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Towards an objective test of chronic tinnitus: Properties of auditory cortical potentials evoked by silent gaps in tinnitus-like sounds

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ABSTRACT

A common method designed to identify if an animal hears tinnitus assumes that tinnitus "fills-in" silent gaps in background sound. This phenomenon has not been reliably demonstrated in humans. One test of the gap-filling hypothesis would be to determine if gap-evoked cortical potentials are absent or attenuated when measured within background sound matched to the tinnitus sensation. However the tinnitus sensation is usually of low intensity and of high frequency, and it is unknown if cortical responses can be measured with such "weak" stimulus properties. Therefore the aim of the present study was to test the plausibility of observing these responses in the EEG in humans without tinnitus. Twelve non-tinnitus participants heard narrowband noises centered at sound frequencies of 5 or 10 kHz at sensation levels of either 5, 15, or 30 dB. Silent gaps of 20 ms duration were randomly inserted into noise stimuli, and cortical potentials evoked by these gaps were measured by 64-channel EEG. Gap-evoked cortical responses were statistically identifiable in all conditions for all but one participant. Responses were not significantly different between noise frequencies or levels. Results suggest that cortical responses can be measured when evoked by gaps in sounds that mirror acoustic properties of tinnitus. This design can validate the animal model and be used as a tinnitus diagnosis test in humans.

1. Introduction

Chronic tinnitus is the continual perception of a sound experienced in the absence of an external sound source. Tinnitus is linked to many etiologies but most commonly associates with hearing damage consequent of noise exposure, ototoxic agents, or the aging process (Shore et al., 2016). The global prevalence of tinnitus is estimated between ~12 and 30% (McCormack et al., 2016), and many of these individuals seek professional help because their tinnitus is so severe. The financial burden on society and health care systems resulting from tinnitus is estimated at over eight billion U.S. dollars (Maes et al., 2013). However at present there is no cure or widely effective treatment (Langguth et al., 2013). To reach these ends, it is necessary to develop animal models in which cellular and molecular correlates of tinnitus can be investigated. Unlike humans, however, animals cannot explicitly report if they hear tinnitus, so tinnitus must be inferred from behavior.

One method to identify tinnitus in an animal measures the amplitude of the startle reflex (muscle contraction) evoked by an intense noise burst, in a procedure called the gap pre-pulse inhibition of the acoustic startle (GPIAS) reflex (Turner et al., 2006) schematized in Fig. 1. In healthy animals, a silent temporal gap within a moderate-level background noise typically inhibits (attenuates) the startle amplitude when the gap precedes the startling noise. However if a noise-exposed animal does not exhibit an attenuated startle response following the gap (i.e., a failure or impairment of gap inhibition), it is presumed that the animal failed to correctly perceive the gap since tinnitus masked or "filled-in" the silence. Unlike other methods used to detect behavioral evidence of tinnitus that typically involve lengthy and costly operant conditioning regimes, the GPIAS is readily measurable and has become an increasingly popular diagnostic tool in animal research (Galazyuk and Hébert, 2015).

The applicability of these findings to human research hinges on the validity of the gap-startle model to objectively detect tinnitus. It

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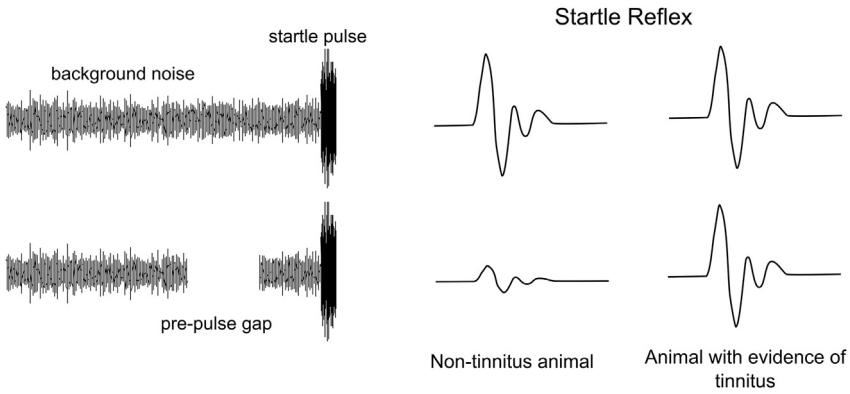

Fig. 1. Gap pre-pulse inhibition of the acoustic startle reflex (GPIAS). A high-intensity noise pulse preceded by an unbroken background noise will evoke a startle response in animals (top row). However when a silent gap is embedded in the background noise preceding the startle pulse, the gap inhibits the startle reflex. In animals with evidence of tinnitus, the reflex is not attenuated. One explanation is that tinnitus "filled-in" the gap prior to the startle pulse.

is then concerning that efforts to replicate the effect in humans with tinnitus have produced equivocal results (Galazyuk and Hébert, 2015). Fournier and Hébert (2013) measured the eye blink reflex (startle response) evoked by a brief intense wideband noise burst (startle elicitor) in young adults with bilateral tinnitus. Each listener rated the similarity of their tinnitus on a 1 to 10 scale to a range of tone frequencies using a validated psychophysical test (Basile et al., 2013), and ratings for this cohort were highest on average at 16 kHz followed by 11.3 kHz. Background noises containing gaps were of a high-frequency (4 kHz, overlapping with the tinnitus perception for most individuals) or of a low frequency (500 Hz, not overlapping with the tinnitus perception). Compared to a control group matched in age and hearing thresholds, those with tinnitus had impaired gap inhibition of the startle response for both high and low frequency background noises. Since impairments were found for low frequencies where tinnitus was not perceived and for those who did not report tinnitus at 4 kHz, the findings suggest that the tinnitus did simply not mask the silent gap. Results may rather suggest a frequency non-specific gap detection deficit, or a general tinnitus-related modification of the reflex circuit that generates the startle response.

A complementary gap detection measure concerns modulation of cortical potentials to noise bursts that follow gaps embedded in background noise. In this design, the focus of measurement is on gap-in-noise modulation of auditory cortical responses instead of the acoustic startle reflex behavior. Berger et al. (2018) found that animals exposed to 120 dB SPL noise, but not 105 dB noise, exhibit modulation failure of cortical responses analogous to modulation failure of GPIAS. The results suggested a neural correlate of tinnitus. Ku et al. (2017) applied a similar design in human tinnitus sufferers purported to have tinnitus approximating 8 kHz. They tested for modulation failure of startle-elicited cortical responses with both 8 kHz and 600 Hz background noises at 20 dB SL, and also gap durations of 20, 50, and 100 ms. In agreement with Fournier and Hébert (2013), Ku et al. found that auditory cortical potentials were similarly not attenuated by preceding gaps, irrespective of high- or low-frequency background noises presented to the tinnitus individuals. Thus the modulation failure found in the tinnitus group was indiscriminate toward the tinnitus pitch. Further, gap impairments in this design were only found for gap durations of 20 ms (a duration requiring cortical involvement in gap detection, Weible et al., 2014), and curiously, modulation failure also occurred for controls in the low frequency condition.

In addition to reflexive and cortical responses evoked by startle elicitor stimuli, other human validation attempts testing more directly for behavioral gap detection impairments which have likewise produced equivocal results. Gilani et al. (2013) found evidence of gap detection impairments in tinnitus sufferers for white noise background sounds compared to controls. However Campolo et al. (2013) and Boyen et al. (2015) found no difference in gap detection between tinnitus sufferers and controls, even when background noises were highly similar to the tinnitus. In the latter study, participants were well matched in thresholds, age and gender, to the control group.

The absence of confirmatory and consistent results across these human studies casts doubt on the validity of gap detection to identify the presence of tinnitus, and threatens to subvert many key tinnitus findings in animal research. Before assuming this conclusion, it is informative to briefly summarize the neurological process thought to give rise to tinnitus, and from this view consider how tinnitus might mask silence such that it can be confirmed in an experimental design. Animal studies have found that damaging noise exposure and ototoxic drugs, which reduce auditory input from the periphery to the central auditory system, can produce hyperactivity (increased spontaneous, synchronous, or burst firing) in neurons of the auditory pathway that are tuned to the frequency regions where damage has occurred (e.g., Noreña and Eggermont, 2003; Noreña and Farley, 2013). The hyperactivity may be consequent of homeostatic mechanisms or changes in activity-dependent plasticity operating to restore the diminished input to normal activity levels or maintain a balance of excitation and inhibition (e.g., Schaette and Kempter, 2006; Shore et al., 2016), even when the damage is not measurable by the audiogram (Schaette and McAlpine, 2011). Despite this compensatory utility, an unwanted consequence of hyperactivity could be the development of the tinnitus perception. However at this time it is unclear which affected brain structures are necessary or sufficient to generate tinnitus, and which types of hyperactivity (e.g., increased spontaneous firing, increased rhythmic burst firing, or increased neural synchrony) are responsible for the tinnitus perception. Neural synchrony is a likely candidate, since it is thought to be necessary for the formation of an auditory object that emerges into conscious perception (Brette, 2012; Ilin et al., 2013; Shore et al., 2016).

If it is assumed that the neurons in the damaged frequency regions are occupied with generating tinnitus, then tinnitus should only be expected to mask silence at frequencies and loudness levels of background noise matched to or contained within this region. In the aforementioned studies, background noises were not precisely matched to the tinnitus frequency and bandwidth (although some, e.g., Campolo et al. (2013), tried to optimally cover the tinnitus frequency range). Frequency regions of the auditory system adjacent to but not affected by tinnitus should still be sensitive to the

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onsets and offsets of gaps in noise, rendering them detectable. This is particularly important for stimuli with sound levels far above the subjective loudness of the tinnitus, which have broader excitation patterns across frequency channels in the auditory system. Because of these shortcomings, we suggest the gap detection hypothesis remains untested.

Other factors relevant to tinnitus may likewise increase variability or introduce confounds which affect gap detection or interpretations of gap detection deficits. First, there is some evidence that directed attention may be impaired in tinnitus (see Roberts et al., 2013 and Tegg-Quinn et al., 2016, for reviews), suggesting that performance on tasks requiring tinnitus participants to make active decisions about stimulus choices (i.e., psychophysical gap detection) could be confounded by modifications to the auditory attention system in some individuals. Second, hearing loss, reported to be in ~85% of tinnitus sufferers (Henry et al., 2005), is known to impair gap detection thresholds (Fitzgibbons and Wightman, 1982). Hearing loss-related factors stress the importance of assessing gap detection within similar frequency regions of audiometric threshold shift when possible, which has not been accomplished in most human tests. Third, reflexive and cortical responses to high-level elicitor stimuli which are modified by gaps are indirect measures of gap detection; a direct measure (e.g., the presence of responses to gaps themselves) would help to clarify the mechanics of the gap masking principle.

A gap detection test that is passive, measures physiological responses directly to the gap, restrained to the tinnitus frequencies, and compared against frequencies also in the hearing loss region could therefore be advantageous. In this vein we propose to measure human neurophysiological correlates of gap detection, such as cortical auditory evoked potentials (CAEP) recorded in the electroencephalogram (EEG), in a stimulus design which does not require overt responses from the participant nor measures responses modulated by gaps (diverging from Ku et al., 2017, and Berger et al., 2018). The N1 potential is one such gap-evoked response with a scalp maximum that occurring ~60−160 ms after the gap onset, depending on stimulus features (Michalewski et al., 2005; Pratt et al., 2005). Neural generators of the gap-evoked N1 are thought to be distributed across cortex but localize to auditory cortex (Pratt et al., 2007), suggesting that the response reflects auditory cortical gap detection. Experimental data suggest that auditory cortex is required for perceptual gap detection for gap durations less than 50 ms while perception of longer gap durations can be achieved by non-cortical areas (Ison et al., 1991; Threlkeld et al. 2008, Weible et al., 2014). Thus inferences about gap durations less than this duration but still higher than gap detection threshold would be optimal for measuring cortical gap detection robustly. In the case of tinnitus, neural populations in the hearing-loss frequency regions at or below the level of auditory cortex are hypothesized to be bound in hyperactive ensembles. If these networks have consequently become less sensitive to outside input, or if their response properties have been altered by hyperactivity, then they may poorly code sound onset and offsets which would generate an N1 response. Thus we hypothesize that N1s evoked by gaps in low-level background sounds matched to the tinnitus sensation should be attenuated when compared to N1s evoked in sounds with frequencies that are not aligned with (e.g., above or below) the tinnitus frequency region. N1 responses evoked in the former context should furthermore be attenuated when compared to N1s evoked by identical conditions in controls. Although there is considerable research examining gap-evoked EEG responses, no previous research has examined gap-evoked CAEPs in tinnitus or in manner suggesting that an internal perception can mask an external event.

The majority of cases of tinnitus are described as a narrowband noise (Fowler, 1944; Reed, 1960; Meikle and Whitney, 1984), with center frequencies matched at and above 3 kHz (Vernon and Meikle, 2003) and experienced at sensation levels (SLs) below 30 dB (Meikle and Taylor-Walsh, 1984; Vernon and Fenwick, 1984; Basile et al., 2013; Hoare et al., 2014). Acoustic stimuli matched to these properties could be considered comparatively "weak" relative to properties of everyday sounds. At present it is unknown if auditory N1s evoked by gaps in tinnitus-like sounds are recordable in the EEG; that is, the signal-to-noise ratio of these responses is expected to be low and responses may not be reliably measureable within the typical level of background noise. Indeed, N1 responses are known to be comparatively smaller in amplitude when evoked by low intensities and with high frequencies (reviewed in Näätänen and Picton, 1987). To date and to our knowledge, there are no present data available showing gap-evoked responses below 45 dB nHL (Pratt et al., 2007) or at narrowband frequencies above 4 kHz (Atcherson et al., 2009). Thus there is no viable context of past literature in which the effect of tinnitus on gap-evoked CAEPs can be predicted, especially since behavioral gap detection thresholds below 30 dB SL are known to be level dependent, but stable above 30 dB SL (Plomp, 1964; Penner, 1977; Fitzgibbons, 1983). Thus before testing the design to tinnitus, it is desirable to determine how to record and detect these responses in the normal hearing system, as well as characterize their properties as a function of stimulus parameters relevant to tinnitus.

In the present study we presented young adults with normal-hearing and no tinnitus two types of background sounds representative of common tinnitus cases. Twenty-millisecond gaps were embedded in the sounds to evoke N1 responses. Here we are the first to report that these events do evoke measureable CAEPs, and describe a method to detect gap-CAEP responses on an individual basis. A concluding discussion will consider the implications of this design on detecting tinnitus.

2. Methods

2.1. Participants

Twelve participants (8 females and 4 males; mean age = 24.5 years, SD = 4.01; all right handed) without tinnitus volunteered through a posting published on an online university message board. Participants provided informed and written consent, and were compensated 15.00 CAD for completing the study. The research ethics board at the University of Montreal approved all procedures. Participants were required to have normal hearing thresholds (<20 dB HL) to a maximum frequency of 8 kHz. All participants met this criterion after we obtained the pulsed pure-tone audiogram in 5 dB steps measured on an Interacoustics AC40 audiometer through calibrated Eartone 3A insert phones.

2.2. Stimuli and materials

Our goal was to design test stimuli with features representative of tinnitus, such as a sound of high frequency (commonly > 4 kHz) and low overall sensation level (<30 dB above auditory threshold). Although some individuals report their tinnitus to be tonal in nature, most cases are described as a narrowband noise with some center frequency and bandwidth (Fowler, 1944; Reed, 1960). In accordance with these properties, all stimuli were narrowband Gaussian noise (NBN) bursts with a one-third octave bandwidth centered at either 5 kHz or 10 kHz. An archetypical stimulus is shown in Fig. 2a. Each stimulus was an NBN burst lasting 5 s in duration. In each NBN burst there were six silent temporal gaps inserted into random temporal positions. We opted to use 20 ms gaps (consistent with durations used in Longenecker and Galazyuk,

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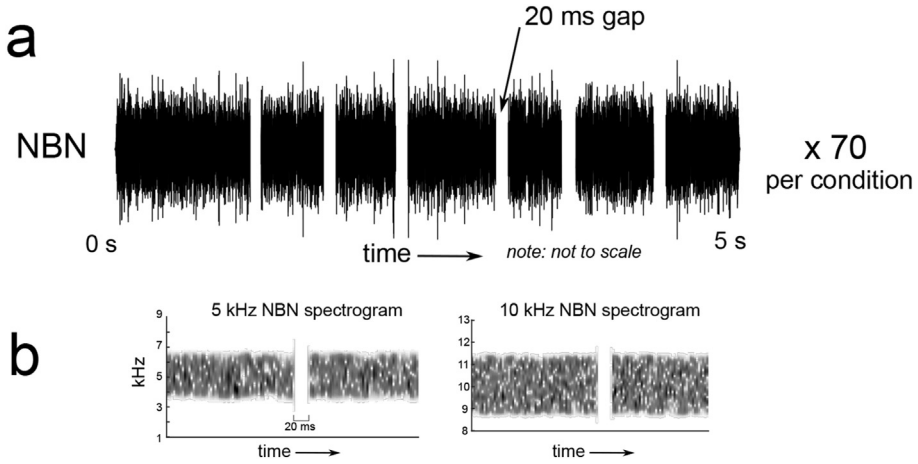

Fig. 2. (a) Example of experimental stimulus. A narrowband noise of 5 s duration contained 6 randomly-positioned silent 20 ms gaps designed to evoke CAEPs. Each condition (5 and 10 kHz center frequencies; 5, 15, 30 dB SL) was presented 70 times to both ears. (b) Spectrograms of the 20 ms gap for 5 kHz and 10 kHz NBN conditions. Shading represents arbitrary units.

2011 and Longenecker et al., 2014) instead of 50 ms gaps used by most GPIAS animal studies (see Galazyuk and Hébert, 2015; Table 1), because 20 ms gaps are comparatively "weaker" sensory events but likely elicit inhibition similar to the one evoked by 50 ms gaps in the GPIAS in humans (Fournier and Hébert, 2016). Gaps commenced no earlier than 600 ms after burst onset, and were randomly and uniformly spaced between 500 and 700 ms from offset to onset. Silent gaps, onsets and offsets, were ramped by cosine functions over 2 ms. Fig. 2b depicts the spectrogram of a gap for 5 kHz and 10 kHz NBN.

Stimuli were generated in MATLAB (The Mathworks, Natick, MA, USA) and reproduced digitally through a Tucker Davis Technologies (TDT, Alachua, FL, USA) RX6 processor, and stimulus levels were controlled with a TDT PA5 programmable attenuator. Stimuli were presented binaurally to each participant using custom electrically-shielded Eartone 3A insert phones as they sat comfortably in an electrically-shielded and sound-attenuated booth.

NBN stimuli were presented in conditions of either 5, 15, or 30 dB sensation level (SL, the level in dB above the threshold of detection) Before the main experiment commenced, thresholds for each NBN stimulus were established separately for each NBN carrier frequency using a modified von Békésy procedure described in the following steps. First, a constant 5 kHz or 10 kHz NBN was presented at a subthreshold level to the participant. Participants were instructed to increase the level of the sound using a computer-linked keypad so that the stimulus was barely audible. When the participant felt this level was met, the level value was logged. Then, we increased this level by 20 dB from the first value so that the sound was audible, and participants were required to decrease the level to the point where it was barely inaudible. These two steps were repeated two additional times. The median value of the six trials was taken as the threshold. Because of a misunderstanding of instructions, one participant set the level of the 10 kHz stimulus to −36.4 dB SPL. After the experiment, the participant verbally confirmed they could not hear the stimulus. 10 kHz data for this participant were omitted in the analysis below. Across all participants, threshold values for the 5 kHz NBN correlated significantly with the audiogram averaged between ears and between the values of 4 and 6 kHz ($r = 0.65$, $p = 0.021$; Pearson's r). Similarly, the 10 kHz NBN level for each participant correlated with their 8 kHz audiometric threshold (we did not measure above this level) averaged across both ears ($r = 0.79$, $p = 0.004$). These correlations suggested that the self-adjusted threshold procedure were similar to thresholds evaluated by standard audiometry.

2.3. Procedure

During the main procedure and EEG recording, participants watched a silent, subtitled film of their choice and were instructed to ignore stimuli. The six experimental conditions (5 or 10 kHz NBN by 5, 15 or 30 dB SL) were presented as trial blocks in a randomly determined order. Each block contained 70 trials, resulting in 420 gap events per condition. Each 5 s trial was separated by an IOI of 1500 ms with a 500 ms Gaussian jitter. Recording time was approximately 55 min.

2.4. EEG recording and processing

The EEG of each participant was sampled at 2048 Hz (recording bandwidth of direct current (DC) to 417 Hz) by a BioSemi Active Two (Cortech Solutions, Wilmington, NC, USA) amplifier referenced to the vertex electrode and stored as a continuous data file. Using custom analysis routines written in MATLAB, offline EEG data were first downsampled to 256 Hz with an anti-aliasing filter. The EEG was then subjected to a two-stage artifact correction and rejection procedure. First, a wavelet-enhanced independent components analysis (wICA; Castellanos and Makarov, 2006) was used to identify and remove linear combinations of spatially and spectrally distinct potential patterns consistent with the high-amplitude, low frequency signature of eyeblinks and other ocular and myographic artifacts, while not affecting the low-amplitude high frequency components associated with neural activity. The wICA method is an automatic procedure, requiring no visual inspection of ICA artifacts before they are corrected (Castellanos and Makarov, 2006) and was applied to continuous 30 s epochs of data. Thereafter, data were re-referenced to the common average. EEG data were segmented into 500 ms trials, commencing 100 ms before gap onset to 380 ms after gap offset. A second artifact rejection procedure removed trials with voltages that exceeded +/−100 μV in any channel, which were considered transient artifacts not corrected using the wICA procedure. All participants retained greater than 90% of trials.

Our goal was to determine if silent temporal gaps evoked statistically-detectable N1 responses in each condition. To maximize sensitivity of the an analysis pipeline to weak evoked

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potentials, we took the approach of 1) measuring N1 responses as global field power (GFP) and 2) determining if bootstrapped distributions of N1 GFP for each person and each condition were larger than the GFP of the 100 ms baseline prior to gap onset. GFP is the spatial standard deviation of the entire EEG montage at a given time point (Lehmann and Skrandies, 1980). When computed for all time points and examined as a time series, the GFP represents the change in variance in the EEG field potentials over a chosen time interval. The advantages of a GFP analysis in the current study are threefold. First, since CAEPs are expected to be small, a measure which incorporates information from all channels, without biasing analysis toward one or a group of channels, is desirable and may increase the likelihood of detecting a CAEP. Second, scalp topographies are expected to differ when testing tinnitus sufferers who have a large range of tinnitus frequencies and loudness levels, and a measure that is not prescribed to select channels can accommodate these differences. Third, a GFP analysis avoids multiple testing corrections that need to be made between channels in a montage when comparing across conditions or when detecting the presence of an N1. However one potential drawback is that noise in individual channels which artificially increases the channel amplitude can likewise inflate the GFP (Files et al., 2016), at worst resulting in a falsely-detected N1. To circumvent this problem, we examined the average root-mean squared (RMS) amplitude of all trials for each channel prior to GFP analysis for each condition, and removed channels that exceeded 2 standard deviations from the mean of all channel RMS values. This occurred in only 23 out of 72 participant by condition instances (between one and six channels removed).

The presence of an N1 measured as GFP was assessed using a bootstrap procedure shown in Fig. 3. Distributions of GFP values for N1 and pre-gap baseline interval were built using a bootstrap resampling procedure which took 250 subsamples of 75% of trials (sampling with replacement). For each subsample, trials were averaged and then filtered from 1 to 20 Hz using a Butterworth 4th order IIR filter. Data were corrected to the −100 to 0 ms pre-gap baseline (Fig. 3a), and the GFP was computed across all time points. To make a reasonable comparison of GFP in the baseline to the N1, we calculated the area under the GFP curve (herein, GFP AUC) for the 100 ms baseline and the 60–160 ms interval post-gap onset where N1 responses are expected to occur (Fig. 3b). We took 250 samples of the N1 and baseline GFP AUC (an example for one participant shown in Fig. 3c). Finally, the 99% confidence interval (CI) was computed for each interval, and an N1 was deemed not statistically present if the CIs of the N1 and baseline estimates overlapped or if the N1 CI was smaller than the baseline CI. A similar approach was used by Ponton et al. (1997), to detect mismatch negativity potentials.

2.5. Statistics

All statistics were computed in MATLAB 2016a using the Statistics and Machine Learning Toolbox. Unless otherwise specified, the alpha criterion was set at 0.05 for all inferential tests and were two-tailed.

3. Results

3.1. Descriptive properties of gap-evoked N1 responses

For illustrative purposes, Fig. 4 shows CAEP waveforms and scalp topographies for each stimulus condition averaged across all participants. Waveforms commence −100 ms before the onset of the gap and terminate after 300 ms. Because gap-evoked N1 responses typically reach a maximum amplitude at frontrocentral scalp sensors, the corresponding Fz channel is plotted. Waveforms for all conditions show a small negative-going peak following gap onset slightly before or after 100 ms, consistent with characteristics of the N1 response. N1 amplitudes were expectedly small, not exceeding 0.3 μV in the 5 kHz condition and 0.12 μV in the 10 kHz condition for this channel, and tended to be smaller for lower SLs. The latency of the peak N1 amplitude for 10 kHz NBN conditions appears to be shorter at this channel compared to the 5 kHz condition, and no clear relationship is descriptively present between SL and N1 latency.

Scalp topographies averaged across participants are plotted below the time series in Fig. 4, which are voltage maps of each channel at the time point where the N1 reached its maximum amplitude. Although there is a clear negativity at frontrocentral sites (darker shading) consistent with the topography of the auditory N1, the voltage concentration is less defined in acoustically "weaker" conditions where the SL is low and more so for 10 kHz NBN. These observations underscore the utility of the GFP metric to detect scalp-wide shifts related to the gap perturbation as opposed to analysis confined to one or a few channels.

3.2. Detection of gap-evoked N1 responses

Table 1 presents the bootstrapped 99% confidence intervals (CIs) of GFP AUC estimates of the −100 to 0 ms baseline interval and the 60–160 ms N1 interval for each stimulus condition and participant. Baseline CIs ranged from 2.3 to 9.2, while N1 CIs ranged from 3.2 to 14.7. CIs for individuals in which there was a greater value and no overlap between the baseline and N1 indicated the presence of an N1. Under this criterion, an N1 was present in all conditions for 11 out of 12 participants. In participant S04, an N1 was not detected for the 5 kHz, 5 dB SL NBN and the 10 kHz, 15 dB SL conditions (Table 1,

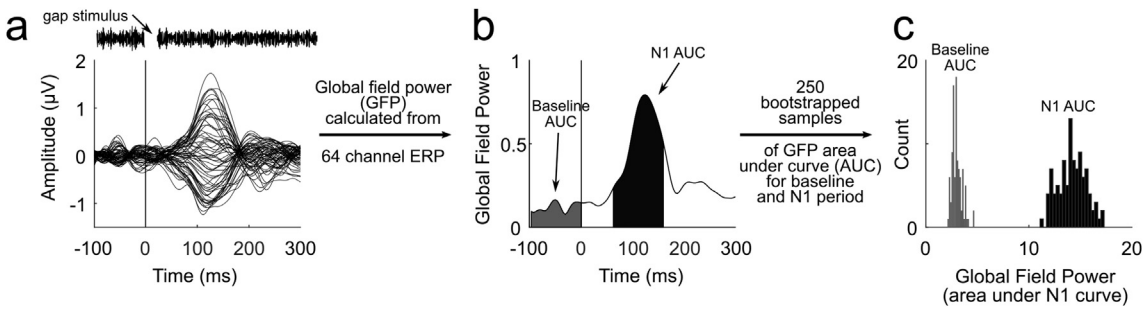

Fig. 3. Analysis pipeline for one representative participant. a) The silent gap evoked a CAEP ~100 ms after gap onset, shown here as a time-domain waveform. Each trace represents one of 64 channels. The time point 0 represents the onset of the gap. b) Global field power (GFP) was calculated from the voltage time series of all channels, and the area under the curve (AUC) of the N1 period and pre-gap baseline were computed. c) Distributions of the GFP AUC for the N1 and baseline period were obtained by bootstrapping subsamples of single trials. It was expected that the N1 distribution would not largely overlap with the baseline distribution if the N1 was present.

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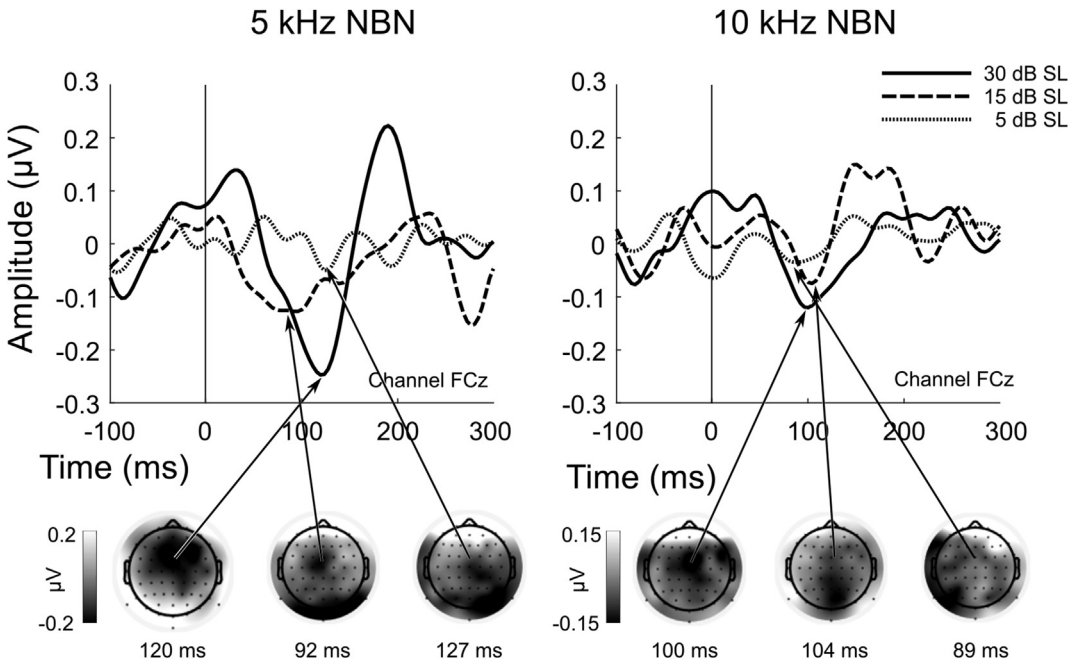

Fig. 4. The time-domain waveforms of the CAEP following a gap (onset of gap is 0 ms) are shown separately for 5 and 10 kHz NBN stimuli. The solid line represents the 30 dB SL condition, for 15 dB SL the dashed line, and for 5 dB SL the dotted line. N1 morphologies appear distributed around 100 ms after the gap onset in each condition. Scalp topographies representing the voltage map at the peak of each N1 waveform (the FCz site indicated by arrows) are shown below each time-domain trace. Latencies of the waveforms are shown below the topographies.

Table 1
N1 GFP AUC 99% confidence intervals (CIs) for baseline and N1 periods of each participant and condition. Bold, asterisked values represent instances where CIs overlapped, indicating that the N1 response was not significantly verifiable.

Participant	30 dB SL		15 dB SL		5 dB SL	
	Baseline	N1	Baseline	N1	Baseline	N1
			5 kHz conditions			
1	2.9–3.1	14.0–14.7	3.1–3.3	11.8–12.51	2.5–2.6	6.3–6.8
2	8.5–9.1	9.3–9.8	6.7–7.1	9.5–10.0	6.2–6.6	7.9–8.4
3	2.3–2.5	4.8–5.0	2.8–2.9	4.5–4.7	2.9–3.1	4.1–4.3
4	4.1–4.3	6.8–7.1	3.2–3.5	6.9–7.2	**4.2–4.5***	**4.3–4.5***
5	3.6–3.7	8.9–9.3	3.6–3.9	7.3–7.8	3.3–3.5	6.8–7.2
6	4.3–4.6	7.7–8.1	2.5–2.6	5.1–5.4	3.7–3.9	4.8–5.1
7	3.5–3.7	6.4–6.9	2.9–3.1	8.3–9.1	2.8–2.9	4.8–5.1
8	4.6–5.0	6.4–7.1	5.1–5.6	6.3–6.9	4.3–4.8	11.2–12.5
9	3.8–4.0	10.3–11.3	4.6–5.0	7.9–8.9	4.2–4.5	10.5–11.9
10	5.3–5.6	10.7–11.5	5.3–5.5	9.8–11.2	8.6–9.2	9.4–10.5
11	3.5–3.7	5.4–5.7	3.4–3.6	6.3–6.7	3.1–3.3	5.6–5.9
12	3.8–4.1	7.1–7.6	3.0–3.1	5.9–6.1	3.2–3.3	5.6–6.0
			10 kHz conditions			
1	2.6–2.8	9.4–10.2	4.0–4.3	5.9–6.4	2.3–2.5	6.2–7.0
2	6.5–7.1	9.9–10.4	7.2–7.6	9.7–10.1	5.3–5.7	10.7–11.5
3	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a*	*n.a.*
4	3.3–3.5	6.9–7.3	**5.1–5.4***	**4.7–5.0***	4.3–4.5	8.4–8.9
5	4.1–4.3	8.1–8.5	3.8–4.0	10.2–10.9	3.0–3.1	5.2–5.5
6	2.7–2.8	6.8–7.1	4.2–4.5	9.2–9.8	3.1–3.3	6.0–6.4
7	3.7–3.8	7.7–7.9	3.1–3.2	5.7–6.1	3.8–4.1	5.7–6.2
8	5.0–5.1	9.5–10.6	4.5–4.8	8.6–9.7	4.1–4.5	8.3–9.0
9	5.5–6.1	10.1–11.1	4.8–5.3	8.8–9.7	5.0–5.4	7.8–8.5
10	5.05–5.4	9.7–10.4	7.0–7.5	9.1–9.9	4.7–4.9	8.6–9.1
11	3.8–4.1	5.6–6.1	4.3–4.6	6.1–6.4	4.2–4.3	6.2–6.6
12	2.8–2.9	5.2–5.4	3.0–3.3	5.1–5.4	2.8–2.9	5.7–6.0

boldfaced values). As mentioned, the 10 kHz conditions for participant S03 were erroneously recorded and are excluded from the table.

3.3. Differences between conditions

To test if acoustic properties altered N1 GFP AUC, we evaluated differences between the conditions evoking N1s using a repeated-

measures analysis of variance (ANOVA) with within-subjects factors of frequency (5 kHz and 10 kHz NBN) and stimulus sensation level (5, 15, and 30 dB SL). Boxplots of N1 GFP AUC for each condition are shown in Fig. 5. No main effect of frequency was found ($F < 1$), but a main effect of SL (F (2,18) = 3.040, $p = 0.073$) approached significance. This effect matches the descriptive observation in Fig. 4 that for each NBN frequency, the N1 magnitude tended to reduce with lower SLs. No interaction was found between SL and NBN frequency conditions ($F < 1$). These tests were run with the absence of participants S03 and S04 for whom data were not collected or N1 responses were not present, respectively. Results did not change when participant S04 was included in the analysis.

3.4. Inter-individual differences

It is important to consider inter-individual factors that may explain N1 GFP AUC magnitude that may lead to difficulties in comparing tinnitus to control groups. We computed correlation matrices (Pearson's r) for all conditions N1 GFP AUC to determine if some participants had consistently overall higher values. However no correlations were found between any individual N1 magnitude (all $ps > 0.1$, Bonferroni-Holm corrected). The average of all SL conditions for N1 GFP AUC at 5 kHz was only weakly correlated to N1 GFP AUC at 10 kHz averaged across SLs, but did not reach significance ($p = 0.09$). The absence of strongly correlated inter-individual differences suggests that idiosyncratic response properties, which could add unwanted variability, may have minimal impact when comparing tinnitus individuals to matched controls.

4. Discussion

4.1. Summary

The aim of this report was to provide a proof of principle that gaps in acoustic stimuli evoke detectable auditory cortical potentials in non-tinnitus listeners when stimuli were of low level and high frequency, which are features characteristic of chronic tinnitus. Because of these stimulus properties, particularly low sensation level, auditory responses were expected to be small and difficult to measure. We found that for two narrowband noises (5 and 10 kHz center frequencies; commonly heard by those with tinnitus) with three relatively low sensation levels (5, 15, and 30 dB SL), auditory N1 cortical potentials expressed as global field power (GFP) were identified in all but one individual, and in that individual only two conditions were not statistically present. Further, we did not find that N1 GFP was significantly different between 5 kHz and 10 kHz conditions, and tended not to change with decreasing sensation level. These findings are the first to suggest that cortical potentials evoked by sounds with weak acoustic properties similar to many cases of tinnitus are viable to record in the multichannel EEG, and can be used to test the hypothesis that tinnitus can mask silent temporal gaps within these sounds.

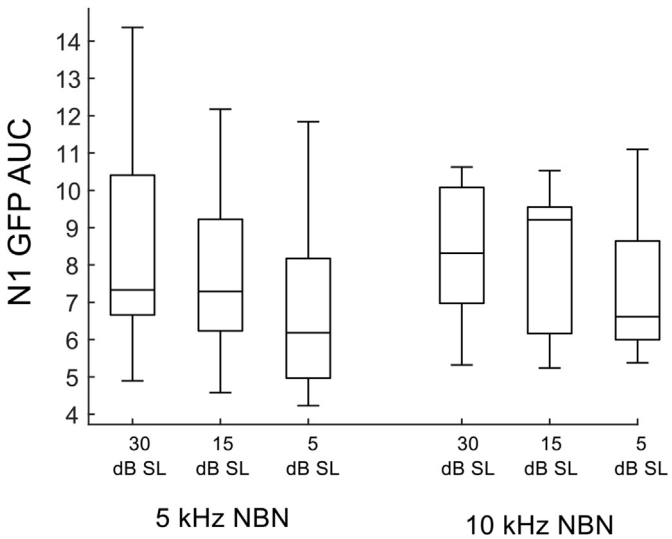

Fig. 5. Boxplots of N1 GFP AUC (ordinate) for each stimulus condition (abscissa). The top and bottoms of the boxes respectively represent the 75th and 25th percentiles of the N1 GFP AUC, and the middle line represents the median. Whiskers extend to ~99.3% coverage (+/− 2.7 SD).

4.2. Stimulus-related differences and individual variability in gap-evoked N1 GFP

The range of possible tinnitus frequencies across a given sample of tinnitus sufferers, and frequencies that we can test within an individual, is expected to be large. Because of this variability it was important to know how gap-evoked CAEPs changed as a function of the frequency of the background sound in which the gap was embedded. N1 amplitude is known to be smaller when evoked by higher frequency stimuli (Antinoro and Skinner, 1968; Picton et al., 1978). By assessing N1s as GFP AUC, we found no significant differences between the magnitudes of the 5 kHz and 10 kHz responses. These results however do not suggest that N1s measured by single-channel amplitudes (and not by GFP AUC) or by other more conventional signal processing approaches are not sensitive to changes in stimulus frequency. Grand averages of channel FCz in Fig. 4 suggested that 10 kHz responses were descriptively smaller than 5 kHz responses by at most ~0.1 μV. Further, sensation level of tinnitus across tinnitus suffers, like frequency, is expected to vary. It is well-documented that stimulus levels are associated with smaller magnitudes of the N1 potential within a more conventional CAEP analysis (e.g., Beagley and Knight, 1967; Picton et al., 1977; Rapin et al., 1966). Our results tend to suggest that N1 GFP AUC was smaller with lower sensation levels for both 5 kHz and 10 kHz stimuli, consistent with general relationships between evoked potential amplitude and stimulus level, but this trend did not reach statistical significance. We further found that there were no significant correlations between participants' magnitude of N1 GFP AUC across conditions or when examined between stimulus frequencies as an average of all sensation levels. This suggests that individuals tested here may not have idiosyncratically large or small responses expressed as N1 GFP AUC.

4.3. Prior studies of gap-evoked CAEPs studies

Our stimulus design was intended to match common acoustic features of tinnitus, and the stimulation method was directed toward validating the gap-masking principle as well as translation into a clinical tool. However our data were also the first, to our awareness, to show recordable gap-evoked CAEPs responses within weak acoustic contexts. As noted, gap-evoked CAEPs have been investigated in many studies (e.g., Pratt et al., 2005, 2007; Michalewski et al., 2005; Atcherson et al., 2009; Harris et al., 2012), but at levels significantly above those used here. Atcherson et al. (2009) used a similar design to the current method, and reported gap-evoked responses for several gap durations in 1/6 octave NBN bandwidths at 70 dB SPL, including 4 kHz center frequency NBN and 20 ms gaps. N1 responses in this condition were present at ~100 ms post gap onset in all individuals. N1 amplitude was on average −3.7 μV (SD = 1.4), which was ~12 dB larger than the average response for the 30 dB SL, 5 kHz condition in the present

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data, and 18 dB larger than the response for the 5 dB SL, 10 kHz average response. Morphology of responses was similar between the two studies, showing observable N1 responses but absent or severely mitigated P2 responses at 20 ms gap duration, although the 50 ms gap condition of Atcherson et al. (2009) as well as other studies using gaps in wideband noise, report CAEPs with clear P2s (Pratt et al., 2005, 2007). Topographical similarities cannot be examined since Atcherson et al. (2009) recorded responses from a 3-channel montage, but topographies provided by Harris et al. (2012) show similar N1 voltage maps reaching a maximum at frontocentral sites as seen for responses in Fig. 4. In sum, CAEPs reported here conform to characteristics reported previously, albeit with drastically smaller amplitudes likely due to the overall low sensation level.

4.4. Caveats

There are two caveats regarding our planned stimuli. First, noise stimuli centered on an individual's tinnitus are sometimes known to induce residual inhibition (RI), which is a decrease in the loudness of tinnitus following noise stimulation lasting ~30 s (Roberts et al., 2008) and can modulate CAEPs in tinnitus sufferers (Roberts et al., 2015). However stimuli of low sensation level lasting less than 10 s do not typically induce RI (Tyler et al., 1984) and thus little to no RI is expected when this design is adapted to tinnitus sufferers. Nonetheless, we intend to introduce frequent long pauses in between trial presentations with tinnitus sufferers to limit the build-up of RI. Second, background noise stimuli containing abrupt gaps can introduce spectral “splatter” at the gap offset and onset. The 2 ms cosine ramp used to gate silence in the current stimuli reduce the splatter, although a small degree of spaltter is observable in Fig. 2b. We intend on adjusting ramp shape depending on stimulus bandwidth in tinnitus sufferers such that spectral splatter does not exceed the targeted tinnitus frequency range.

Tinnitus disproportionately affects adults older than 40 years of age (Shargorodsky et al., 2010). The present data demonstrated gap-evoked CAEPs in younger adults, only who are estimated to comprise ~20% of tinnitus suffers. It is possible older adults may not have as readily detectable CAEPs, and trends of sensation level and frequency effects reported herein may not generalize to older adults irrespective of tinnitus presence. Behavioral evidence of gap detection in older adults however suggests that no gap detection deficits are present at gap durations greater than 9 ms (Harris et al., 2012) or with inter-gap intervals starting well below 500 ms, the minimum used in this study (Schneider and Hamstra, 1999). The consequence of aging on gap-evoked CAEPs using gap durations and sensation levels used in this study however are not clear.

5. Conclusions

Measurement of gap-evoked CAEPs by tinnitus-like sounds is possible in human listeners, suggesting this approach is can plausibly be used to determine if such responses are masked by tinnitus. If this masking effect is observed, the design described herein could serve as a basis for the first objective tinnitus diagnostic tool in humans, capable of being used by clinicians already trained in electrophysiology. The design would furthermore provide a valuable research tool that helps to correspond tinnitus-affected hearing regions with other auditory and cognitive factors implicated in the neuroscience of tinnitus.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heares.2018.04.005.

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