive malfunctioning. A recent systematic review and meta-analysis has shown associations between tinnitus and performance in several distinct domains of cognition (Clarke et al., 2020). Much attention has been paid to the impact of tinnitus on the executive control of attention (Mohamad et al., 2016; Tegg-Quinn et al., 2016). Specifically, it has been suggested that, while tinnitus patients do not necessarily suffer from a general attentional deficit, they exhibit a diminished ability to resolve conflict among responses and to voluntarily regulate the allocation of attentional resources (Heeren et al., 2014). This reduced top-down executive control can express itself in a diminished performance on selective attention paradigms (Jackson et al., 2014), but also as a deficit in semantic fluency (Cardon et al., 2019). Other cognitive domains affected by tinnitus include processing speed, short-term memory, and learning and retrieval (Clarke et al., 2020).

The search for efficient therapies for tinnitus is severely hampered by our limited understanding of its underlying neurophysiology. Thus, there is an urgent need for knowledge on underlying neural and/or neurobehavioral correlates that might function as potential biomarkers for tinnitus. Since multiple neural sources along the auditory pathway have been suggested to contribute to the tinnitus percept, various potential biomarkers evaluating the entire pathway ranging from simple to complex auditory and cognitive processing should be evaluated. We hypothesize that in tinnitus patients, auditory-cognitive processing is altered and that a combination of assessments, evaluating different aspects, will provide a more comprehensive model. Such a combination of different biomarkers has already been recommended in other research domains, such as chronic pain and dementia (Brooks and Loewenstein, 2010; Wideman et al., 2019). For instance, the integration of physiological biomarkers and cognition was recently shown to be superior in predicting the conversion from mild cognitive impairment to Alzheimer's disease (Darmanthe et al., 2021).

Thus, the aim of this study was to determine whether there exists a combination of EEG-based biomarkers and/or cognitive measures that can distinguish between tinnitus patients and controls. In a first part, we investigate how auditory evoked activity, estimated underlying source activity, brain signal variability, cognitive performance, and speech perception differ between tinnitus patients and matched controls. Then, we employ the results of these analyses to construct a logistic regression model for the detection of tinnitus cases, examining whether such a model is able to accurately distinguish tinnitus patients from controls in previously unseen data.

Table 1
Demographic characteristics of all participants.

	Tinnitus	Control
Age: mean (SD)	51.6 (11.8)	52.2 (11.9)
Gender: male/female (n)	12/8	12/8
Education level: primary/secondary/higher education (n)	1/5/14	0/4/16
Hearing level: PTA ₁₋₂₋₄ kHz (SD)	16.2 (7.9)	15.4 (7.8)
TFI: mean (SD)	47.6 (17.3)	–
Tinnitus laterality: bilateral/unilateral right/unilateral left (n)	14/3/3	–

PTA₁₋₂₋₄ kHz: pure tone average of 1, 2 and 4 kHz of the worst ear; TFI: Tinnitus Functional Index.

2. Material and methods

2.1. Subjects

All participants were recruited and tested at the Antwerp University Hospital. Patients with tinnitus presenting at the tertiary tinnitus center (TINTRA – Tinnitus Treatment and Research center Antwerp) were invited to participate. Tinnitus patients were included if the tinnitus had persisted for at least 3 months and if their Tinnitus Functional Index (TFI) scores ranged between 25 and 90. This inclusion criterion was chosen to recruit from a population of patients for whom tinnitus constitutes an important complaint, in order to adhere to the clinical reality as closely as possible. A considerable variability in tinnitus severity was observed, with TFI scores of the included participants ranging from 28 to 88. Exclusion criteria included a clear somatic origin of the tinnitus, pregnancy, active middle ear pathology, and hearing implants. Fourteen subjects experienced tinnitus in both ears, while the remaining six perceived their tinnitus unilaterally. Control subjects were recruited via advertising, with self-reported tinnitus considered as an exclusion criterion for the control group. In order to exclude possible effects of confounding factors, subjects were carefully matched for age, sex, education level, and hearing level (pure tone averages of 1, 2 and 4 kHz for each ear separately). All subjects had normal hearing for their age. To rule out putative confounding effects of anxiety or depression, participants scoring higher than 11 on either subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) were excluded from the study. All subjects were right-handed, as evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). Mean age of all subjects was 51.9 years (range: 23–72). Demographic characteristics of all participants are summarized in Table 1.

The Committee for Medical Ethics of the Antwerp University Hospital approved the study (file numbers: EC 16/43/450, EC 17/18/228, EC 18/33/365). All participants gave written informed consent before testing.

2.2. Cortical auditory evoked potentials

2.2.1. Recording

Electroencephalography (EEG) was recorded using the Micromed™ SD LTM 64 Express system (Gilat Medical™ Event Related Potentials system). Thirty-one Ag/AgCl electrodes were arranged according to the 10–20 Standard International Electrode System, referenced to a chin electrode. The ground electrode was placed on the right mastoid, with an additional electrode located below the right eye to record the vertical electrooculogram. CAEPs were elicited using an oddball paradigm. Participants were instructed to press a button each time a rare stimulus (2 kHz, probability of 20%) was presented in between frequent stimuli (1 kHz). Duration of both stimuli was 100 ms, with rise and fall times of 5 ms. A total of 175 stimuli were presented to the participants, with an interstimulus interval of 2.2 s. Stimuli were delivered through shielded headphones (Audio Technica ATH

M30x Refaeds) via the Presentation™ software (Neurobehavioral Systems Inc., Berkeley, USA). EEG data was sampled at a sampling rate of 1024 Hz with 22-bit A/D resolution. Electrodes were prepared using a conductive gel and impedances were kept below 10 kΩ. Patients were instructed to lean back and avoid excessive movements, especially eye and head movements, when possible. Participants were able to execute the task highly accurately, with average correct response rates of $99.79 \pm 0.60\%$ and average reaction times of 0.445 ± 0.080 s.

2.2.2. Processing

EEG data were processed using the Fieldtrip toolbox implemented in Matlab (MATLAB version 9.11.0.1769968 (R2021b), The Mathworks, Inc, 1994–2021) (Oostenveld et al., 2011). Reporting of EEG processing and analysis is in line with current publication guidelines (Keil et al., 2014; Picton et al., 2000). Offline bandpass filtering was applied to continuous EEG data to improve the signal-to-noise ratio, using a default Butterworth IIR filter between 0.5 and 45 Hz. Bad channels were identified according to standardized criteria (i.e. excessive noise or low activity). Independent component analysis (ICA) was used to separate components indicating eye blinks based on the time course and localization of the components. Components containing the eye blinks were removed from the data using the inverse ICA procedure. Next, data were segmented into two-second epochs time-locked to the stimuli. Artifacts were rejected by means of a manual rejection procedure based on visual inspection of the amount of variation in the data. On average, 23.38 ± 6.88 trials were rejected (13.36% of all trials). The number of rejected trials did not differ between the tinnitus and control group ($t = 1.30$, $p = 0.21$). Excluded channels were interpolated using a weighted algorithm, estimating the signal of a bad channel based on the activity of the neighboring channels. The average number of interpolated channels was 0.95 ± 1.18 , with no differences between both experimental groups ($t = 1.14$, $p = 0.27$). Epochs were corrected to a baseline period of 0.2 s preceding stimulus presentation and detrending was applied to remove linear trends from the data. Finally, responses to target and non-target tones were averaged separately.

2.2.3. Group analysis

First, grand averages for each subject group and time point were constructed to visually inspect possible differences in the CAEP waveform. As no major differences between electrodes were identified, an average waveform across all electrodes was constructed purely for visualization purposes. The Fieldtrip toolbox was used to detect differences between subject groups on a global average and on a scalp level (Oostenveld et al., 2011). Tinnitus and control groups were contrasted using a paired t -test for each time point and electrode ($p < 0.05$). Permutation testing using the Monte Carlo method with 1000 iterations was applied to detect clusters displaying significant differences between subject groups.

2.2.4. Source estimation

Source estimation was performed on a standard boundary element headmodel including scalp, skull, and brain tissue. Correct

alignment of the headmodel and the electrode arrangement was ensured via visual inspection. Next, a leadfield was computed with a resolution of 10 mm, resulting in 4050 vertices. Source activity was visualized on the canonical cortical sheet available within the Fieldtrip toolbox. Minimum norm estimation was used to estimate the source of the data across the time domain. Subject groups were contrasted using a paired *t*-test for each time point and vertex ($p < 0.05$). Similar to the group analysis of the CAEP waveform, the results were corrected for multiple comparisons via permutation testing using a Monte Carlo simulation with 1000 iterations. Cluster-based permutation testing was performed as a nonparametric statistic procedure, in which samples were clustered in connected sets on the basis of temporal and spatial adjacency. Cluster-level statistics were calculated by taking the sum of *t*-values within every cluster. Regions were determined by cross-referencing with the Automated Anatomical Labeling (AAL) atlas included in the Fieldtrip toolbox (Tzourio-Mazoyer et al., 2002).

2.2.5. Brain signal variability analysis

Complexity and predictability of the EEG signal was analyzed using multiscale entropy (MSE), a method for characterizing non-stationary dynamic changes and long-range correlations in neural signals (Courtillot et al., 2016; Wang et al., 2018). Eye blinks were not removed from the EEG data for this analysis, as it has been shown that the removal of eye blink artifacts may negatively affect accuracy of the MSE calculation (Eldridge et al., 2014). Instead, raw data were immediately segmented into 1.2 s epochs time-locked to the stimuli. Artifact rejection, baseline correction and detrending were performed as described above. Concatenated segments of twenty seconds were used for each subject as input for MSE calculation. Signal complexity was analyzed in R (version 4.0.5, The R Foundation for Statistical Computing, 2021) using the *MSMVSampEn* package (Areshenkoff, 2021). Full details of the MSE calculation procedure can be found in (Costa et al., 2002, 2005). In short, through a coarse-graining method, a profile of entropy inherent in the brain signal across multiple time scales can be determined. An important distinction can be made between MSE values on fine time scales, linked to local neural interconnectivity, and values on coarse time scales, representative of more distributed information processing. MSE was calculated for each electrode separately on 20 timescales. Following several studies applying MSE to EEG signals, the similarity criterion *r*, used to compare vectors, was set at 0.15, while the vector length *m* was fixed at 2 (Bosl et al., 2011; Costa et al., 2005; Sleimen-Malkoun et al., 2015). For statistical analysis, the 31-electrode data were summarized by averaging the MSE in 8 regions of interest (ROIs: prefrontal, occipital, and bilateral frontal, temporal and parietal regions), each consisting of 3 or 4 electrodes. A linear mixed model was performed with subject as random factor and Group, ROI and the interaction Group*ROI as fixed factors.

2.3. Cognitive testing

Cognitive functioning was evaluated using the Repeatably Battery for the Assessment of Neuropsychological Status, adjusted to test hearing-impaired individuals (RBANS-H). The RBANS-H has been developed to examine the cognitive function of individuals suffering from hearing impairment (Claes et al., 2016). To this end, a number of adjustments have been made in accordance to the RBANS guidelines (Randolph et al., 1998). The RBANS assesses five broad domains of cognition, i.e. immediate memory, visuospatial / constructional processing, language, attention and delayed memory, and consists of 12 subtests. A detailed overview of all different subtests can be found in (Claes et al., 2016). The RBANS-H total score and five domain scores were compared between the tinnitus and control group using paired *t*-tests ($\alpha = 0.05$).

2.4. Audiological evaluation

2.4.1. Pure tone audiometry

Pure-tone linear audiometry was performed according to current clinical standards (International Organization for Standardization [ISO] 8253-1:2010), using a two-channel AC-40 audiometer (Interacoustics, Assens, Denmark) in a soundproof booth. Air conduction thresholds were measured at standard frequencies ranging from 125 Hz to 8 kHz. Pure tone averages of 1, 2 and 4 kHz were averaged for each ear separately.

2.4.2. Speech comprehension in quiet and noise

Speech comprehension in quiet (SPIQ) was evaluated using the Dutch NVA lists, developed by the Dutch Society for Audiology (NVA) (Bosman and Smoorenburg, 1995). Four lists of 12 monosyllabic words (consonant-vowel-consonant) were presented at the participants through TDH-39P audiometric headphones, with the first word used for training purposes. The speech recognition score is defined as the percentage of correctly defined items. To examine speech comprehension in noise (SPiN), the Leuven Intelligibility Sentences Test (LIST) was used (van Wieringen and Wouters, 2008). Lists of ten sentences were presented through headphones. The sound level of the speech signal was increased or decreased in 2 dB steps according to the participant's response, while the noise level was kept constant at 65 dB SPL. The levels of the five last sentences and the imaginary 11th sentence were then averaged to acquire the speech reception threshold. Calibration of the equipment was performed every three months according to the approved clinical standards. Both SPIQ recognition scores and SPiN reception thresholds were compared between both subject groups using a paired *t*-test ($\alpha = 0.05$).

2.5. Logistic regression model

A logistic regression model was fit to the data in order to classify subjects as tinnitus patients or controls. As the dataset was characterized by a relatively low number of predictor variables, a logistic regression model was selected rather than more complex machine learning methods in order to optimize interpretability of the results. First, a full model was constructed, including CAEP and MSE measures, RBANS-H total score and domain scores, and SPIQ and SPiN recognition scores. A backward stepwise regression was applied, with variables not contributing to the model gradually being eliminated. This feature selection process was performed within a 10-fold cross-validation. Goodness of fit of the final model on the training data was determined by McFadden's pseudo R^2 , a metric of logistic regression model fit (McFadden, 1974). Then, the final model was tested on a new dataset containing an additional 10 tinnitus and 10 control participants, data of whom were not included in the development of the model. Data were split into training and test sets using random selection. Demographic characteristics of all participants included in the test set are provided in Table 2. Model evaluation was based on accuracy, sensitivity and specificity, as well as area under the curve (AUC) of the receiver operating characteristic (ROC) and precision-recall curves. Statistical significance of model performance on the testing dataset was assessed by the Mann-Whitney U statistic, which can be seen as equivalent to the AUC of the ROC (Bamber, 1975).

3. Results

3.1. The P300 component is significantly less pronounced in tinnitus patients than controls

Group averages of the CAEP waveform in response to a target tone are presented in Fig. 1. Data were compared between groups

Table 2
Demographic characteristics of participants included in the test set.

	Tinnitus	Control
Age: mean (SD)	52.4 (12.3)	52.1 (14.0)
Gender: male / female (n)	6/4	6/4
Education level: primary / secondary / higher education (n)	0/6/4	1/2/7
Hearing level: PTA ₁₋₂₋₄ kHz (SD)	19.7 (10.7)	17.0 (14.1)
TFI: mean (SD)	51.7 (16.0)	–
Tinnitus laterality: bilateral / unilateral right / unilateral left (n)	8/1/1	–

PTA₁₋₂₋₄ kHz: pure tone average of 1, 2 and 4 kHz of the worst ear; TFI: Tinnitus Functional Index.

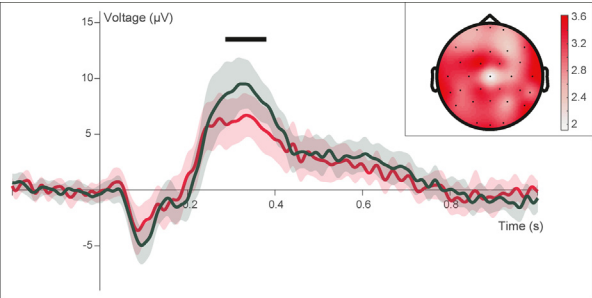


Fig. 1. The P300 component is less pronounced in tinnitus patients compared to controls. Average CAEP waveform of the tinnitus group is presented in red, control group in green. Shaded boundaries represent 95% confidence intervals. Average activity is given in μV from 0.2 s before to 1 s after stimulus presentation. A horizontal black line represents the cluster containing significant pairwise differences between tinnitus and control group (0.287–0.380 s; $p_{\text{cluster}} = 0.02$). Inset: topographic map to illustrate the difference in activity at the identified cluster of significant differences between tinnitus and control group. Dark red areas represent the regions where the difference between the tinnitus and control group is largest.

across all time points and electrodes. A cluster containing significant pairwise differences was identified between the latency times 287 and 380 ms after presentation of the stimulus, corresponding to the P300 component ($p_{\text{cluster}} = 0.02$). In this cluster, activity in the tinnitus group was significantly lower than in the control group. This corresponded to a decreased P300 amplitude in the tinnitus group compared to the control group. This cluster encompassed all electrodes, although differences were most noticeable at temporal and frontal areas (Fig. 1). No other significant clusters were identified. Thus, of all elicited CAEP components (including P50, N100, P200, N200 and P300), only the P300 differed significantly between the tinnitus and control group. In the CAEP responses to a non-target tone, no group differences were identified.

3.2. Source estimation revealed a cluster encompassing temporal cortex, insula and parahippocampus

Minimum norm estimation was performed to estimate underlying sources of the observed activity in response to a target tone. A cluster containing significant pairwise differences between both groups was found, encompassing large parts of the bilateral temporal cortex, insula, and parahippocampus (Fig. 2). In this cluster, source activity was significantly lower in the tinnitus group compared to the control group between the latency times 226 and 317 ms after presentation of the stimulus ($p_{\text{cluster}} = 0.04$). In the response to a non-target tone, no group differences in underlying source activity were found.

3.3. EEG brain signal variability on finer time scales is higher in tinnitus patients

Average MSE values over all electrodes for 20 time scales are represented in Fig. 3A. MSE values for finer time scales, representative of a priority placed on local over global information pro-

cessing, were higher in tinnitus patients. These fine time scale (1–10) MSE values were calculated for 8 different ROIs and normalized to the average MSE on coarse time scales (16–20) to obtain a subject-specific measure of fine time scale variability. A linear mixed model showed that overall, these MSE values on fine time scales were significantly higher in tinnitus patients ($p < 0.0001$). Neither ROI nor the interaction Group*ROI contributed significantly to the model, indicating that the identified group difference is consistent over all regions. Thus, MSE values on fine time scales were found to be significantly higher in tinnitus patients, regardless of brain region. Therefore, average MSE values on fine time scales across all regions were calculated for further analyzes. Boxplots of these average MSE values for both groups are represented in Fig. 3B.

3.4. Delayed memory performance is worse in tinnitus patients

Total RBANS-H scores, representing global cognitive performance, were slightly but significantly lower in tinnitus patients compared to controls ($t = 2.10$, $p = 0.04$) (Fig. 4A). Next, scores on the 5 cognitive domains (immediate memory, visuospatial / constructional processing, language, attention, and delayed memory) were compared between both groups. Only scores on the delayed memory domain were significantly lower in tinnitus patients ($t = 2.97$, $p = 0.006$) (Fig. 4B). No other significant differences were identified. Mean CAEP activity in the cluster containing significant differences between tinnitus patients and controls, corresponding to the P300 component, correlated significantly with total RBANS-H scores in both groups (tinnitus group: $R = 0.46$, $p = 0.04$; control group: $R = 0.51$, $p = 0.02$) (Fig. 4C).

3.5. Speech comprehension in quiet and noise do not differ between tinnitus patients and controls

Speech recognition scores in quiet and speech reception thresholds in noise were compared between both experimental groups. No significant differences were found for either parameter (Fig. 5A,B). To investigate the specific influence of hearing levels and/or cognition on speech recognition in noise, a linear mixed model (LMM) was constructed with pure tone averages (PTA) of 1, 2 and 4 kHz and RBANS-H total scores as fixed factors. In both groups, speech recognition in noise scores were well explained by hearing levels (LMM: $p < 0.0001$), while cognitive performance did not have an influence (LMM: $p = 0.47$) (Fig. 5C).

3.6. The presence of tinnitus can be detected based on EEG measures and cognitive performance

A logistic regression model was constructed to separate tinnitus patients from controls. A backward stepwise elimination was performed within a 10-fold cross-validation in order to select the optimal set of features for the classification task. The final model included three parameters: (1) mean cortical evoked activity at the cluster of pairwise significant differences corresponding to the

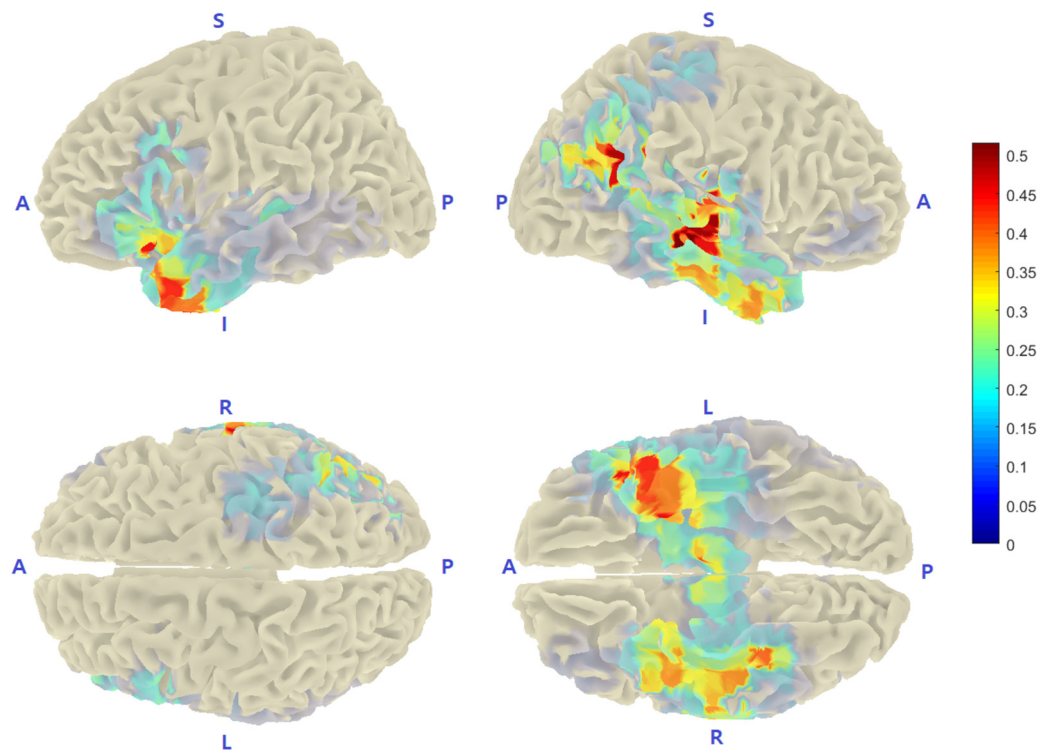


Fig. 2. Normalized differences in source power between the tinnitus and control group. A cluster in which source activity was significantly lower in the tinnitus group (226–317 ms) is projected on a canonical cortical sheet. This cluster encompasses temporal cortices, insula, and parahippocampus. Group differences are normalized to the maximum difference in source power within this cluster. Red areas represent the regions where group differences in underlying source activity are largest. A: anterior, P: posterior, L: left, R: right, S: superior, I: inferior.

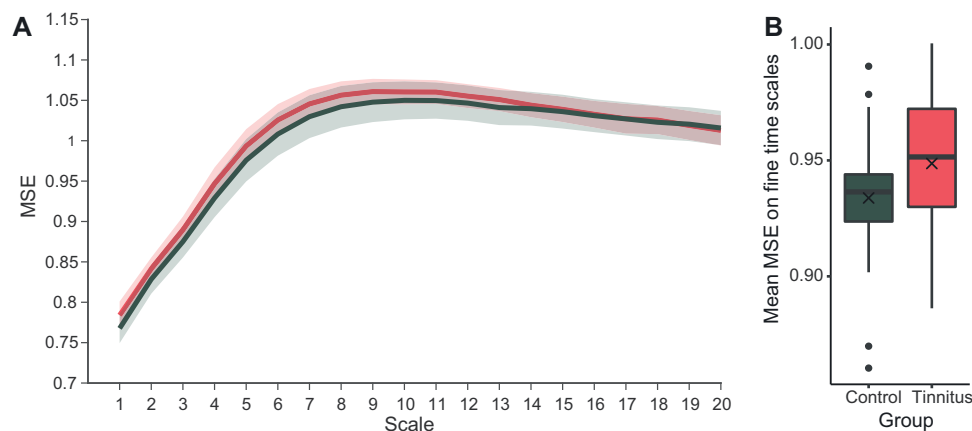


Fig. 3. Differences in multiscale entropy (MSE) between tinnitus patients and controls. A: Average MSE values over all electrodes for tinnitus patients (red) and controls (green). Shaded boundaries represent 95% confidence intervals. B: Average MSE values for fine time scales (scale 1–10). Irrespective of brain region, these values are significantly smaller in tinnitus patients than controls (linear mixed model: $p < 0.001$).

P300 component, as identified in Section 1, (2) normalized mean MSE values for fine time scales, as calculated in Section 3, and (3) RBANS-H Delayed Memory index scores. McFadden's pseudo R^2 , a metric of logistic regression model fit, amounted to 26.35%, corresponding to an excellent fit (McFadden, 1979). Variance inflation factors of the three parameters in the model ranged from 1.05 to 1.25, indicative of a low level of multicollinearity. Performance of the final model was tested on a dataset containing measurements of 10 tinnitus patients and 10 control subjects that were not included in the above analyses. Performance accuracy was 75%, corresponding to a sensitivity of 70% and a specificity of 80%. Area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.86, while the AUC of the precision-recall curve was

0.85 (Fig. 6). The model performed significantly above chance level (Mann-Whitney U: $p = 0.003$).

4. Discussion

Here, we present the results of an observational study comparing potential biomarkers for tinnitus between tinnitus patients and matched controls. Our most important finding is the development of a logistic regression model that can accurately detect tinnitus cases based on three proposed biomarkers. These include cortical evoked activity corresponding to the P300 component, brain signal variability on fine time scales, and delayed memory cognitive performance. Learning which parameters can distinguish between

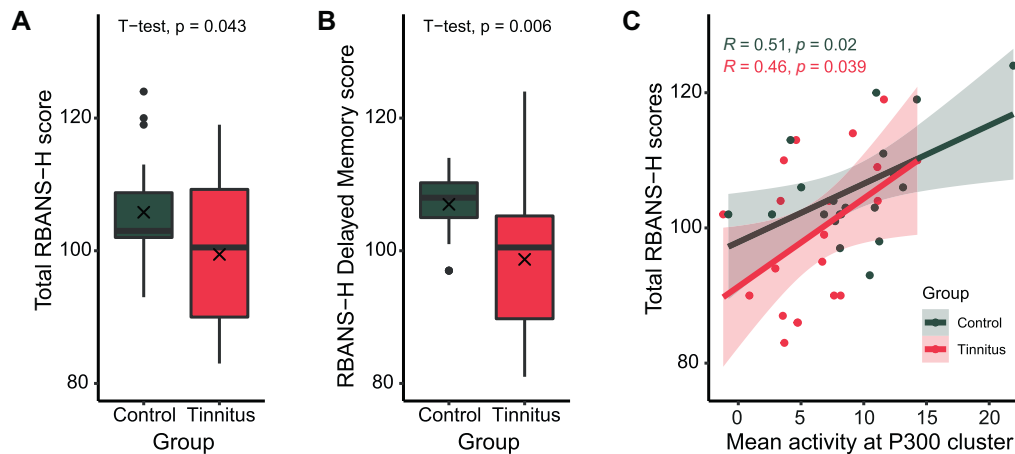


Fig. 4. RBANS-H scores indicating cognitive performance are significantly lower in tinnitus patients than controls. A: Boxplot of total RBANS-H scores in tinnitus patients and controls. B: Boxplot of Delayed Memory index scores in tinnitus patients and controls. C: In both groups, total RBANS-H scores are significantly correlated to the mean CAEP activity in the cluster corresponding to the P300 component. Mean scores in A,B are represented by a cross symbol. The tinnitus group is presented in red, control group in green.

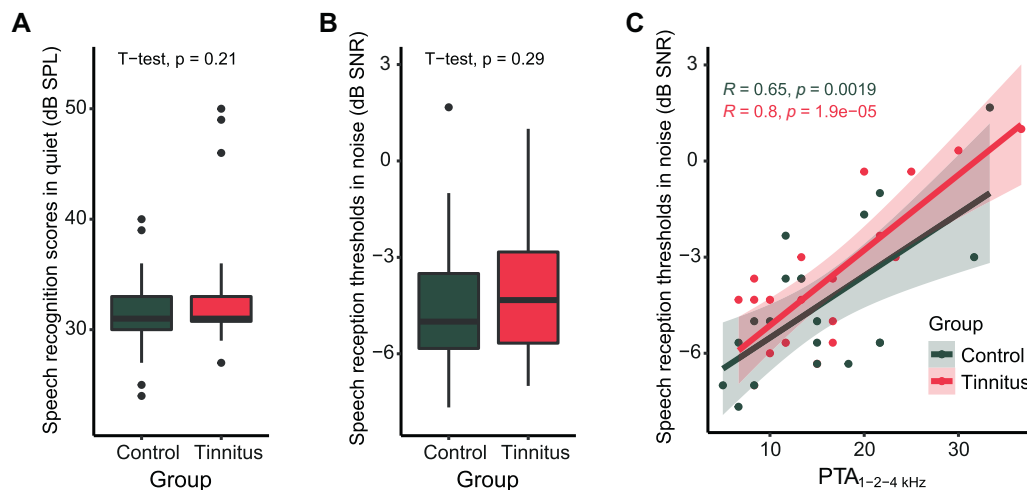


Fig. 5. Speech comprehension in quiet and noise are similar in tinnitus patients and matched controls. A: Boxplot of speech recognition scores in quiet for tinnitus patients and controls. B: Boxplot of speech reception thresholds in noise for tinnitus patients and controls. C: In both groups, speech reception thresholds in noise are strongly correlated to pure tone averages. The tinnitus group is presented in red, control group in green. PTA_{1-2-4 kHz}: pure tone averages of 1, 2 and 4 kHz of the worst ear.

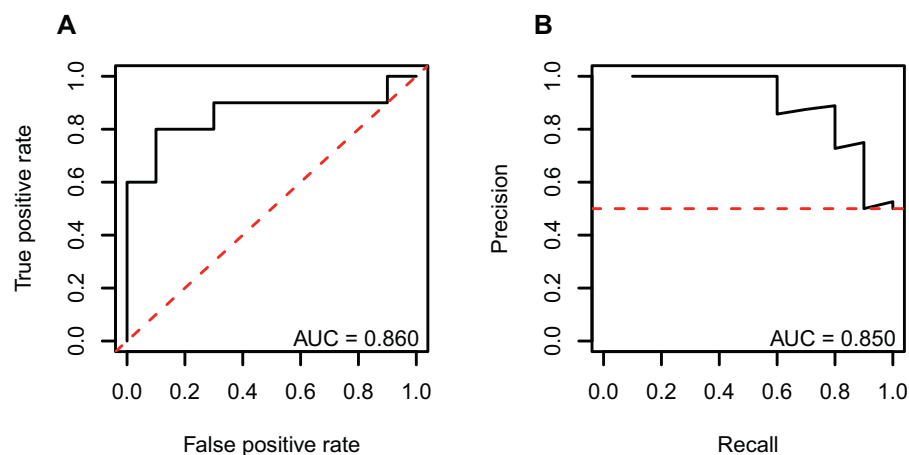


Fig. 6. Performance of the logistic regression model on unseen data. A: Area under the receiver operating characteristic curve is equal to 0.86. This performance is significantly above chance level (Mann-Whitney U: $p = 0.003$). B: Area under the precision-recall curve is equal to 0.85. Red dotted lines represent classifiers without skill performing at chance level.

tinnitus patients and controls could potentially provide insight into the underlying pathophysiological mechanisms of tinnitus.

The proposed model is based on parameters that can be measured objectively, including cortical auditory evoked potential (CAEP) activity and brain signal variability, as well as cognitive performance. This model had an excellent fit on the data used for training, and exhibited above chance level accuracy and excellent performance on a test dataset, as evidenced by the high area under the receiver operating characteristic curve. Although we used the results of the statistical analyses performed on the training dataset to inform the model, its final performance was tested on an unrelated dataset not used for these analyses. As such, we provide an unbiased evaluation of the final model fit. Strict measures were taken to ensure that this model would be tinnitus-specific. For instance, tinnitus and control subjects were accurately matched for hearing levels and all included subjects had normal hearing for their age. As hearing loss is known to have significant effects on both cognitive performance and CAEP (Alain et al., 2013; Claes et al., 2018; Rufener et al., 2014), limiting the confounding effect of hearing loss is crucial in analyzing these parameters. Furthermore, included subjects did not exhibit clinical signs of anxiety or depression, and both groups were matched for other important demographic factors including age, sex, education and handedness. Of course, it might be the case that different confounding factors, particularly hearing loss, age and signs of anxiety and depression, modulate the perception of tinnitus in different ways. In order to chart putative influences of these factors on tinnitus perception, the proposed model may be expanded in the future to include different patient groups. For instance, a grouping of participants based on age or the presence of hearing loss might be considered in future research.

Analyzing the cortical auditory evoked potentials in response to an infrequent target tone, we identified a cluster of significant differences in evoked activity between tinnitus patients and controls. Activity in this cluster was significantly lower in tinnitus patients. This cluster corresponded precisely to the P300 component, a response to unexpected but relevant stimuli. A recent systematic review and meta-analysis found that the amplitude of the P300 component was specifically decreased in tinnitus patients compared to controls, whereas earlier exogenous sensory components were similar in both groups (Cardon et al., 2020). Using a data-driven approach, we were able to confirm these findings in our matched subject groups. A diminished P300 response has been linked to an impairment in top-down information processing, as evidenced by abnormal cortical connectivity profiles, and cognitive efficacy (Hong et al., 2016; Polich, 2004). Specifically, the decreased P300 component in tinnitus might be related to an altered functionality of key structures in the so-called 'salience network', such as the anterior cingulate cortex and insula (Cardon et al., 2020; Menon and Uddin, 2010). In the absence of external stimuli, the increased activation in these regions in tinnitus patients has been linked to the salience attributed to the tinnitus sound (De Ridder et al., 2011). It is possible that, when presented with an auditory stimulus, this importance awarded to the tinnitus percept overrules the salience assigned to a target sound, thus resulting in a diminished P300 response. Indeed, a source estimation procedure revealed a decreased underlying source activity in the insula in response to the target tone, as well as the bilateral temporal cortices and parahippocampus. Previous EEG studies have shown hyperactivity under resting-state conditions in all of these areas in tinnitus patients (Adamchic et al., 2014; Moazami-Goudarzi et al., 2010; Vanneste and De Ridder, 2013). The observed decreased activity in these regions in response to a target tone might indicate that priority is given to the tinnitus percept at the expense of external stimuli, further confirming the importance of top-down attentional processing in tinnitus perception.

To our knowledge, this is the first paper investigating a measure of EEG complexity in tinnitus patients. We compared multiscale entropy (MSE), a measure of brain signal variability, between tinnitus patients and controls. This measure has been introduced relatively recently as an index of the brain's capacity of information processing (Wang et al., 2018). Important to note is the difference between MSE values on fine and coarse time scales. Signal variability on fine scales is strongly linked to interconnectivity among local neural populations, while variability on coarse scales is representative of distributed information processing (McIntosh et al., 2014; Vakorin et al., 2011). We found that MSE values on fine time scales, i.e. at higher temporal frequencies, were significantly higher in tinnitus patients compared to controls, regardless of brain region. This finding suggests that tinnitus patients are more strongly reliant on local information processing. Future research is necessary to determine whether this effect is only seen in response to auditory stimuli, or rather a general property of EEG signals measured in tinnitus patients. Brain signal variability as measured via MSE has been suggested as a potential diagnostic tool for neurological disorders (Chu et al., 2017). For instance, both in children and adults with attention deficit hyperactivity disorder, MSE values calculated from the EEG measured during an attention paradigm were higher than in controls, especially on fine time scales (Chenxi et al., 2016; Ke et al., 2014). Interestingly, we found no relationship between the P300-related activity and MSE values. In fact, both features were highly complementary and contributed independently to the model detecting tinnitus cases. This finding reinforces the recommendation made by Courtiol et al. that MSE analysis should be supplemented with complementary methods to maximize the amount of information gained from this technique (Courtiol et al., 2016).

Global cognitive performance, as measured by total RBANS-H scores, was slightly but significantly worse in tinnitus patients. Total RBANS-H scores were also strongly correlated to P300-related activity, both in the tinnitus and the control group. This clear relationship between the P300 component and cognitive performance reinforces the role of the P300 component as an index of cognitive efficiency (Polich, 2004). Specifically, lower amplitudes and longer latency times have historically been related to diminished performance on several cognitive tests, such as the Mini-Mental State Exam or digit span tasks (Braverman and Blum, 2003; Dong et al., 2015; Polich, 2007). Moreover, the finding suggests that the impaired cognitive performance in tinnitus patients can be explained by a deficiency in top-down attentional processing, owing to the well-established role of the P300 response in information processing. Of all cognitive subdomains, solely scores on the Delayed Memory domain were significantly lower in tinnitus patients. Tinnitus-related deficits in learning and retrieval are well established (Andersson et al., 2013, 2003; Hallam et al., 2004). In their meta-analysis on tinnitus and cognitive performance, Clarke et al. suggest a link between diminished retrieval performance and long-term memory retrieval as a significant feature of tinnitus generation and maintenance (Clarke et al., 2020). Specifically, the formation of pervasive memory traces has been suggested as a potential underlying mechanism in the physiology of tinnitus, with the tinnitus percept functioning as a salient memory trace pulled from (para)hippocampal memory (De Ridder et al., 2014b; Sedley, 2019). Thus, moving beyond the classical spotlight on the executive control of attention and employing a broad cognitive test battery enabled us to identify important tinnitus-related deficits in cognitive performance, possibly linked to tinnitus generation and maintenance.

Although we identified crucial differences regarding several potential biomarkers between tinnitus patients and controls, some features investigated here did not show any differences between both groups. Particularly, we found similar speech in noise com-

prehension levels between tinnitus patients and controls. Although some papers have reported an impact of tinnitus on speech perception in noise (Gilles et al., 2016; Tai and Husain, 2020), recent research suggests that this might only be the case in individuals with hearing loss (Oosterloo et al., 2020). This hypothesis would explain why we did not find any differences in our study sample consisting of subjects with relative normal hearing for their age. Moreover, in a recent study reporting comparable performance between tinnitus patients and controls on several perceptual tasks, Zeng et al. suggest that separate, independent pathways are responsible for the perception of tinnitus and external sounds, i.e. a bottom-up pathway for external sound and a top-down pathway for tinnitus (Zeng et al., 2020). The strong correlation between speech in noise comprehension and hearing levels, coupled to the lack of effect of cognition on speech in noise understanding, found in the current study seems to support this hypothesis. Future research comparing speech in noise comprehension in hearing loss patients with and without tinnitus might help to further elucidate the relative contributions of these independent pathways.

Although the strict matching between tinnitus and control subjects for several important factors can be seen as a distinct advantage of the current study, it has resulted in a relatively small sample size. The current size of the subject groups did not enable us to perform brain-wide regression analyses on the measured CAEP data, for instance with the purpose of investigating neural correlates of RBANS-H scores or speech in noise comprehension. Investigations in a larger sample would aid us in substantiating the proposed relationships between tinnitus perception, top-down information processing and bottom-up perceptual pathways. Of particular interest would be to examine possible neural correlates of subjective tinnitus loudness and/or severity as measured via questionnaires, in order to link these proposed biomarkers to the subjectively perceived tinnitus complaint. Future potential applications of the proposed biomarkers could also include repeated within-subject measurements before and after tinnitus treatment (Jacquemin et al., 2019), to investigate which of these parameters might possibly have prognostic value. For instance, in major depressive disorders, both multiscale entropy and auditory evoked potentials have been proposed as predictors of antidepressant treatment response (Jaworska et al., 2018; van Dinteren et al., 2015). As the outcomes of different tinnitus therapy modalities are often variable, prognostic factors predicting treatment response would be of special interest in a clinical setting (Simoes et al., 2019).

In summary, we show that tinnitus cases can be detected accurately based on cortical auditory evoked potentials, brain signal variability, and cognitive performance. These three potential biomarkers for tinnitus contributed independently to our proposed model for tinnitus detection, confirming our hypothesis that the combination of different neurophysiological and cognitive assessments provides a more comprehensive model. Our results point towards a significant contribution of top-down information processing in the perception of tinnitus, highlighting the complex neurophysiology of tinnitus and calling into question the sufficiency of the central gain hypothesis as the decisive explanation for tinnitus generation.

CRedit authorship contribution statement

Emilie Cardon: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Hanne Vermeersch:** Investigation, Data curation, Writing – review & editing. **Iris Joossen:** Investigation, Data curation, Writing – review & editing. **Laure Jacquemin:** Methodology, Writing – review & editing. **Griet Mertens:** Writing – review & editing. **Oliver M. Vanderveken:** Writing – review & editing. **Marc J.W. Lammers:** Con-

ceptualization, Writing – review & editing. **Paul Van de Heyning:** Conceptualization, Supervision, Writing – review & editing. **Vincent Van Rompaey:** Conceptualization, Supervision, Writing – review & editing. **Annick Gilles:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

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