Prediction of tinnitus masking benefit within a case series using a spiking neural network model.

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MD designed and performed the study. PS undertook the processing of the EEG. NK, AW, ZD, MD and PS participated in modelling the EEG data. G.D.S had overall responsibility for the study, manuscript, and with NK and PS undertook behavioural data analysis. All authors contributed to the manuscript. Some software modules used for the implementation of the proposed method can be found at http://www.kedri.aut.ac.nz/neucube/ and https://kedri.aut.ac.nz/areas-of-expertise/data-mining-and-decision-support/neucom.

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Abstract.

Masking has been widely used as a tinnitus therapy, with large individual differences in its effectiveness. The basis of this variation is unknown. We examined individual tinnitus and psychological responses to 3 masking types, energetic masking (bilateral broadband static or rain noise [BBN]), informational masking (BBN with a notch at tinnitus pitch and 3-dimensional cues) and a masker combining both effects (BBN with spatial cues). Eleven participants with chronic tinnitus were followed for 12 months, each person used each masking approach for 3 months with a 1 month washout-baseline. The Tinnitus Functional Index (TFI), Tinnitus Rating Scales, Positive and Negative Affect Scale and Depression Anxiety Stress Scales, were measured every month of treatment. Electroencephalography (EEG) and psychoacoustic assessment was undertaken at baseline and following 3 months of each masking sound. The computational modeling of EEG data was based on the framework of brain-inspired Spiking Neural Network (SNN) architecture called NeuCube, designed for this study for mapping, learning, visualising and classifying of brain activity patterns. EEG was related to clinically significant change in the TFI using the SNN model. The SNN framework was able to predict sound therapy responders (93% accuracy) from non-responders (100% accuracy) using baseline EEG recordings. The combination of energetic and informational masking was an effective treatment sound in more individuals than the other sounds used. The mechanisms underpinning tinnitus masking are discussed.
**Introduction**

We define tinnitus masking as the replacing, or partial replacing, of the perception of tinnitus with the perception of a true sound. Tinnitus masking has a long history (Stephens, 2000). Its systematic evaluation began in the 1970’s (Feldman, 1971) and emerged as a clinical treatment through wearable hearing aid-style “maskers” shortly afterwards (Vernon and Schleuning, 1978). The application of masking has varied from complete to partial covering of the tinnitus (Vernon and Meikle, 2000) including a concept of mixing of sound and tinnitus – not with the goal of masking per se, but as a means to facilitate habituation (Jastreboff, 1999). Some recent forms of sound therapy are not designed as maskers, instead they are purported to modify specific putative neurophysiological tinnitus mechanisms (e.g. desynchronization of neural activity (Eggermont and Tass, 2015) and lateral inhibition (Okamoto et al., 2010)). This study is focused on masking.

The sounds used for masking are, generally, broadband – they contain a broad spectrum of frequencies (e.g. “noise” and “nature” sounds). Various forms of masking, usually accompanied with counselling or instruction, have been widely adopted into practice (Hoare et al., 2012). Most hearing aid manufacturers offer broadband sound maskers as an option in their devices, and desktop maskers and mobile phone masking apps are available (Sereda et al., 2017a, Sereda et al., 2017b). Despite widespread use, the benefits of masking are - at best - uncertain (Mckenna and Irwin, 2008) and there is strong debate as to its best application (Tyler et al., 2012, Henry et al., 2006). The mechanisms underpinning sounds’ effects on tinnitus are surprisingly vague, but include concepts of interference (the “line-busy” effect) and inhibition (Eggermont, 2012). Masking has its scientific foundations in psychoacoustics, rather than neurophysiology, and so our knowledge of effects are primarily behavioural observations (Tyler and Conrad-Armes, 1984, Feldman, 1971). In psychoacoustics masking is divided into
“energetic” and “informational” forms. Energetic masking occurs when an interfering sound disrupts, or removes, the ability to process target sound in the auditory periphery (cochlea and/or auditory nerve) (Brungart et al., 2006, Ihlefeld and Shinn-Cunningham, 2008). Informational masking describes the elevation of auditory thresholds in the presence of masking stimuli which cannot be accounted for by energetic masking alone (Arbogast et al., 2002, Ihlefeld and Shinn-Cunningham, 2008, Kidd et al., 2002). Tinnitus does not always follow the normal energetic masking patterns seen to external sounds. Tinnitus may be effectively masked by sounds containing information that demand central processing, creating greater cognitive interference (Searchfield et al., 2016). Informational masking may be achieved by speech, time and frequency varying tones (Kidd et al., 2002, Oh and Lutfi, 1999), and by sounds that overlap spatially (Arbogast et al., 2002, Ihlefeld and Shinn-Cunningham, 2008). Often there is no specific relationship between tinnitus frequency spectrum and effectiveness of masking. Tinnitus perceived as a broadband sound can be covered by a masker of a single tone or pitch (Tyler and Conrad-Armes, 1984, Feldman, 1971). In some people unilateral tinnitus can be effectively masked by tones presented contralaterally to that where tinnitus is perceived (Feldman, 1971) and a masker in one ear may reduce tinnitus heard in both (Vernon and Meikle, 2000). This reflects interactions between the masker and tinnitus consistent with “binaural” processing. This has been termed “central” or “neural” masking of tinnitus (Feldmann, 1984). While the precise mechanisms of such masking are not completely understood, competing for the brain’s cognitive resources may be a key factor (Knobel and Sanchez, 2008). The description of tinnitus masking being either excitatory or informational is a fairly new classification (Searchfield et al., 2012). Searchfield et al. (2016) conducted a series of studies using masking with spatial cues and compared its effectiveness to conventional bilateral energetic masking. The spatial masking used intensity, timing and frequency cues that created the perception of sound overlapping the space corresponding to where the person with
tinnitus perceived their tinnitus to originate from (Searchfield et al., 2016). This masking was hypothesized to recruit “where and what” sound processing pathways and therefore require greater cognitive processing. Several small trials found a preference for the spatial masking, but strong individual preferences were identified (Searchfield et al., 2016).

To meet the full potential of tinnitus masking we must discover its underlying physiological and psychological mechanisms, and factors that predict its success. The ability to identify the mechanisms of masking is severely hampered by the heterogeneity of tinnitus (Cederroth et al., 2019) and variability in individuals response to sound (Durai and Searchfield, 2017). We believe that an ecological approach to tinnitus masking research will prove beneficial (Searchfield, 2014). Instead of assessing single measures across groups of sufferers, greater benefit will be achieved by assessing multiple subjective and objective measures in single participants. Single-case (SC) methodology refers to the prospective and intensive study of the individual who acts as their own control (Tate et al., 2014). Interventions are measured repeatedly and frequently across time. In SC experiments the individual is the unit of analysis (Tate et al., 2014), but the strongest SC studies commonly include more than one participant (Lobo et al., 2017). SC research (including case series and cohort studies) have been viewed as inferior to randomized controlled trials (RCTs), but they can be designed to have strong internal validity for assessing causal relationships between interventions and outcomes (Lobo et al., 2017). The dependent variable is measured repeatedly across time with varying interventions or levels of intervention, termed phases, allowing for fine grained time-series analysis (Purswell and Ray, 2014, Blackwell and Holmes, 2010, Lobo et al., 2017). External validity is improved by replication across phases and participants (Lobo et al., 2017). This case series approach can provide insight into the interaction of individual neuropsychological
components and enable development of predictive algorithms that can then be applied to large populations. The value of well-designed SC studies have been recognized in neurorehabilitation (Tate et al., 2014, Lobo et al., 2017) neuropsychology (Wilson, 1987), behavioural psychology (Skinner, 1956) and speech language pathology (McReynolds and Thompson, 1986, Connell and Thompson, 1986). The approach has had limited application to tinnitus. Tyler et al. (2015) used a case studies approach to investigate the effects of different tinnitus therapy sounds through cochlear implants. Seven participants trialled different sounds over several days to months, and were regularly assessed for tinnitus loudness, annoyance and the acceptability of sound. The results showed a general improvement in tinnitus with the addition of background sound to the implant, but also large inter and intra participant variability in ratings of the different sounds’ effects (Tyler et al., 2015).

There is a need for personalized tinnitus treatments (Searchfield et al., 2017). Close examination of individual differences may be able to identify factors that contribute to tinnitus therapy success in some patients and not others; e.g. personality measures (Durai et al., 2017, Kleinstäuber et al., 2018), case history information (Simoes et al., 2019), severity (Mazurek et al., 2006) hearing level and localisation of tinnitus (Theodoroff et al., 2014) have been identified as potential markers for the success of different therapies. Physiological measures such as magnetic resonance imaging (MRI) and electroencephalography (EEG) may also have a role in predicting therapy success. Functional MRI measurements from five brain regions (right insula, right inferior parietal lobule, bilateral thalami, and left middle temporal gyrus) were effective at classifying improvement after a narrow-band noise therapy (Han et al., 2019). Functional connectivity changes correlated with changes in tinnitus handicap. It was concluded that the connectivity of the thalamus at baseline was a predictor of clinical outcome of a sound therapy. EEG has also identified neural activity that predicts tinnitus therapy success (Kim et al., 2016). EEG recorded prior to and then 3 months following directive counselling found
changes in Tinnitus Handicap Index scores were positively correlated with the baseline activity of the left insula left rostral and pregenual anterior cingulate cortices (rACC/pgACC). Activity of the right auditory cortices and the parahippocampus, negatively correlated with loudness ratings. Ratings of tinnitus perception (time aware of tinnitus) correlated positively with baseline activity of the bilateral rACC/pgACC (Kim et al., 2016).

The presence of biological subtypes of tinnitus across individuals suggests a more tailored approach to intervention is needed. However, before this can happen, inexpensive tools need to be developed that can more accurately identify and model connectivity change over time. EEG measures the electrical activity of the brain with excellent temporal resolution across the scalp; and is relatively inexpensive. However, maximising the utility of EEG data requires the integration of both temporal and spatial characteristics.

Our team has developed sophisticated analytical tools based on one of the most promising trends of Artificial Intelligence (AI) techniques, called brain-inspired Spiking Neural Networks (SNN). SNNs are computational models of the brain that process data as a sequence of “spikes” representing action potentials (Kasabov, 2014, Kasabov and Capecci, 2015, Ponulak and Kasinski, 2011, Grüning and Bohte, 2014). Tinnitus, and its susceptibility to therapy, can be modelled by changes in spiking neuron models (Domínguez et al., 2006), and models that link spiking activity to large scale brain models have been suggested as being a valuable method for studying tinnitus neurophysiology (Schaette, 2014). The brain-inspired SNN models can incrementally learn from brain dynamics gathered over time, in a three-dimensional (3D) space and capture meaningful patterns from brain data (Kasabov, 2014). EEG data are fed into the model and converted into spike sequences that are mapped onto a 3D template (e.g. Talairach space) with input ‘neurons’ based on electrode positions. Here, the term neuron is used to
represent the centre co-ordinate of one cubic centimetre area from the 3D Talairach Atlas (Talairach and Tournoux, 1988). The SNN model has been used to understand personal differences in mindfulness success with depression (Doborjeh et al., 2019) and so might be used to examine variables that predict change in tinnitus. During a learning process the connection between SNN neurons is altered based on the timing of postsynaptic action potentials relative to the pre-synaptic spikes. Using this method, the complex spatio-temporal relationships of auditory resting state EEG can be classified to enable predictions of change over time.

This study examined the individual effects of informational masking and energetic masking in detail. Behavioural and electrophysiological measurements were undertaken to evaluate potential mechanisms of effect and factors that might predict tinnitus masking success. It was hypothesized that the combination of energetic and informational masking would be more effective in treating tinnitus than maskers incorporating energetic masking or informational masking alone (since these are thought to affect the perception of tinnitus at different stages of processing), and that individual factors will be able to predict masking outcome.

The aims of this research were:

1. To investigate the effect of energetic, informational and combined masking on individuals’ tinnitus.

2. To investigate if participant phenotypes (behavioural and EEG) might predict responders and non-responders to masking.

**Methods**
This study was approved by the University of Auckland Human Ethics Committee.

This study followed the Single-Case Reporting Guideline in Behavioural Interventions (SCRIBE) 2016 (Tate et al., 2016). It was an alternating treatment design with multiple baselines. Participants were recruited from the University of Auckland Tinnitus Research Volunteers Database. Eligible participants were: aged over 18, had no more than a moderate hearing loss, were not undergoing treatment for tinnitus, had chronic tinnitus that they described as impacting their quality of life, and were able to accurately match the pitch and location of their tinnitus using our tinnitus testing software. For baseline data and characterization of participants, questionnaires were completed by email: the Tinnitus Case Sample History Questionnaire (Langguth et al., 2007), Tinnitus Functional Index (TFI; (Meikle et al., 2012)), Rating scales (1 five point (overall), 5 10-point rating scales (loudness, discomfort, annoyance, unpleasantness, and ignorability of the tinnitus), the Depression Anxiety and Stress Scale (DASS, (Parkitny and McAuley, 2010)), and the Positive and Negative Affect Schedule (PANAS, (Watson et al., 1988)).

**Participant characteristics**

Twenty-eight potential participants provided written informed consent to participate. Participation and attrition are shown in Figure 1A. Three potential participants did not respond to invitations to attend study sessions, 7 withdrew, 1 was ineligible as they began trialling hearing aids.

Eleven participants (7 males and 4 females, mean age = 58.8, SD = 14.5) completed the trial. The mean duration of time since tinnitus onset was 16.7 years (SD = 9.1). Four participants had tinnitus localized solely to the left ear/side, 6 participants had binaural tinnitus and 1
participant had tinnitus localized to a position in their head. Four participants reported the tinnitus as a hiss or buzzing, 3 as ringing, 1 as cicadas, 1 as TV static and 2 as tones.

Six participants (2 males and 4 females, mean age = 52.3, SD = 14.6) were excluded as they did not complete all the treatment phases. The mean duration of time since tinnitus onset for this group was 12.5 years (SD = 5.1). Four participants had tinnitus localized to the left ear/side, 2 participants had tinnitus localized to both ears. Four participants reported the tinnitus as a buzz or hiss, 2 as high-pitched ringing. A comparison of the audiogram and tinnitus characteristics of the participants who completed the study and those who did not are provided in Supplementary material Table 1 and SFig 1.

Figure 1 About here

Hearing assessment

All participants had pure tone audiometry (0.25–16 kHz) undertaken using a two-channel audiometer (either GSI - 61, Grason Stadler, MN; or AC40, Interacoustics, DK). Standard frequency measurements (0.25–8 kHz) were made using headphones (TDH - 50P; Telephonics, NY) or insert earphones (E.A.RTONE 3A, 3M, MN); high frequency (8–16 kHz) thresholds were obtained using headphones (HDA 200, Sennheiser, De). Audiometry was conducted using the modified Hughson-Westlake procedure (Carhart and Jerger, 1959).

Tinnitus assessment

Tinnitus characteristics were assessed using tinnitus testing software (© The University of Auckland) installed on a DELL Latitude E6400 laptop computer with Sennheiser HDA-200 circumaural headphones. Methods are described in detail elsewhere (Searchfield et al., 2015).
EEG recordings were undertaken approximately 1 week following the initial hearing and tinnitus assessments, after masking and after a 1 month washout period prior to the next masking phase. They were run in a dimly lit sound attenuating room. Participants were seated comfortably in an armchair and recordings were made in an awake state in a passive condition using the Biosemi ActiveTwo system (https://www.biosemi.com/activetwo_full_specs.htm). Electrophysiology measures were undertaken using 66 active (Ag/AgCl) surface electrodes referenced to the common mode sense active electrode and grounded to the driven right leg passive electrode, placed on the scalp according to the international 10/20 system array through attachment to an appropriately sized Biosemi 64 electrode head cap with SignaGel electrode gel. EEG signal quality was assessed by measuring voltage offsets using Biosemi ActiView software. A 10-minute resting-state continuous EEG measurement was obtained while participants sat in silence (earphones in, no sound playing, watching a grey cross presented in the centre of the computer monitor screen). EEG signals were recorded continuously at a sampling rate of 8192 Hz and downsampled to 256 Hz. Off-line pre-processing and analysis were conducted using MATLAB and EEGLAB Software. The PREP pipeline (Bigdely-Shamlo et al., 2015) was applied to re-reference data to a robust average reference of all electrodes, remove line noise, and interpolate bad channels. Data were filtered with a 1Hz high pass finite impulse response filter and Independent Component Analysis artefact rejection was used to remove ocular artefacts including eyeblinks. Each dataset was examined visually to select one minute of continuous data with minimal noise and artefacts. Data was exported for analysis (see analysis section).
Masking sounds

LabVIEW™ 8 was used to generate the static broadband noise stimulus. The Rain stimulus was a recording of natural rain. Both maskers were analyzed and adjusted using Adobe Audition sound editing software so that the sound had equivalent long-term average intensities (dB SPL). The maskers were edited using Adobe Audition so that the Energetic masker was in stereo, the same stimulus to left and right ears, similar to conventional tinnitus masking. The Informational masker was created using a 3D audio plug-in function in Adobe Audition software. An adaptive in situ procedure was used in which the participant listened to sounds using the same headphones used in the trial and indicated when the sound moved in 3D acoustic space overlapped with the same spatial position as tinnitus (spatial masking, (Searchfield et al., 2016)). The Informational masker had a critical band notch applied at the participant’s tinnitus pitch (to reduce the contribution of energetic masking). The notch filter applied was an equivalent rectangular bandwidth (ERB) filter \( \text{ERB}(f) = 24.7 \times (4.37 f / 1000 + 1); \) where \( f \) was the Tinnitus Pitch (Hz) of the individual. The Combination masker was the same as the Informational masker, but without the notch (thereby having both energetic and informational masking content). Example spectra are shown in Supplementary material SFig 2.

Allocation

At the beginning of the trial all eligible participants were randomly divided into two groups to receive one of the two base sounds during the trial: static and rain BBN. Within each group, they were then randomly allocated to the order of receiving the three masking types. After random allocation, checks were manually made to ensure that all masker combinations were used (Figure 1B).
Sound player and instructions.

Sounds were loaded and presented through MP3 devices with in-ear phones. (Philips ViBE SA4VBE08KF/97 4GB MP3 Player and Panasonic RP-HJE290GUK Premium Black Earphones with a Budloks Earphone Sports Grip earpiece attached (for retention and comfort)). Participants were instructed to set the volume at their desired listening levels (DLLs) so that it was audible, comfortable and interfering with the perception of tinnitus. Participants were given the following instructions: “Please listen to this for a minimum of 2 hours per day over the following 3 months (you can do quiet activities while listening to the sounds, e.g. reading, gardening, etc.). The level of sound should be set at an audible and comfortable listening level.” Participants listened to each of 3 masking conditions for 3 months, with a 1 month wash-out period between the next trial. Participants were blinded as to the sounds used and did not receive tinnitus counselling.

Intermediate evaluations

Each participant was contacted 2 weeks, 1 and 2 months following the provision of each masking sound and they were asked to complete the TFI, rating scales, DASS & PANAS. Any technical or use issues with the MP3 players were managed on an as needed basis.

Follow-up appointment (Three months after the fitting appointment)

At the three-month follow-up appointment, participants completed the TFI, rating scales, DASS & PANAS and had their tinnitus psychoacoustic matching redone with the tinnitus testing software for Pitch, Loudness, and Maskability. Participants had an EEG recording undertaken, identical in set-up to the initial EEG. A one month wash-out period began at the end of this appointment where participants handed in their MP3 players and did not undergo any sound therapy.
Fitting appointment & Follow-up appointments: Second and Third Treatment Sound

The fitting and follow-up appointments for the second and third treatment sound were identical in format to the first treatment sound.

Analysis

Behavioural data.

A systematic analysis of the case series behavioural data was carried out (Kratochwill et al., 2010). The primary outcome measure was the TFI. Visual analysis of data was undertaken independently by GS and PS, the consensus is reported. The visual analysis evaluated the level, trend and stability within phases and immediacy of effect and consistency of effects between phases of baseline and intervention. Effect sizes (Hedges’ $g$, $g = (\text{mean sample 1} - \text{mean sample 2}) / \text{pooled standard deviation with small sample correction}$) were calculated for each participants’ change in TFI from baseline between the 3 interventions. Baseline questionnaire, psychoacoustic, and audimetry data were examined using NeuCom$^1$ software to rank variables and produce classification models in order to determine which measures taken at the start of the study could be used to predict whether an individual would respond to the first sound treatment (of the three). Of the 11 participants, four responded (clinically meaningful change in TFI: 13 points improvement on the scale compared to baseline) to the first treatment (P4, 7, 8, 11), and seven did not (P3, 6, 9, 12, 13, 17). Variables that contained missing data for any participant were removed for all participants. Eighty-one variables were ranked in a

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NeuCom is a generic knowledge engineering environment for data analysis, modelling and knowledge discovery, developed by the Knowledge Engineering and Discovery Research Institute (KEDRI), Auckland University of Technology. It includes various techniques for: Feature selection; Signal-to-Noise Ratio (SNR); Correlation; Classification and Prediction model creation, model testing and model optimization
signal-to-noise ratio (SNR) analysis that measured the discriminative ability of each variable in determining one class (signal) from the other class (noise). Top ranked variables were included in inductive Multiple Linear Regression (MLR) and Evolving Classification Function (ECF) models. Models were cross-validated using a leave-one-out procedure. The MLR model was produced using a least squares fit on the top seven ranked variables for each class. The ECF classified based on clustering of data (Goh et al., 2004). Briefly, the model is made up of layers of input nodes that receive the data, fuzzy member nodes that determine the likelihood that a datapoint belongs in a cluster, rule nodes that determine which combinations of cluster membership for given variables belong to which class, and output nodes. To increase the accuracy of the ECF model two of the seven variables were removed, only results from the final model are reported.

**EEG**

Each dataset consisted of fifteen samples of four seconds each (1024 data points per sample). For the computational modeling of EEG data, responders were defined as those participants who showed a clinically significant improvement (13 points on TFI) from baseline in TFI scores after a sound treatment, that was maintained at the 3 month follow up appointment for that treatment. This resulted in 5 responders (combined masker n = 3 [P7,9,11], informational masker n = 1 [P8], energetic masker n = 1 [P4]). Non-responder data from 5 participants were matched by condition (combined n = 3 [P3,6,12], informational n = 1 [P13], energetic n = 1 [P17]). Only data from one treatment condition were included in the analysis for any one individual. One participant was excluded from the computational modeling (P10) because EEG data from their three month follow up appointment were unavailable.
The computational data modelling followed the steps described in Doborjeh et al. (2019). EEG sequences were encoded into spikes where increases in signals above a threshold generated positive spikes, decreases below a threshold produced negative spikes. If thresholds were not crossed, no spikes were generated. Data were mapped onto a 3D SNN reservoir of 1471 neurons in Talairach space (Talairach and Tournoux, 1988), with 64 electrode inputs positioned according to their talairach coordinates. The Spike Timing Dependent Plasticity (STDP) learning rule (Masquelier et al., 2009) was used to train the model in an unsupervised learning mode. Separate models were trained for responders and non-responders at before (T1) and after (T2) masking. Visualisations of the models for each group and time point were produced. Quantitative information was extracted from the models for further statistical analysis and to explore effects of masking treatments on EEG data. Finally, an output layer classifier was trained in supervised mode to learn the association between class label information (responder versus non-responder) and SNN connectivity.

**Results.**

**Behavioural outcomes.**

Each participant completed three 3-month sessions of sound therapy using either a static BBN or rain-like BBN manipulated to be an energetic, informational or combination masker. Individuals showed variability within and between treatments and across the different measures used (Figure 2, Table 1, and supplementary material SFig3). Seven participants showed an improvement of at least 13 points on the TFI from baseline at one or more assessment points during at least one of the therapy periods (P4, P7, P8, P9, P11, P12, P13, Figure 2). Four participants did not demonstrate any clinically significant improvement during any of the therapy periods (P3, P6, P10, P17, Supplementary material SFig3). The significant reduction
in TFI score most often occurred during the first therapy period (4 participants) then 2nd (3 participants). No clinically significant change occurred in the final trial period, although in some cases (P4, P8, P11, P12) improvements seen in earlier treatment periods persisted across the remaining trial periods. An average 13 point change throughout the treatment period was observed during energetic masking for 1 participant (P4, 22.8 points), during informational masking for 1 participant (P8, 17.5 points) and the combination masker in 3 participants (P7, 25.0; P9, 36.4; P11, 44.0 points) (Table 1, Figure 3). An average increase of 13 points occurred during the informational masker for two participants (P7 increase of 22.7 points; P9 increase of 17.1 points). The effect size (Hedges g) for the difference between pairs of therapy (Energetic vs Informational, Informational vs Combination, Combination vs Energetic) were calculated using the average difference between the repeated measures of TFI and the preceding baseline for each participant (Table 1). Using a criteria of effect size of greater than 1, criteria indicated that changes occurring during the informational masking period were more positive than energetic for 3 participants (P3, P8, P10), and energetic over informational masking for 6 participants (P4, P6, P7, P8, P12, P13). There was a large effect size for 3 participants whose TFI scores during Energetic masking were better than the Combination masker (P4, P6, P12) while Combination masker period TFI results were more positive compared to the Energetic masking period in another 3 cases (P7, P9, P11). A large effect size was found for 5 participants whose TFI scores during the Combination masker were more positive than the informational masker (P4, P7, P9, P11, P13) while the reverse was the case for 2 participants (P8, P10). These effect sizes do not necessarily indicate benefit of treatment, one treatment can be associated with a large change that is less negative than another but is not an improvement in TFI.
Visual analysis of the secondary measures indicated that the tinnitus rating scales followed a similar pattern to TFI scores over time (especially the annoyance rating) but with more variation between successive time periods. Where the TFI score fluctuated during the therapy period, the rating scales mirrored the TFI response. Within most participants each scale followed the same pattern. For some participants (P8, P10) there was divergence in the rating measures, and the scores did not strongly follow the TFI pattern. In one case (P4) there appeared to have been a time lag in which the rating scale change followed an earlier TFI change. PANAS measures did not appear to follow any pattern consistent with the other measures, except in the case of Participant 11 for whom negative affect followed the same pattern as the rating scales. In some cases stress (from the DASS) followed a similar pattern to the tinnitus measures, but this was not the case for all participants. Depression and Anxiety measures on the DASS did not appear to bear any relationship to other scales in general, although for Participant 11 the decrease in depression score followed a similar reduction as the TFI, but later than changes in the tinnitus measures. The audiogram of most participants showed fairly symmetrical hearing between the two ears, with normal hearing in the low and mid frequencies (125-2000 Hz) sloping to a moderate hearing loss in the high speech frequencies (6000-8000 Hz) and sloping further in the extended high frequencies to a profound loss between 14000-16000 Hz. Participant 11 had normal hearing thresholds. Tinnitus pitch did not differ greatly across the 12 months of the study for 7 participants. Tinnitus pitch match markedly increased in frequency with time when compared to baseline for two participants (P3, P6) neither of these participants had a clinically meaningful improvement in TFI. Two participants demonstrated an increase in tinnitus pitch following the first treatment that then returned to closer to baseline pitch match frequency following the next treatment periods, in both cases the therapy sound was the combination masker, but there did not appear to be any similarity in other results. Most participants demonstrated tinnitus loudness matches at or
below 10 dB SL with little variation over time. Tinnitus loudness matches increased following the baseline measure for two participants (P7, P10) that did not relate to changes in TFI. MML reduced for some participants when treatment was successful in lowering the TFI (P4, P8, P11, P13) and increased consistent with an increase in TFI for some periods (P9, P13). Variability within and across participants, and scales, was a feature of the behavioural measures.

**Table 1 about here**

**Figure 2 about here**

**Figure 3 about here**

**Prediction of outcomes using behavioural data.**

Baseline demographic and behavioural measures were examined using a Signal to Noise analysis as to their ability to predict clinically meaningful change in TFI. The top ranked variables were: 1. Loud noise worsens tinnitus (case history). 2. Stress effect on tinnitus (case history). 3. MML (psychoacoustic). 4. Loudness rating (case history). 5. Relationship between sleep and tinnitus (case history). 6. Comorbid pain syndromes (case history). 7. Loudness varies day to day (case history). Using Multiple Linear Regression, the overall accuracy of the model was 27.27%. All four responders were misclassified, and four out of the seven non-responders were misclassified. When the MML and Loudness rating variables were removed, an Evolving Classification Function model correctly classified 100% of participants using the other 5 top ranked variables. Rules that depict the combination of the variables defining responder and non-responder profiles for each class using the ECF method were extracted (Table 2).
were four rules, the first one was for class 1 (Responders), and next three were for class 2 (Non-responders).

Rule 1. According to the model, if all of the following conditions were met, the individual was predicted to belong to the responder class. (n = 4)

1. Loud noise did not make their tinnitus worse (or they responded that they did not know if it did, in which case it probably did not).
2. Stress worsened their tinnitus.
3. There was no relationship between sleep at night and their tinnitus in the day (or they responded that they do not know if there was, in which case there probably was not).
4. They did not suffer from other pain syndromes.
5. Tinnitus loudness varied from day to day.

Rule 2. According to the model, if all of the following conditions were met, the individual was predicted to belong to the non-responder class (n = 1).

1. Loud noise did not make their tinnitus worse.
2. Stress did not worsen their tinnitus.
3. There was no relationship between sleep at night and their tinnitus in the day.
4. They did suffer from other pain syndromes.
5. Tinnitus loudness did not vary from day to day.

Stress, pain syndromes, loudness changes differed from responders (rule 1).

Rule 3. According to the model, if all of the following conditions were met, the individual was predicted to belong to the non-responder class (n = 2).

1. Loud noise made their tinnitus worse. The membership value here is 0.5, so it is not a strong indicator.
2. Stress worsened their tinnitus.
3. There was no relationship between sleep at night and their tinnitus in the day.
4. They did not suffer from other pain syndromes.
5. Tinnitus loudness did vary from day to day.

Loud noise effect on tinnitus differed from responders.

Translation of Rule 4: According to the model, if all of the following conditions were met, the individual was predicted to belong to the non-responder class (n = 4).

1. Loud noise made their tinnitus worse.
2. Stress worsened their tinnitus.
3. There was a relationship between sleep at night and their tinnitus in the day.
4. They did suffer from other pain syndromes.
5. Tinnitus loudness did vary from day to day.

Loud noise and sleep effects on tinnitus, and pain syndromes differed from responders.

**Computational Modeling of EEG Data Using Brain-Inspired SNN Architecture**

*Experiment 1. SNN Connectivity.*

Four SNN models were separately trained using different EEG data sample sets corresponding to: responder group (N = 5) at T1 and T2, and non-responder (N = 5) group at T1 and T2. The SNN connections evolved differently during the unsupervised learning with EEG data related to response to masking (Figure 4). Experimental results in the SNN are illustrated mainly to represent the visual exploration of the models, but numerical information (such as connection weights) is also facilitated and can be exported from the models. Different SNN models can be compared in terms of the “connection weights” in their activated neural areas.
The differences between the SNN models pre-masking and post-masking for each group were calculated by subtracting the two correspondingly trained SNN models (T1, T2). This allowed visualisation of the changes in neural connectivity as a result of masking over time (Figure 5). In Figure 5 if a positive connection at T1 was weaker or absent at T2, this resulted in a negative connection weight in the difference figure (red line), where baseline connection weights were subtracted from the T2 connection weights. The greatest changes in connectivity for responders occurred in the right hemisphere (contralateral to where the majority experienced their tinnitus), especially at occipitoparietal sites.

The differences between the SNN models of T1 and T2 can be also studied by computing the number of spatiotemporal interactions between the EEG variables using a Feature Interaction Network (FIN). In order to analyse the information interaction between the brain areas in response to masking across the two groups, the total temporal interactions (in terms of spike communication) between 64 input neurons indicating average one-to-one interaction between the input neurons (EEG channels) were calculated (Figure 6). Interaction lines formed between the 64 EEG channels of non-responders at T1 and T2 were grossly similar. Lines connecting AFz and F5 are thick indicating strong interaction at T1 (Figure 6A). At T2 there was greater interaction between POz and right parietal occipital regions (Figure 6B). The FIN representation for responders at T1 indicates more numerous connections between right and left parietal and parietal-occipital regions (Figure 6C). A strong interaction is shown between FPz and F7. There are fewer interactions at T2 compared to T1 for responders. The FIN at T2 for the two groups is similar, but with responders demonstrating greater levels of interaction (thicker lines Figure 6D compared to Figure 6B). The connections for responders between FPz and FP1 and F7 are reduced at T2 (thinner lines Figure 6D) than at T1 (Figure 6C). Greater interaction is shown between P1 and C6, and left (PO7) and right (PO8) parietal-occipital
regions after masking in responders, consistent with more spikes being transmitted between the neurons in these areas, reflecting changes in the recorded EEG.

The average connection weights between input neurons and clusters of neighbouring neurons provides another way of visualising the results (Figure 7). Whole brain connectivity was higher at T1 for non-responders compared to responders. The differences in whole of brain connectivity at T1 and T2 appeared small, except for responders P7 and P11, where visibly larger increases in connectivity weights occurred at T2 (Figure 7B). When separated into brain regions and hemispheres pre (T1) – post (T2) masking connection weights were similar for non-responders (Figure 7C). Following the masking, connection weights for responders increased to resemble non-responder values.

Experiment 2. Pattern classification.

To investigate whether the SNN architecture can be used for prediction of response to sound therapy, an SNN model was trained (using only the EEG data collected at T1) to predict the output classes at time T2 (the three month follow up appointment). The predictive outcomes were the two groups of participants (i.e. responders and non-responders to sound therapy as measured by improved TFI scores). Classification was based on a leave-one-out cross-validation (LOOCV) method. The model had an overall accuracy of 96.67%; it classified non-
responder samples with 100% accuracy, and responder samples with 93.33% accuracy, suggesting that the model has the potential to be developed into a tool capable of predicting the likelihood of successful outcomes for individuals were they to use masking.

Discussion.

The understanding of the underlying psychological and neural mechanisms of tinnitus masking is currently limited. This study used a behavioural case series, alongside EEG and a computational SNN architecture, to evaluate the effect of three masking sounds on tinnitus and associated symptoms across 12 months. This research reinforces the heterogeneity of the tinnitus experience between individuals and how it can vary with time. A clinically meaningful reduction in TFI occurred at at least one time point during masking for 64% of participants and was sustained across a period of masking at that level for 45% of participants. The combination of informational masker (spatial-localisation information) and energetic masker (sound energy covering the same frequency band as pitch matched tinnitus) was the effective masking sound for the majority of responders to masking (60%). This percentage was consistent with previous studies exploring this masker (Searchfield et al., 2016). Comparisons between the maskers within individuals showed large effect sizes, reinforcing the visual analysis. The informational masking (notched noise with spatial cues) coincided with less improvement in TFI scores than the other maskers. The benefit of masking was most often observed in the first, of three, masking periods. When benefit was not seen in the first period, only the combination masker was associated with clinically significant change in the TFI (in the second masking period).

The SNN based methodology was used to visualise EEG connectivity between brain regions; connectivity for non-responders to masking was grossly similar before and after masking. For
responders to masking there were large changes in strength of connectivity, centred around parietal-occipital regions. Examination of the difference figures (Figure 5) suggests that the greatest changes in connectivity for responders occurred in the right hemisphere (contralateral to where the majority experienced their tinnitus), especially at occipitoparietal sites. There were also changes at frontal, central, and temporal sites, again more heavily weighted to the right hemisphere but with some changes apparent in the left as well, notably at temporal sites. Our results are largely consistent with previous findings (Ueyama et al., 2013, Han et al., 2019), but further extend them to reveal the connectivity intensity across different brain regions affected by masking. This supports the theory that the perception of tinnitus relies on a distributed neural network (De Ridder et al., 2014), and successful treatment resulted in a reduction in connectivity between these auditory and non-auditory regions. Sound therapy may alter tinnitus by its presence altering tinnitus audibility or replacing its perception, by creating context and reality around the perception of a phantom sound, and change in reaction to sound (Searchfield et al., 2019). The parietal cortex, implicated in the present results as a locus for masking effects, is involved in spatial attention and association. One putative reason for the persistence of tinnitus is that patients are unable to adapt to the phantom sound because they cannot associate it with an external object, and so it continues to monopolize attention (Searchfield, 2014). The most effective masker, in terms of number of responders, included spatial information. The sound therapy in the present study may have provided context for the perception of sound, enabling participants to disengage attention from their tinnitus. The spatial masking may have interrupted processing by the dorsal “where” pathway of the dual stream hypothesis (Alain et al., 2001). Tinnitus loudness ratings, and in several cases MML, were reduced consistent with the changes in connectivity modelled at temporal sites. The non-auditory regions also play an important role in the tinnitus experience, representing cognitive components as opposed to purely perceptual factors. This is an important point to consider as
treatments, such as cognitive behavioural therapy, tend to focus on mitigating emotional and attentional aspects of the tinnitus experience.

An unexpected observation was that TFI scores were poorer from baseline by 13 points for two individuals during the informational masking. Assuming an increase in 13 points is a clinically significant increase in tinnitus, and that the change in tinnitus was not due to another variable that was not measured, the result indicates that at least one type of masking may make tinnitus worse in some people. The informational masker was designed to have energy removed around the measured tinnitus pitch by a notched filter. Notched filters have been suggested as a method to reduce tinnitus through a lateral inhibition mechanism (Okamoto et al., 2010). The goal of the notch in this study was to remove masking energy at tinnitus pitch, the goal was not lateral inhibition. We cannot exclude the possibility that the notch had a lateral inhibition effect. Independent of its mechanism of effect the informational masker had the least benefit of the masker types and coincided with increased tinnitus in two individuals. It has been speculated that passive sound therapy with BBN might have negative effects (Attarha et al., 2018) although most clinical evidence and experience suggests this is not the case (Henry et al., 2019). We strongly believe that sound therapy in general is positive and this outweighs negative effects, however we suggest caution in the presumption that all masking will have positive effects. We recommend that the use of masking, as with any treatment, be monitored and adjusted as needed by clinicians. Unsupervised, self-help, use of sounds (especially novel sounds without an established risk-profile) may carry low-level risk of increasing tinnitus.

A goal of this study was to ascertain whether the heterogeneity in benefit from tinnitus masking could be predicted on the basis of behavioural or EEG measures prior to therapy. The best
combination of behavioural predictors of tinnitus success were from the individuals case history, specifically: that loud noise did not make their tinnitus worse, stress worsened their tinnitus, there was no relationship between sleep at night and their tinnitus in the day, they did not suffer from other pain syndromes, tinnitus loudness varied from day to day. Negative response to sound, i.e. “loud sounds make tinnitus worse”, is a barrier to effective use of masking. Masking has been proposed to provide a sense of control and relief from the perception of the tinnitus sound (Vernon and Meikle, 2000). This effect may explain the relationship with baseline stress measures. Reduction in tinnitus variation day to day as a variable contributing to response to masking possibly reflects an elevation of adaptation level to the masking sound (Searchfield et al., 2012) that reduces the contrast with the tinnitus. Fluctuations in perception of tinnitus become less obvious when periods of tinnitus absence are filled with sound. The perceptual ratings of tinnitus and, more variably, psychoacoustical loudness match and minimum masking level, tended to mirror changes in the TFI. The results from the DASS and PANAS did not resemble the patterns of change observed in TFI. This result is consistent with the masking primarily altering the perception of the tinnitus sound, rather than feelings of depression, anxiety and affect. We speculate that daytime masking may be less effective in modifying sleeping patterns related to tinnitus and psychosomatic complaints such as chronic pain. These factors could be more responsive to counselling or CBT. The individuals non-responsive to sound might be responsive to counselling, CBT or mindfulness. In the SNN study of mindfulness in depressed patients, frontocentral and temporal activation reached non-depressed levels in persons responsive to mindfulness but remained low in non-responsive depressed participants (Doborjeh et al., 2019). Persons who responded to sound might also demonstrate tinnitus benefit and changes in connectivity in those regions related to reaction to tinnitus if the sound therapy was accompanied by a psychological intervention.
The SNN model was used to process EEG data and learn patterns of spiking that could distinguish response to masking from non-response. The SNN models were trained by the EEG data from T1 to detect, whether a participant was likely to respond to the masking at T2. This was performed by classifying the EEG data of T1 into two classes of participants (responders and non-responders based on the TFI score change at T2 of greater than 13 points). The classification accuracy was 93% for responders and 100% for non-responders. This finding indicates that the designed SNN-based methodology may be used in the future to predict response to tinnitus masking. The development of a non-invasive tool for predicting benefit of masking and guiding sound selection would be a significant step-forward for sound therapy and tinnitus management generally.

This study had some limitations, primarily regarding the retention of participants. The study required a high commitment from participants due to repeated measures over 12 months of 3 different interventions. Travel and time inconvenience of multiple assessments (especially EEG) played a role. It is possible that those who withdrew from the study were more likely to be dissatisfied with the intervention (Lobo et al., 2017) and more strongly motivated to see the interventions succeed. Self-reported measures of tinnitus function, loudness, comfort, and annoyance were systematically obtained alongside measures of affect, depression and stress, psychoacoustic matches of loudness and minimum masking level, and EEG. While multiple dimensions of tinnitus and assumed modulators were measured across the period of the study it is quite possible that other variables, not measured, affected results. This complicates interpretation of Single-case designs. RCTs can minimise such effects through averaging and
regression to the mean, but it does not mean these effects are absent. The repeated measures and phases of Single-case limit extraneous events accounting for changes in the dependent variable as that extraneous event must have its effects and ineffect corresponding with the introduction and withdrawal of the dependent variable. Multiple measures at timepoints during the baseline and washout periods would have enabled stronger evaluation of the baseline stability. The study explored 6 potential maskers (2 base sounds: rain and static BBN with 3 manipulations: Energetic, Informational and Combination maskers) this limited the replication across participants. Although the rain and static BBN masker were used, their separate effects were not explored in detail, however results for the base masking sounds across the masker types appeared equivalent. Although EEG was measured at multiple times across 12 months only the baseline and post one masking sound was analysed alongside behavioural measures. For the SNN analysis the recordings for the different effective masking types were collapsed into masker responders and non-responders. This was a pragmatic approach to having sufficient numbers in each category for the NeuCube modelling. Future work will explore the effects of different maskers, and other treatments, using SNN modelling. Participants all had chronic tinnitus of varying duration. It is possible the chronicity of the disorder affects outcomes, future efforts in evaluating effects in acute cases of tinnitus would be valuable.

The strengths of the study is its in-depth evaluation of individuals rather than group means (Lobo et al., 2017), and its use of EEG and modelling of data. There were few missing data points. Single-case study designs are a valuable research tool in assessing the impact of specific interventions on a patient, as individual differences are masked in the large group trials (Wilson, 1987). Case series research can assist in exploring the longevity of treatment effects, and in the identification of prognostic factors (Dobie, 1999). RCTs are not well suited to the
development of precision health, where treatments are applied on the basis of individual characteristics not the population mean (Lobo et al., 2017).

SNN models can be used in future tinnitus research to obtain new findings, such as tracing a trajectory of neural brain activities, which cannot be obtained with the use of traditional statistical methods. The designed SNN has several advantages over traditional machine-learning techniques or deep-learning neural networks: it preserves the spatio and temporal information together in a model matched to a brain template; it learns spatio-temporal patterns from data through biologically plausible learning rules; and enables interpretation of interactions and between brain areas (Kasabov, 2014).

The SNN-based methodology enabled a spatio-temporal understanding of how tinnitus masking could affect individuals’ brain activity. The results give strong support for exploring the potential for predicting tinnitus masking outcomes.

**Conclusion.**

This study illustrates individual variability in effects of different masking sounds. The masker that most frequently coincided with a reduction in tinnitus was a combination of informational masking (with spatial cues) and energetic masking (sound energy at tinnitus pitch). There is a need for individualized therapies for tinnitus and this study provides objective evidence of changes in connectivity with sound therapy. The SNN analysis holds promise as a means to predict tinnitus therapy success. The classification results of EEG patterns learned in an SNN model confirmed that the model can discriminate the spatio-temporal patterns before and after tinnitus masking and predict responders from non-responders. Through understanding when and where masking effects arise in the brain, we can begin to improve the effectiveness of the masking, and potentially, enable real-time modification of sound to suit the individual’s brain
state. Future applications could focus on the clinical setting utilising this model in a practical way to optimise treatment plans that can be tailored specifically to the tinnitus profile and brain architecture of an individual. This should improve the precision of clinical decision making, therapy benefit, and reduce service costs.

References.


SCHAETTE, R. 2014. Tinnitus in men, mice (as well as other rodents), and machines. *Hearing Research*, 311, 63-71.


Figures and Tables:

A

Recruitment
N=28 volunteers

3 did not respond further

Initial assessment

8 did not begin trial
- 7 withdrew due to time required
- 1 was ineligible due to use of hearing aids

Masker use

6 could not complete trial, due to time or travel

Analysis
N=11

B

Initial assessment

Balanced allocation

Random allocation

3 months
Energetic Combined Informational Energetic Combined Informational

Washout 1 month

3 months
Informational Energetic Combined Combined Informational Energetic

Washout 1 month

3 months
Combined Informational Energetic Informational Energetic Combined

Analysis

Figure 1. Attrition. B. Participant allocation and timing of behavioural measures. EEG was measured prior to and after 3 months of sound therapy.
P4 BBN
P7 Rain
P8 Rain, PNAS & DASS not obtained at 3 months for combination sound.
P9 Rain
P11 Rain
Figure 2. i-vii. Behavioural results for seven participants who demonstrated at least one period during treatment of a reduction of 13 points on the TFI. A. TFI results across the 3 periods of masking delineated by vertical dashed lines (E, energetic; I, informational; C, combined masking). The grey shaded box highlights a clinically significant change of 13 points. B and C. Rating scale scores (0-10, except “overall” 0-5; the higher number the greater the effect of tinnitus). D. PANAS scores. E. DASS scores. F. Audiogram. G. Tinnitus pitch match. H. Psychoacoustic loudness match and minimum masking level (MML).
Figure 3. Average change in TFI in response to the 3 masking sounds for each participant compared to baseline score preceding the therapy period. Negative scores indicate worse tinnitus. The error bars are +/- 1 standard deviation.
Figure 4. i. Connectivity plots for non-responsive group. The red lines are negative connections while the blue lines are positive connections. High connectivity in occipitoparietal areas for 3D representation A. before and B. after treatment and 2D representation C. before and D. after treatment. Connectivity in central and temporal areas appears to be maintained after treatment and even increase on the left side. Frontal connectivity appears sparse at T1, and increases slightly at T2 but left side especially remains fairly sparse. ii. Connectivity plots for sound therapy responsive group. 3D representation A. before and B. after treatment and 2D representation C. before and D. after treatment. High connectivity in occipitoparietal areas at T1, reduced after treatment. Right centroparietal areas appear to show a reduction in connectivity at T2. Greater engagement of frontal regions appears to occur after sound therapy.
Figure 5. Difference between the connection weights at T2 and T1 A. Non-responders 3D and B. 2D. C Responders 3D and D. 2D. The red lines are negative connections that represent reduction from T1 to T2, while the blue lines are positive connections that indicate increasing connectivity weights from T1 to T2.
Figure 6. The Feature Integration Network (FIN) illustrating the total connection weight interaction between the 64 electrode sites during the STDP learning for non-responders and responders at baseline (T1) and at the three month follow up session (3mFU; T2). FIN nodes represent input neurons (electrode sites), and lines represent connectivity weights between them (thicker lines indicate greater causal interaction between neural areas around the EEG electrodes).
Figure 7. Over the whole brain, non-responders (A) appeared to show more connectivity than responders (B) at baseline (T1). Total average connection weight remained stable for non-responders. It increased for responders P7 and P11 but remained lower than for non-responders. C. When data were grouped and split into regions: Left Frontal (Fp1, AF3, AF7, F5, F3 and F1); Right Frontal (Fp2, AF4, AF8, F6, F4 and F2); Left FrontoCentral (FC5, FC3, FC1, C5, C3 and C1); Right FrontoCentral (FC6, FC4, FC2, C6, C4 and C2); Left Temporal (T7, FT7, T7 and TP7); Right Temporal (F8, FT8, T8, TP8); Left CentroParietal (CP5, CP3, CP1, P7, P5, P3, P1); Right CentroParietal (CP6, CP4, CP2, P8, P6, P4 and P2); Left OccipitoParietal (O1 and CB1); and Right OccipitoParietal (O2 and CB2). Responders (solid black line (o)) showed less connectivity than non-responders (solid grey line (x)) at T1, and then showed increases to levels similar to or lower than non-responders at T2 (dashed lines). Exceptions to this pattern were in the occipito-parietal sites, where both R and NR groups showed similar connectivity at T1 and similar decreases at T2.
### Tables:

Table 1. Participant characteristics and results for the primary outcome measure (TFI). The average change in TFI from the baseline score for each therapy period is shown (average change (standard deviation)). Values in **bold** indicate a sustained clinically meaningful improvement (13 points) in TFI. Negative values indicate an increase (worse) TFI from baseline, scores *underlined* indicate a sustained increase of 13 points. Hodges' g effect sizes are shown (Hg) comparing the average change in TFI from baseline for each potential paired comparison of sound therapy. Large effects are in **bold**, for direction effect refer to TFI change scores and the text description.

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*49*
Table 2. Extracted rules for the combination of variables to define a profile for each class using an Evolving Classification Function.

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