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ALTERATIONS IN STEADY-STATE SYNCHRONISATION BETWEEN ACUTE AND CHRONIC TINNITUS SUGGESTS REDUCTION IN THE NEURAL CORRELATES OF TINNITUS OVER TIME

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ABSTRACT

The mechanism of tinnitus remains unclear as the generation and persistence of tinnitus is not widely understood. The acute tinnitus population serves as an ideal subject for investigating the mechanisms behind the origin and persistence of tinnitus, from its initial onset to its subsequent chronification. One of the neural markers for measuring tinnitus are central gain and alterations in neural synchrony or central gain, linked to tinnitus can be measured using the Auditory Steady State Response (ASSR). The experiment was carried out on 39 participants with acute tinnitus (18 followed back six months post baseline), 30 with chronic tinnitus, and 27 controls. The results revealed cross sectionally, there were no significant differences in both absolute amplitudes of ASSR across intensities and the slope of ASSR growth function between the groups. However, longitudinally, there was a near significant increase in ASSR amplitude at low and medium intensity levels over time. Our findings indicate that the near significant differences in ASSR amplitude is attributable to changes in neural synchronisation, attentional modulation, tinnitus-related distress, and diminished GABAergic inhibition coinciding with the onset of tinnitus, which typically decreases over time. The alterations occurring at the onset may facilitate the persistence of tinnitus.

Keywords: *Neural synchronization, GABA, acute tinnitus, tinnitus generation.*

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1. INTRODUCTION

Tinnitus has been found to originate most commonly because of hearing damage, which can be either an audiometrically detectable hearing loss or an undetectable kind of 'hidden' hearing loss such as cochlear synaptopathy [1]. In principle, for optimal functioning of the auditory system, each hierarchical level should have an input/output function that maintains a stable and optimum range of output values despite potentially large changes in the range of inputs. But, due to peripheral auditory insults, input to the central auditory system is reduced, thus altering the equilibrium of the input/output function. In order to maintain the input/output function, the brain typically changes the slope function by increasing the rate of excitatory to inhibitory firing to achieve homeostasis [2,3]. This alteration of slope in the input/output function is gain and helps achieve homeostatic plasticity [3].

One of the objective markers of gain is the use of Auditory Steady State Response (ASSR) [5]. Amplitude Modulation (AM) results in neurons exhibiting a *mixed coding* response at the level of primary auditory cortex, which encompasses both phase locking to the modulation frequency, and an elevated firing rate in response to the unmodulated tone [6]. The 40 Hz ASSR has been used in tinnitus studies as a potential measure of neuronal sensitivity in tinnitus [6]. The slope typically dictates the degree of excess input/output function, which cannot be fully deduced from a single data point (intensity) measurement and requires at least 2 data points (intensities). Therefore, it is necessary to do an intensity dependence analysis (across different intensities) of the steady-state response, which will provide the slope function to facilitate the determination of central gain related to the ASSR.

The generation and persistence of tinnitus has been unclear and although there have been studies that talk

about possible mechanisms of tinnitus generation and persistence, they are either from first principles, chronic tinnitus studies, or animal studies. There needs further research on acute tinnitus individuals as they are the ideal population to study how tinnitus generates and how does it transit from acute to chronic stages of tinnitus. According to the sensory precision model [3], tinnitus arises from changes in the brain's estimation of sensory precision following hearing loss. In the acute phase, reduced auditory input leads to a down-weighting of peripheral signals and an up-weighting of internal predictions, resulting in the emergence of tinnitus as a compensatory percept. Over time, if the altered sensory precision persists, the brain may recalibrate to treat the internally generated tinnitus signal as behaviorally relevant, leading to chronic tinnitus. This model suggests that persistent tinnitus reflects a maladaptive stabilization of heightened precision attributed to non-auditory predictive signals. Keeping this literature in mind, we hypothesize that central gain diminishes as a regression towards the mean from the Acute to the Chronic stage, leading us to predict a decline in ASSR slope and amplitude over time.

2. METHODS

2.1. Participants

We studied 39 participants with Acute Tinnitus (which we defined as duration 3 days to 6 weeks, with one outlier having a duration of 12 weeks), 30 participants with Chronic Tinnitus (defined as duration more than 6 months), and 27 hearing-matched (to the acute tinnitus group) non-tinnitus controls. Participants were recruited through community advertising on Google Ads, and internally within Newcastle University's research volunteer pool. The 39 Acute Tinnitus participants were invited for reassessment after a minimum of 6 months from tinnitus onset (which we took to indicate their chronic stage), and 18 of them volunteered for and completed this further testing. We refer to this as the 'Post Acute' group, to distinguish it from the group recruited during the chronic stage of tinnitus.

Control participants were matched to the acute tinnitus group for age, sex, hearing, and stimulus frequency and presentation ear.

2.2. Audiological assessment

The experimenter interviewed the subjects before the experiment, verifying a medical history consistent with subjective tinnitus and the absence of atypical symptoms or concerns regarding an undetermined underlying cause. Participants underwent a Pure Tone Audiometry (PTA) test to establish hearing thresholds at octave frequencies ranging between 250 Hz up to 8 KHz. Thresholds were estimated based on the initial presented level at either 40 dBHL or above depending on the participant's residual hearing [7]. The frequency and loudness of tinnitus were assessed using a *tinnitometry* (i.e. psychoacoustic measurement of tinnitus characteristics) approach for patients with acute or chronic tinnitus. In instances of unilateral Tinnitus, matching stimuli were delivered contralaterally, whereas in bilateral tinnitus, they were administered bilaterally. Participants initially matched the loudness of their tinnitus, followed by matching its frequency, commencing at a reference frequency of 6 kHz.

2.3. ASSR stimuli

The ASSR stimuli comprised 15 stimuli per frequency (5 stimuli for each of three intensities per frequency) within a total experiment duration of 15 minutes. These stimuli were Amplitude Modulated sounds with a modulation frequency of 40Hz and a modulation depth of 100% at 1 kHz and the participant's matched tinnitus frequency (or, for controls, the matched tinnitus participant's frequency), each lasting 30 seconds, with an interstimulus interval of 2 seconds.

For every frequency, three different intensities were presented. Stimuli were presented in one block, with intensities and frequencies fully randomized within that block. To account for hearing loss, loudness recruitment and hyperacusis, whilst keeping the stimuli clearly audible yet comfortable, stimulus intensities were presented in accordance with each participant's dynamic range, i.e. the range between their hearing threshold and uncomfortable loudness level, which were established for the specific experimental stimuli at both 1 kHz and the tinnitus frequency. Figure 1 depicts the intensity levels presented.

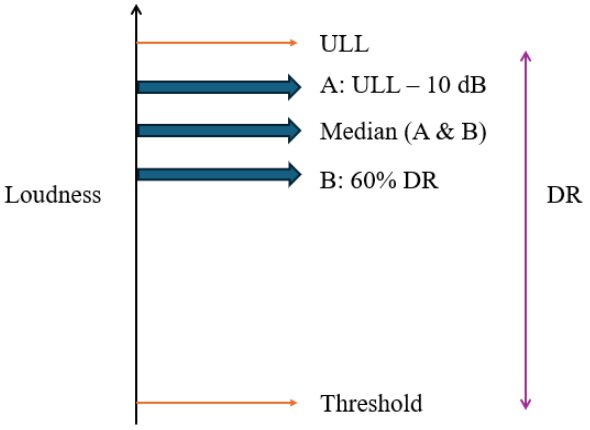

Figure 1: Stimulus presentation levels across 3 intensities based on tailored dynamic range for each subject
ULL: Uncomfortable Loudness level, DR: Dynamic Range.

2.4. EEG and Data analysis

Data were processed in MATLAB, version R2019a, using the EEGlab toolbox [8] and customized code. Data were re-referenced to the P9/P10 (Linked mastoids) montage. The data were further segmented into 30 seconds epoch around each trigger which was followed by a baseline correction. Following the segmentation of the EEG data into 50% overlapping 1s Hanning-windowed sub-epochs, a frequency analysis was conducted utilizing a Fast Fourier Transform (FFT) to transfer the time-domain data into the frequency domain, facilitating the identification and extraction of spectrum peaks, notably at 40Hz.

After pre-processing, we used customized code to perform automatic peak detection at 40Hz and signal to noise ratio calculation to determine the ASSR amplitude and signal to noise ratio. We did this using data from FCz to measure the peak amplitude for ASSR at 40Hz for both 1Khz and tinnitus frequency. Similar analysis was done for noise floor estimation, where the FFT amplitudes were averaged across the neighboring frequencies between 38 and 39, and between 41 and 43, Hz of Amplitude Modulation. The presence of a meaningful ASSR was ascertained via visual evaluation of the response at 40Hz and objectively through F-statistics [9], which analyzed the variance of peak amplitude and noise floor values; a meaningful response was judged to be present only if the ASSR response was significantly larger than the noise floor values based on a value of $p < 0.05$. Each subject had amplitude and noise floor calculated for 3 intensities across 2 frequencies of 1 kHz and tinnitus frequency. From these, the ASSR slope function at each frequency was calculated as the quotient of the Amplitude Dynamic Range (ADR: relative difference of the high and low ASSR amplitude) and Stimulus Dynamic Range (SDR: relative difference of the high and low stimulus intensity). Statistical analysis was carried out for both, across groups between acute, chronic, and controls along with a within group statistical analysis between acute and post-acute tinnitus.

3. RESULTS

3.1. ASSR Amplitude

The ASSR mean amplitude was individually evaluated among the Acute, Chronic, and Control groups for both 1 kHz and tinnitus frequencies. Before comparing amplitudes at low, medium, and high levels, we assessed the absolute stimulus presentation levels (dBSL) to establish whether possible differences in measured amplitude could be explained by stimulus presentation level. A MANOVA was carried out to establish the effect of groups (Acute, Chronic, and Controls) on the stimulus presentation levels (low, medium, and high).

3.1.1. 1 kHz

To determine the effect of group and intensities on the ASSR amplitude, we conducted a two-way Analysis of Covariance (ANCOVA) with two factors: groups (Acute, Chronic, and Controls) and intensities (low, medium, and high), with two covariates: stimulus presentation levels (low, medium, and high), and hearing thresholds at 1 kHZ. Results revealed no statistical significant main effect of intensities ($F(2,277) = 2.348$, $p = 0.097$, partial $\eta^2 = 0.017$) and statistically significant main effect of groups ($F(2,277) = 3.066$, $p = 0.048$, partial $\eta^2 = 0.022$) with near-significant difference between Chronic Tinnitus and Controls ($p = 0.055$) and no significant difference between Acute Tinnitus and Chronic Tinnitus ($p = 1$) and between Acute Tinnitus and Controls ($p = 0.142$). Controls had higher overall amplitude ($M = 1678.7$, $SE = 84.93$) when compared to Chronic Tinnitus ($M = 1388.95$, $SE = 79.62$). There was no statistically significant interaction between the groups and intensities on the amplitude ($F(4,277) = 0.279$, $p = 0.891$, partial $\eta^2 = 0.004$). With respect to the longitudinal comparison, a repeated measures 2-way ANOVA was performed to compare the effect of groups and intensities on the amplitude. Results revealed a main

effect of intensity ($F(2,16) = 23.814$, $p < 0.001$, Wilk's $A = 0.251$), no main effect for group ($F(2,16) = 2.667$, $p = 0.135$, Wilk's $A = 0.873$), and no interaction effect between groups and intensities ($F(2,16) = 0.957$, $p = 0.405$, Wilk's $A = 0.893$). We however carried out a simple main effect analysis using paired t test to determine the impact of group on amplitude for individual intensities, and the results indicated presence of near-significant difference between Acute and Post Acute Tinnitus for low intensity ($t(17) = -1.896$, $p = 0.075$) and medium intensity ($t(17) = -2.080$, $p = 0.053$) with Post Acute tinnitus (low intensity: M = 1475.97 SD = 670.05, medium intensity: M = 1674.48, SD = 771.61) having larger amplitude than Acute tinnitus (low intensity: M = 1313.82 SD = 762.2, medium intensity: M = 1456.56, SD = 809.1). No significant difference was found for the high intensity ($t(17) = -0.772$, $p = 0.451$). There was no impact of stimulus presentation levels on the obtained ASSR amplitude with no significant difference between Acute and Post Acute Tinnitus on low, mid, and high stimulus intensity presentation levels.

3.1.2. Tinnitus Frequency

Equivalent analysis was performed at tinnitus frequency and revealed no statistically significant difference for both cross sectional and longitudinal comparisons. Figure 2 depicts the cross-sectional changes in amplitude and figure 3 depicts the longitudinal changes in amplitude

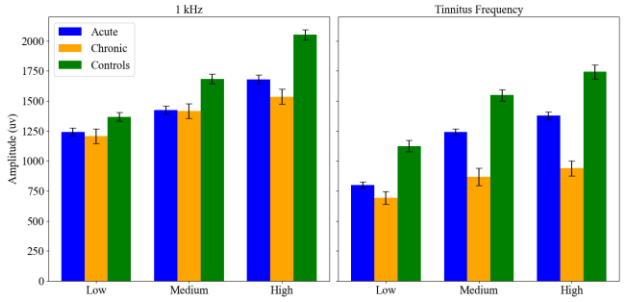

Figure 2*:* Differences in ASSR amplitude at low, medium, and high intensities between Acute, Chronic, and Controls for both 1 kHz and tinnitus frequency.

There is no statistical difference between the groups for any intensities across either frequency. However, controls show a non-significant increased amplitude when compared to both the tinnitus groups.

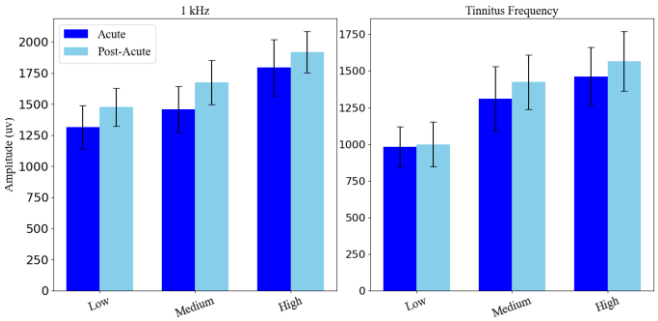

Figure 3: Differences in ASSR amplitude at low, medium, and high intensities between Acute and Post Acute Tinnitus for both 1 kHz and tinnitus frequency**.** *There is a near significant difference (increase in ASSR amplitude) between Acute and Post Acute Tinnitus for low and medium intensity at 1 kHz and none for high intensity. No differences in any loudness categories were noted for Tinnitus frequency.*

3.2. ASSR Slope

In analyzing the variations in slope among the Acute, Chronic, and Control groups, as well as between the Acute and Post Acute Tinnitus groups, we focused on three variables: the Stimulus Dynamic Range (SDR), defined as the difference between high and low stimulus presentation; the Amplitude Dynamic Range (ADR), which represents the difference between high and low ASSR amplitude; and slope, calculated as the ratio of SDR to ADR. Determining whether SDR differed will provide insight into the possible confounding factors that might affect the obtained ADR and slope. Assessing ADR in conjunction with slope will provide a comprehensive understanding of the amplitude growth function for ASSR across different groups

3.2.1. 1 kHz stimuli

A one-way MANOVA was carried out to establish the effect of group on slope, SDR, and ADR; this revealed a significant difference in overall response based on groups ($F(6,184) = 3.964$, $p < 0.001$, Wilk's $A = 0.526$, partial $\eta^2 = 0.114$). An overall main effect was seen for SDR ($F(2,94) = 10.215$, $p < 0.001$, partial $\eta^2 = 0.179$) with difference between Acute Tinnitus and Controls ($p = 0.007$), Chronic Tinnitus and Controls ($p < 0.001$), and no differences between Acute Tinnitus and Chronic Tinnitus ($p = 0.317$). Controls had higher SDR (M = 19.74, SD = 5.94) when compared to Acute (M = 15.42, SD = 5.81) and Chronic Tinnitus groups (M = 13.19, SD = 4.95). There was an overall main effect of group seen for ADR ($F(2,94) = 6.346$, $p = 0.003$, partial $\eta^2 = 0.119$)

with difference between Acute Tinnitus and Controls (p = 0.049), difference between Chronic Tinnitus and Controls (p =0.002), and no difference between Acute Tinnitus and Chronic Tinnitus (p = 0.585). Controls (M = 640.39, SD = 396.70) had higher ADR when compared to Acute Tinnitus (M = 435.73, SD = 344.19) and Chronic Tinnitus (M = 328.49, SD = 263.19). There was, however, no main effect of groups on slope (F (2,94) = 0.961, p = 0.386, partial η^2 = 0.02). There was an effect on SDR of group, which could also be a potential confound. This warranted us to carry out individual one-way ANCOVA to establish the effect of the group on ADR and slope individually, with covariates of SDR and hearing thresholds at 1 kHz. With respect to Slope and ADR, there was no significant effect of group on the values of slope (F(2,92) = 1.279, p = 0.279, partial η^2 = 0.027) and there was no significant effect of group on the values of ADR (F(2,92) = 1.774, p = 0.17, partial η^2 = 0.037) (refer figure 4.5 and 4.6). Longitudinal comparisons between Acute Tinnitus and Post Acute Tinnitus revealed no significant difference in the slope values (t(17) = 0.806, p = 0.431), ADR (t(17) = 0.319, p = 0.754), and the SDR (t(17) = -1.177, p = 0.256) values respectively.

3.2.2. Tinnitus Frequency

Similar analysis was carried out for the tinnitus frequency using nonparametric tests and yielded no statistically significant differences for both cross sectional and longitudinal comparisons. Figure 4 depicts the cross-sectional changes in slope and figure 5 illustrates the longitudinal changes in slope.

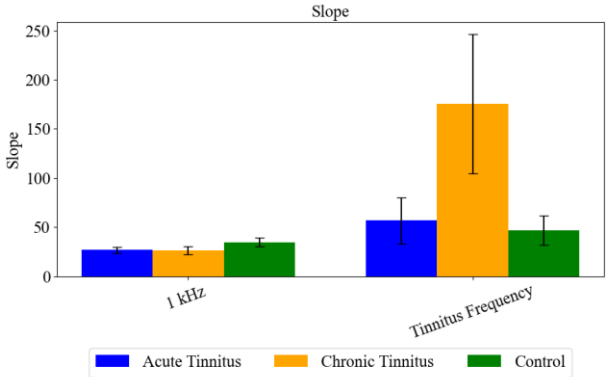

Figure 4: Slope between Acute, Chronic, and Controls at both 1 kHz and tinnitus frequency

Slope values denote Amplitude Dynamic Range/Stimulus Dynamic Range and there were no significant difference in slope across the groups for both frequencies.

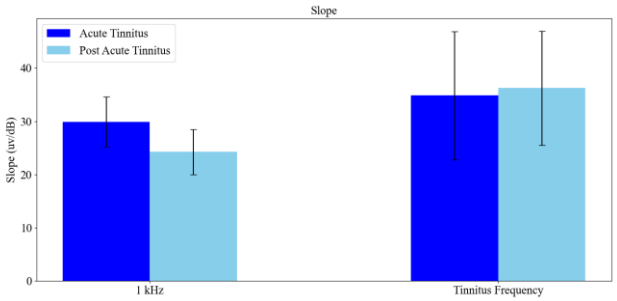

Figure 5: Slope between Acute and Post Acute Tinnitus at both 1 kHz and tinnitus frequency

There was no significant difference in slope between the groups for both frequencies.

4. DISCUSSION

The principal results indicate that there was a near significant increase in the ASSR amplitude at low and mid-level intensities for Post Acute Tinnitus when compared to Acute tinnitus at 1 kHz. Tinnitus frequency did not yield any longitudinal differences. No variations in the slope were seen in either 1 kHz or tinnitus frequency. There were no cross-sectional differences across the groups in either ASSR slope or amplitude. However, there was a non-significant increase in controls for both absolute amplitude and slope, and this finding would help us contextualize the longitudinal changes as we saw increase of amplitude over time which is in the direction toward the Controls.

4.1. No cross-sectional variations across the groups for Acute, Chronic, and Non-Tinnitus Controls

Our first findings indicate that there were no cross-sectional changes among the Acute, Chronic, and Non-Tinnitus Control groups, with respect to either slope and absolute amplitude indicating that the presence of tinnitus isn't associated with the ASSR amplitude. The customised presentation level for the subjects according to their dynamic range may have influenced the outcomes, as the level of hyperacusis has been compensated. In this case, the tailored ASSR presentation level may have curbed the influence of hyperacusis. This was in support of the findings by Paul et al. who investigated the influence of attention on the auditory steady-state response in individuals with and

without tinnitus and their results highlighted that tinnitus patients exhibited diminished attentional modulation of the 5 kHz ASSR, unlike the control group, suggesting that attentional resources may be preferentially allocated to the tinnitus percept, thus limiting further modulation [10]. The findings by Diesch et al. further suggested that the alterations of ASSR in tinnitus individuals when compared to Controls may be partially influenced by attentional processes that imply the complex interplay between tinnitus, attention, and auditory processing. The study further emphasizes the importance of considering attentional factors when interpreting ASSR findings in tinnitus research [11]. Sedley reviewed the role of gain in tinnitus mechanism and highlighted literature that tend to show an increased ASSR amplitudes for tinnitus individuals that is closer to the tinnitus frequency. In our case we did not obtain significant differences at the tinnitus frequency [12]. These studies collectively contribute to our understanding of the neural mechanisms underlying tinnitus and the potential of ASSR as a tool for assessment and treatment.

4.2. Changes between Acute and Post Acute Tinnitus

Concerning the variations seen between Acute and Post Acute, we observed a near significant rise in ASSR amplitude at low and medium intensity levels over time for Post Acute Tinnitus at 1 kHz when compared to Acute Tinnitus. We here consider this finding in the context of our hypothesis that central gain reduces over time, following the onset of tinnitus, as a regression to the mean following a period of hypersensitivity in which tinnitus first occurs. It is to be noted that the finding is in the direction of our hypothesis with reduced ASSR amplitude over time, if ASSR amplitude is interpreted as a positive indicator of central gain. Conversely, we instead interpret increased ASSR amplitude over time as a stabilizing measure as it not only trends towards the pattern of controls but also the absolute amplitude is inversely related to distress. Due to the absence of Acute Tinnitus studies concerning ASSR, we aim to compare the present findings with Chronic Tinnitus studies conducted before and after treatment, as well as the observed alterations in ASSR amplitude. Pantev et al. examined the effects of Tinnitus Retraining Therapy on ASSR and found significant reductions in tinnitus related ASSR following TRT [13]. Sadeghijam et al. utilized binaural beats in stimulating tinnitus patients over a month, measuring the changes in ASSR amplitude between the baseline and post-stimulation. Their results indicated an increase in ASSR amplitude following binaural beat stimulation when compared to baseline, which was attributed to enhanced synchronisation from repeated exposure to binaural beats and an improved temporal map that facilitated a higher stimulation rate [14]. The fact that improved synchronization increased ASSR amplitude is in support with our finding where we attribute that habituation of the tinnitus over time increased ASSR amplitude and in this instance. Further to collaborate the direction of ASSR, we would also lean towards controls as an indicator as there was a non-significant increased amplitude seen in controls.

4.3. Changes in neural synchrony and adaptation

We consider our longitudinal design to be more robust due to which we interpret the current findings based on the longitudinal designs. The generation of ASSR is thought to be a superposition of the Middle Latency Response and Auditory Brainstem Response with a predominant generation at the level of Heschl's gyrus (primary auditory cortex), and possibility of contributions from the auditory belt regions, which are secondary auditory cortical areas [15]. The generation of AM tones throughout the auditory pathway is heavily dependent on mechanisms such as phase locking, temporal envelope coding, rate coding, and population coding (group of neurons firing for different modulation frequencies) [16]. When it comes to tinnitus, it has been posited that consequently to decreased input due to hearing loss, there is aberrant (increased) neural synchrony specifically in the delta band oscillations that manifests as tinnitus [17]. The abnormal increase in neural synchrony of spontaneous activity within the cortical system may have an impact on the incoming acoustic signals, where the neural synchrony is reduced to incoming sounds due to a lack of phase locking, which is essential for the formation of auditory steady-state responses (ASSR). In our case, we attribute that the tinnitus is an ongoing neural response that increases the desynchronization causing reduction of the magnitude of ASSR.

4.4. Gamma Amino-Butyric Acid (GABA) and Tinnitus

Gamma-Aminobutyric acid (GABA) is an inhibitory neurotransmitter in the central nervous system that is an amino acid which is non-proteinogenic in nature [18]. GABAergic neurons releases GABA that plays a significant function of regulating neuronal excitability throughout the nervous system [19]. The amplitude of

ASSR has been associated with changes in GABA. Sugiyama et al. found that boosting GABAergic transmission via lorazepam, a benzodiazepine, increased the 40 Hz ASSR in the early auditory cortex [20]. However, this is an indirect effect mediated through GABA receptors, not a direct effect of GABA itself. Toso et al. further discusses how boosting GABAergic transmission increases the amplitude of the 40 Hz auditory steady-state response in the early auditory cortex [21]. They administered a GABAergic modulator, such lorazepam, and found that this neuromodulator led to a significant increase of the 40 Hz ASSR at both the early transient and later sustained components when compared to the administration of placebo and memantine [21]. This indicates that GABAergic neuronal inhibition contributes significantly to the modulation of the 40 Hz auditory steady-state response in the human auditory cortex. GABA has been linked to tinnitus. A prevailing theory is that the reduced GABAergic inhibition in the auditory pathway may contribute to the onset of tinnitus due to increase in hyperexcitability and this has reflected with the presence of lower levels of GABA at the level of the auditory cortex for tinnitus individuals [22]. However, other research suggests a more nuanced role for GABA, for example, one study found increased GABA-mediated tonic inhibition in the auditory thalami of rats with noise-induced tinnitus which further suggests that GABAergic mechanisms might also play a causative role in tinnitus, potentially by being excess and resulting in thalamocortical dysrhythmia [23]. Our overall interpretation would be that reduced ASSR amplitude during the onset of tinnitus might be attributed to reduction in GABA too which tends to gradually increase over time with increase in ASSR amplitude. However, it is to note that this finding needs more validation, and it is unclear whether GABA would be cause or effect of tinnitus or even whether it plays a role for central gain.

4.3. Summary

The current study indicates that tinnitus-related alterations in ASSR (reduction of 1 kHz amplitude compared to controls) peak at onset and thereafter diminishes, possibly impacted by alterations in neural synchronisation, tinnitus-related distress, GABAergic inhibition and/or attentional modulation. This may or may not suggest a shift in neural activity like central gain, given there were no cross-sectional differences between the groups, particularly between Acute Tinnitus and Controls. The longitudinal variations, particularly at low and medium intensity levels, suggest that the tinnitus activity in isolation diminish over time, that may or may not affect central gain. Figure 6 integrates the above-mentioned arguments and depicts the decline of neural responses linked to tinnitus with time, attributable to enhanced neural synchronisation. This activity represents a continuous stimulation that diminishes phase locking to the incoming signal, while a reduction in tinnitus enhances phase locking to the incoming signal.

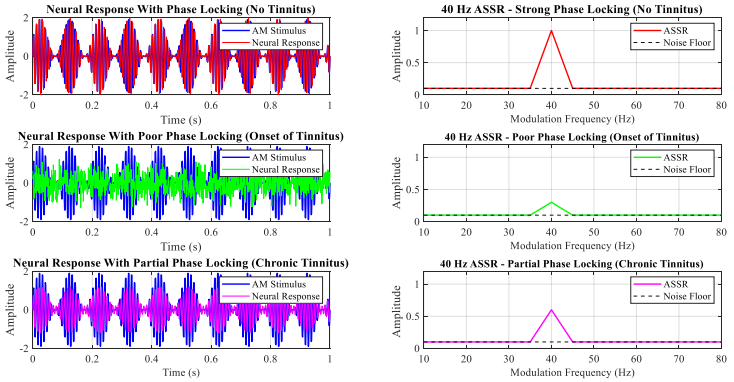

Figure 6: Differences in neural response of AM tones across 3 conditions of No Tinnitus, Acute Tinnitus, and Chronic Tinnitus.

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