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## Research paper

## Gap detection deficits in humans with tinnitus as assessed with the acoustic startle paradigm: Does tinnitus fill in the gap?

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## ABSTRACT

The measurement of tinnitus in humans relies on subjective measures such as self-report, visual analog scales and questionnaires. Gap detection impairments have been tested in animals in an attempt to objectify the presence of tinnitus. The main purpose of this study was to investigate the gap startle paradigm in human participants with high-frequency tinnitus. Fifteen adults with bilateral high-frequency tinnitus but normal hearing at standard frequencies and seventeen matched controls without tinnitus were tested. The psychoacoustic characteristics of the tinnitus spectrum (pitch and loudness) were assessed using novel participant-directed custom-made methods. The startle task consisted of startle-alone, prepulse inhibition and gap-in-noise condition at low- and high-background noise frequencies. All measurements were retested after several months. Data indicate normal prepulse inhibition but higher reactivity to the startle sounds in the tinnitus group in comparison with controls. Most importantly, the tinnitus group displayed a consistent deficit in gap processing at both low- and high-background noise frequencies. All effects were identified consistently and were reproducible at retest. We propose that the higher reactivity to startle might reflect hyperacusis and that the gap deficit might be an index of abnormal cortical auditory processing in tinnitus.

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## 1. Introduction

The acoustic startle reflex (ASR) is a simple, primitive reflex produced by a sudden and unexpected loud sound, thought to play a critical role in protecting against head blows (Yeomans et al., 2002). It has been abundantly documented in rodents, primates, and humans. Its circuit includes the cochlea, the auditory portion of the 8th cranial nerve, the ventral cochlear nucleus, the lateral lemniscus nuclei, the nucleus reticularis pontis caudalis (PnC), which activates the spinal interneurons and motor neurons to elicit the startle reaction (Davis et al., 1982; Lee et al., 1996). Only three synapses are involved, and latency is short, around 6–8 ms in rats and 60 ms in human (For review see Koch, 1998).

*Abbreviations:*  $\eta^2$ , Eta square; dB, decibel; HL, hearing level; Hz, Hertz; ISI, Inter-Stimulus Interval; ITI, Inter-trial-interval; min, minute; ms, millisecond; mV, microvolts; PPI, prepulse inhibition; s, second; SEM, standard error of the mean; SL, sensation level; SPL, sound pressure level.

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ASR can be inhibited by inserting a soft, non-startling sound (*a prepulse*) 30–500 ms before the startling sound (Swerdlow and Geyer, 2000), thus providing a natural modulatory mechanism of ASR function. In the laboratory, the *prepulse inhibition* (PPI) paradigm provides an operational measure of pre-attentive *sensori-motor gating*. The basic PPI circuitry has been localized to the brainstem, as PPI can be observed in animals with surgically (Bowen et al., 2003) or chemically suppressed cortical function (Ison et al., 1991; Threlkeld et al., 2008) as well as in humans during sleep (Silverstein et al., 1980). However, PPI itself is subject to modulation via descending projections from central brain structures such as the auditory cortex and limbic system (Li et al., 2009). Accordingly, deficient PPI responses are observed in cases of failure to filter cognitive, sensory, emotional, or motor information, as may occur in schizophrenia (Braff et al., 1978), Huntingdon's disease (Swerdlow et al., 1995), post-traumatic stress disorder (Grillon et al., 1996), and primary insomnia (Frau et al., 2008; Hairston et al., 2010).

The *gap paradigm*, a modified PPI protocol, was recently proposed to model tinnitus in animals, replacing previous time-consuming or painful conditioning paradigms (e.g., electric shocks, food deprivation). In the gap paradigm, a continuous

background noise is presented, into which a silent gap is introduced, followed by a loud startling noise. In normal rats, the gap decreases the startle reflex, similar to a prepulse sound (Ison, 1982; Turner et al., 2006). In contrast, in rats with salicylate- (Turner and Parrish, 2008) or noise- (Turner et al., 2006) induced tinnitus, there is little or no inhibition of the startle reflex, presumably because the gap is partially or totally filled by the tinnitus sound. Accordingly, the lack of inhibition is specific to background noise with a putative frequency close to the tinnitus (i.e., high-frequency). The gap paradigm has therefore been proposed to provide an objective measure of tinnitus (Turner et al., 2006) and has been used in both rats and mice (Turner et al., 2006; Yang et al., 2007; Turner and Parrish, 2008; Wang et al., 2009; Holt et al., 2010; Kraus et al., 2010; Ralli et al., 2010; Zhang et al., 2010; Engineer et al., 2011; Longenecker and Galazyuk, 2011; Mao et al., 2011; Middleton et al., 2011).

Since in humans, evaluation of tinnitus relies heavily on subjective measures such as self-reports, questionnaires and visual analog rating scales, the development of an objective measure is highly desirable. The main purpose of this study was to investigate the gap paradigm in humans with high-frequency tinnitus. Importantly, only participants within normal-hearing threshold limits were included to avoid problems related to decreased overall sensitivity (audibility of background noise, prepulse and startling sounds) or hearing loss at tinnitus frequency (Norena et al., 2002; Roberts et al., 2008). Although high- and low-frequency background noises were not matched to the tinnitus frequency, the high-frequency of the tinnitus was verified with a new method of tinnitus pitch- and loudness-matching.

## 2. Methods

### 2.1. Participants

Fifteen tinnitus participants (ten men) and seventeen controls without tinnitus (eight men) were recruited through posted ads and word of mouth. All tinnitus participants had had bilateral, continuous, high-pitch tinnitus for at least 6 months (mean duration = 9.3 years, range = .5–37) and reported a ringing tinnitus. Four participants also reported some other sounds. Sociodemographic characteristics of both groups are presented in Table 1(A). It is worth noting that these young participants were similar to older tinnitus participants included in several previous studies from our lab (Hebert et al., 2004; Hebert and Carrier, 2007; Hebert and Lupien, 2007, 2009), as reflected by their higher hyperacusis (Khalifa et al., 2002) and BDI-II scores (Beck et al., 1996). Participants were recruited on the basis of hearing thresholds of

less than 35 dB HL at any frequency between 250 Hz and 4 kHz in either ear. An otoscopic examination was performed to rule out wax compaction or middle-ear infection. Participants with uncontrolled medical conditions (e.g., hypertension, diabetes) and heavy smokers (>10 cigarettes/day) were also excluded (Kumari et al., 1996). Participants who were non-responsive to the acoustic startle were also excluded from the study ( $N = 3$ ) see below. For the retest part of the study, ten of the tinnitus participants (seven men) and nine controls without tinnitus (four men) were tested again after an average delay of 20 weeks (range: 5–47). Their socio-demographic characteristics are presented in Table 1(B). The study was approved by the local ethics committee of Université de Montréal and was conducted with the understanding and written consent of each participant.

### 2.2. Apparatus and procedure

#### 2.2.1. Hearing tests

Hearing detection thresholds were assessed monaurally from 250 Hz to 16 kHz in both ears in  $\frac{1}{2}$  octave steps by a clinical audiologist following the standard modified Hughson–Westlake procedure (Harrell, 2002) with an AC-40 Interacoustic clinical audiometer. Testing started with left or right ears in counter-balanced orders between participants. TDH-39p headphones were used for frequencies of 250 Hz–8 kHz and Sennheiser HDA-200 headphones for very high frequencies (>8 kHz). The audiometric equipment was calibrated in a soundproof booth (revised version of ANSI S3.6-1993 standards).

#### 2.2.2. Tinnitus-matching

For frequency – and loudness – tinnitus-matching, we used a participant-directed custom-made program running under Max/MSP software (Cycling 74, San Francisco, USA) controlling a touchscreen (Élo TouchSystems, Menlo Park, CA). Stimuli were 1-s pure tones ranging from 250 Hz to 16 kHz by  $\frac{1}{2}$  octave steps (slightly different from the audiometry) generated by a Fireface sound card (RME, Haimhausen, Germany). Participants pressed a green button on the screen to initiate the presentation of a pure tone. They first rated the likeness of the tone to their tinnitus on a Likert-type scale (where 0 = does not at all match my tinnitus and 10 = matches my tinnitus perfectly). During the same trial, they matched the loudness of the tone, that is, the sound level at which that specific frequency contributed to their tinnitus, by moving a visual slider that smoothly increased and decreased the sound level in 1 dB steps, from 0 to 100 dB SPL. The program allowed participants to control the number of times they could listen to each stimulus. Once done, participants pressed “next” to activate the following trial. Pure tones were presented three times each in a pseudo-random order in which no two identical frequencies were presented in a row. Stimuli were presented binaurally using closed dynamic headphones «DT 770 Pro/250» (Beyerdynamic, Heilbronn, Germany).

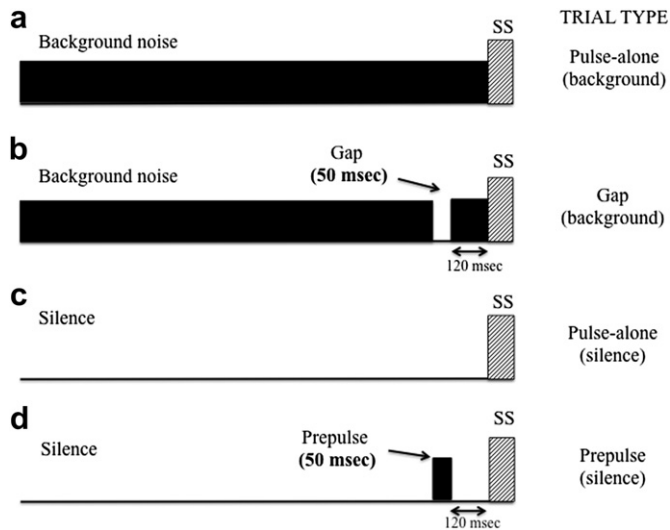
Before starting the matching procedure, the concept of octave confusion was carefully explained to the participants with the use of an audiometer (Moore et al., 2010). After verification that the participants understood the concept of octave confusion, they completed the tinnitus-matching task. Two trials served as practice trials.

#### 2.2.3. Startle stimuli and task

A schematic view of Startle, Gap, and Prepulse trials is shown in Fig. 1. Startle noises were 50 ms broadband noise bursts (20 Hz–20 kHz) set at 105 dB(A) SPL with near instantaneous rise–fall time (<1 ms). Startle trials consisted of startle noises preceded by either a low- or high-frequency continuous background noise set at 65 dB(A) SPL. The low-frequency background noise was

**Table 1**  
Sociodemographic characteristics (standard deviation) of Tinnitus and Control participants in the (A) test and (B) retest session.

(A)	Tinnitus ( $N = 15$ )	Controls ( $N = 17$ )	$P$ -value
Sex (Male/Female)	10/5	8/9	n.s.
Age	28.5 (6.0)	23 (2.9)	$p < .005$
Education in years	17.5 (1.9)	17.4 (2.5)	n.s.
BDI-II	9.4 (8.4)	3.7 (4.7)	$p < .05$
Hyperacusis questionnaire	23.5 (9.9)	10.9 (6.5)	$p < .005$
(B)	Tinnitus ( $N = 10$ )	Controls ( $N = 9$ )	$P$ -value
Sex (Male/Female)	7/3	4/5	n.s.
Age	29.3 (6.2)	24.3 (3.5)	$p = .05$
Education in years	17.4 (1.9)	17.9 (3.0)	n.s.
BDI-II	9.2 (8.8)	2.2 (2.2)	$p < .05$
Hyperacusis questionnaire	25 (9.9)	9.22 (5.2)	$p < .005$
Delay in weeks between test and retest sessions	23(13)	16 (14)	n.s.



**Fig. 1.** A schematic view of Startle (a), Gap (b), Startle in silence (c) and Prepulse (d) Trials (SS = startle Sound). Startle trials consisted of a continuous background noise and a Startle sound. Gap trials consisted of the same condition but included a 50 ms silent gap presented 120 ms before the Startle sound. Prepulse trials consisted of a silent background with a 50 ms prepulse presented 120 ms before the Startle sound. Startle in silence consisted of a startle in silence background.

centered at 500 Hz (200–1200 Hz) and high-frequency background noise at 4 kHz (3.5–4.5 kHz). Gap trials were similar to startle trials, except that a 50 ms silent gap was inserted between two segments of background noise starting 170 ms (Inter-Stimulus Interval = 120 ms) before the startle noise. Prepulse trials were either low- or high-frequency 50 ms noise bursts set at 65 dB(A) SPL presented in quiet, followed by a 120 ms (ISI = 120 ms) interval of silence and a startle noise. The inter-stimulus interval (ISI) of 120 ms was selected to maximise magnitude inhibition (Braff et al., 1978). Both prepulses and gaps had near instantaneous rise–fall time (<1 ms). The Inter-trial-interval (ITI) time was randomly set at a value between 15 and 23 s in each block. Both background noise and silence were present for the entire ITI duration of the gap and prepulse conditions, respectively. Finally, startle trials in silence consisted of a silent background (no background noise) with a startle noise as described above. All stimuli were created using Max/MSP software program (Cycling 74, San Francisco, USA).

#### 2.2.4. EMG measures

EMG activity of the eyeblink was measured by two 4 mm Ag/AgCl shielded recording electrodes positioned 1.5 cm apart on the orbicularis oculi muscle under the left eye and a ground electrode on the forehead, according to guidelines (Blumenthal et al., 2005). Signal acquisition was made using the Acqknowledge 4.1 software connected to a Biopac MP150 system (Biopac Systems, Inc., Santa Barbara, CA). Signals were amplified by 1000 and bandpass filtered at 90–500 Hz. The amplified signal was then transformed using the root mean square. The sampling rate was set at 1 kHz. The system was coupled to a Fireface sound card (RME, Haimhausen, Germany) of a PC-computer, which was used for stimulus presentation as well as for sending a trigger to the Acqknowledge acquisition system. The trigger was a square-wave that was synchronized with startle noises and was used to precisely determine the window of responses for magnitudes and latencies of the eyeblink (see Data processing below).

Participants (informed that the task required no direct participation) were asked to sit quietly and to refrain from moving. They were asked to stare at a white cross in the middle of the screen and to listen to the sounds presented binaurally through closed dynamic

headphones DT 770 Pro/250. The test session began with a 2 min acclimation period consisting of a high-frequency background noise of 65 dB(A) SPL which ended with four pulse-alone stimuli for habituation before the beginning of block 1. The task consisted in three blocks of trials. In the first, five high- and five low-frequency background startle trials were randomly mixed with five low- and five high-frequency gap trials. Block 2 started with 1-min acclimation period of silence followed by two startle noises, and then by ten high- and ten low-frequency prepulse trials, randomly mixed with ten startle trials in silence. The third block was identical to the first one except that the acclimation period was low-frequency background noise followed by two startle noises. Short breaks between blocks allowed us to monitor participants' drowsiness or lack of attention and to check that they were still comfortable. There were 70 stimuli, lasting for a total duration of about 25 min.

All stimulus types were calibrated before each testing session with an SE SoundPro DL 1/3 octave level meter (Quest Technologies, USA) using an EC-9A artificial ear coupler (Quest electronics, Oconomowoc, Wis., USA) with appropriate rates, that is, impulse for startle noises/prepulse and slow rate for background noise, using the A-weighting frequency curve.

#### 2.3. Data processing

All trials were visually inspected for excessive noise in the EMG signal and for any spontaneous blink occurring immediately before the startle stimuli. These trials were very few (2.3% for test, 3.5% for retest) and rejected from further analysis. The baseline was assessed for each participant by selecting the highest RMS amplitude value occurring between –20 ms to startle noise onset, averaged across startle-alone trials only. The peak-to-peak amplitude of each startle response occurring between 20 and 120 ms from pulse onset was extracted from the transform root mean square (RMS) data. Data for each trial type were averaged for each background noise for each participant. Any peak-to-peak amplitude value of any trial (i.e., prepulse, gap, startle) that was smaller than two standard deviations above the average baseline was considered a non-response. Non-responses were assigned a magnitude of zero. In addition, participants displaying more than 25 non-responses out of a total of 70 stimuli were considered non-responders and were excluded from the study (one participant for test, two participants for retest). Percentage of inhibition was calculated for each condition (gap or prepulse) using the following formula: % inhibition = [(pulse-alone) – (gap/prepulse)] / [(pulse-alone) × 100]. Startle facilitation was assessed by comparing the magnitude of the mean response for pulse-alone trials in the three different conditions (silence, low- and high-frequency background). Peak latency was obtained from the same window time but calculated from the raw EMG waveform following guidelines (Blumenthal et al., 2005). Data on each trial type were averaged for each background noise for each participant. Data above three standard deviations from the group mean were replaced by the average value of the appropriate group (Tinnitus, Control) for each trial type and background noise (4.7% for test, 6.6% for retest).

#### 2.4. Statistical analyses

Hearing thresholds were averaged for each frequency for each ear and were then compared between groups using independent sample *t*-tests.

For the tinnitus-matching task, the mode of individual likeness rating scores for each frequency was used; the median was used when the mode failed to reveal a single rating value. Likeness ratings were averaged across each frequency. The test–retest differences and reliability were assessed using paired sample

*t*-tests and Pearson correlations, respectively, between the frequency with the highest rating at test and retest.

For the loudness-matching procedure, loudness scores for each frequency were obtained using the mean value in dB SPL. Trials for which frequency was rated 0 on the likeness rating scale were not considered since no loudness could be matched. The loudness scores were averaged across each frequency. The test–retest differences and reliability were assessed using paired sample *t*-tests and Pearson correlations, respectively, between the loudness of the frequency with the highest rating at test and the loudness of the frequency with the highest rating at retest.

The number of participants who gave a given frequency a rating  $\geq 1$  on the likeness rating scale was also calculated and plotted as an overall tinnitus spectrum to verify that tinnitus was high-frequency only.

On EMG data, statistical analyses were run separately on magnitude, percentage of inhibition (%Inhibition), startle facilitation, and latency. For magnitude, a  $2 \times (2 \times 3)$  mixed ANOVA was run with Group (Tinnitus vs. Control) as a between-subject factor and Frequency (High vs. Low) and Stimulus type (gap, prepulse, pulse-alone) as within-subjects factors. For %Inhibition, a  $2 \times (2 \times 2)$  mixed ANOVA was run with Group (Tinnitus vs. Controls) as between-subject factor and Frequency (High vs. Low) and Stimulus type (gap vs. prepulse) as within-subject factors. For startle facilitation, a mixed  $2 \times (3)$  ANOVA was run with Group (Tinnitus vs. Controls) as the between-subject factor and Background condition (High-frequency, Low-frequency and Silence) as the within-subject factor. For latency, a  $2 \times (3 \times 2)$  mixed ANOVA was run with Group (Tinnitus vs. Controls) as the between-group factor and Frequency (High vs. Low) and Stimulus type (gap, prepulse and pulse-alone) as within-subjects factor. Significant interactions were followed up by ANOVA or *t*-tests upon circumstances. Bonferroni's correction for multiple comparisons was used for *t*-tests when appropriate in order to keep the alpha level to .05 throughout all analyses. Therefore, the *p* values reported in this paper are corrected values. The only exception to the Bonferroni's correction was for hearing thresholds because a factor correction of 16 was considered too conservative. Paired sample *t*-tests and Pearson correlations were used to assess test–retest differences and reliability of all measures.

### 3. Results

#### 3.1. Hearing thresholds

Overall, for both ears, there were no significant differences in hearing thresholds between tinnitus and control groups for standard frequencies from 250 Hz to 8 kHz. For the higher frequencies, the only difference between groups was in the right ear at 16 kHz,  $t(24) = -2.3$ ,  $p < .05$  (data not shown). For the left ear, the tinnitus group had significantly higher thresholds at 12.5 kHz,  $t(24) = -3.4$ ,  $p < .005$ , 14 kHz,  $t(24) = -3.1$ ,  $p = .005$  and 16 kHz,  $t(24) = -4.3$ ,  $p < .001$  (Fig. 2(A)).

At retest (within-group differences), the only significant differences for the tinnitus group were at 1.5 kHz in the right ear with a mean difference of 2 dB HL,  $t(9) = 2.4$ ,  $p < .05$ , and at 8 kHz in the left ear with a mean difference of 3.5 dB HL,  $p < .05$ . For the control group, a mean difference of 2.8 dB HL was noted at 4 kHz for the left ear,  $t(8) = 3.3$ ,  $p < .05$ , and a mean difference of 3, 2, 5 and 3 dB HL at 750, 1000, 3000 and 6000 Hz for the right ear respectively,  $p < .05$ .

#### 3.2. Tinnitus-matching

Mean likeness ratings and sound levels for each frequency in the tinnitus-matching task are shown in Fig. 2(A). The frequency with

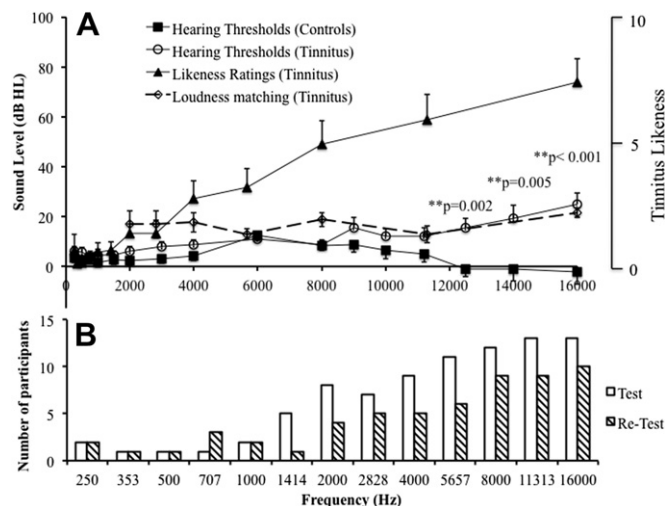


Fig. 2. (A) Hearing thresholds (SEM) for the Tinnitus and Control groups, left ear (plain line). Hearing thresholds are higher in the Tinnitus group for frequencies above 12.5 kHz. Mean likeness ratings of the tinnitus are following the trend of the hearing loss with higher likeness ratings corresponding to the frequency regions more affected by the hearing loss. The dB SL levels are very low across frequencies (dotted lines). (B) The tinnitus frequency spectrum of the tinnitus-matching task. The most reported frequencies (13 out of 15 participants) are 11 kHz and 16 kHz.

the highest likeness rating was 16 kHz with a mean rating of 7.4, followed by 11.3 kHz (mean rating = 5.9) and 8 kHz (mean rating = 4.9).

When comparing test–retest data for the likeness rating task, the mean frequency difference was  $-430.9$  Hz (SD: 2671) and was not statistically significant ( $p = .59$ ) (Table 2).

The test–retest reliability was  $r = .754$ ,  $p = .005$ .

The matched sound level in dB SPL at 16, 11 and 8 kHz were 55.0 (SD: 17.8), 24.5 (SD: 4.8) and 30.0 (SD: 8.0), respectively. In order to be able to graphically represent those results, the matched sound levels transformed in dB SL, are shown in Fig. 2(A). Corresponding SL values are  $-3.3$  (SD: 7.0), 0.8 (SD: 11.8) and 10.1 (SD: 9.5) for 16, 11 and 8 kHz respectively.

When comparing test–retest data for the loudness task, the mean difference was .98 dB SPL (SD: 11.4) and was not statistically significant ( $p = .77$ ). The test–retest reliability was  $r = .91$ ,  $p < .001$ .

The tinnitus frequency spectrum is shown in Fig. 2(B), representing the number of participants who gave each of those frequencies a rating  $\geq 1$  on the likeness rating scale. Overall, the high frequencies were reported more often than lower frequencies as part of the tinnitus spectrum. The most often reported frequencies were 16 kHz and 11.3 kHz, with 13 participants out of 15 reporting a contribution of those frequencies. Very few participants rated frequencies  $\leq 1$  kHz as part of their tinnitus, confirming a very minor contribution of lower frequencies in the tinnitus percept. The same trend was observable at retest time.

#### 3.3. Startle magnitude

As shown in Fig. 3, overall the Tinnitus group displayed greater startle magnitude responses than the Control group, as supported by a main effect of Group,  $F(1,30) = 4.2$ ,  $p = .048$ , with means of 0.173 mV and 0.106 mV for the two groups, respectively. There was a significant interaction between Stimulus type and Frequency,  $F(2,60) = 4.1$ ,  $p = .022$ . Following up on this interaction, magnitudes for high-frequency conditions were greater than for low-frequency background in the Gap condition,  $t(31) = 5.3$ ,  $p < .003$ , and for the prepulse condition,  $t(31) = 2.6$ ,  $p = .048$ , but not for the Pulse

**Table 2**Paired sample *t*-test and Pearson correlations between the test and retest sessions.

Measure		Paired <i>t</i> -test	<i>P</i> -value	Pearson's correlation coefficient	<i>P</i> -value
Magnitude	Pulse-alone trials				
	High-frequency background	$t(18) = -0.1$	0.92	0.91	<0.001
	Low-frequency background	$t(18) = 0.0$	1.00	0.85	<0.001
	No background (silence)	$t(18) = 1.2$	0.23	0.93	<0.001
	Pulse + discrete prepulse trials				
	High-frequency discrete prepulse	$t(18) = -1.2$	0.25	0.83	<0.001
	Low-frequency discrete prepulse	$t(18) = -1.5$	0.16	0.72	=0.001
	Pulse + gap prepulse trials				
	High-frequency background	$t(18) = -0.2$	0.85	0.86	<0.001
	Low-frequency background	$t(18) = -0.2$	0.84	0.70	=0.001
Latency	Overall	$t(62) = -1.3$	0.20	0.40	=0.001
	%Inhibition				
%Inhibition	Pulse + discrete prepulse trials				
	High-frequency discrete prepulse	$t(15) = 1.1$	0.31	0.73	=0.001
	Low-frequency discrete prepulse	$t(15) = 0.2$	0.85	0.80	<0.001
	Pulse + gap prepulse trials				
	High-frequency background	$t(15) = -0.72$	0.49	0.39	n.s.
Tinnitus frequency	Low-frequency background	$t(15) = -1.6$	0.12	0.51	=0.046
	Overall	$t(11) = -0.56$	0.59	0.75	=0.005
Tinnitus loudness	Overall	$t(11) = 0.3$	0.77	0.91	<0.001

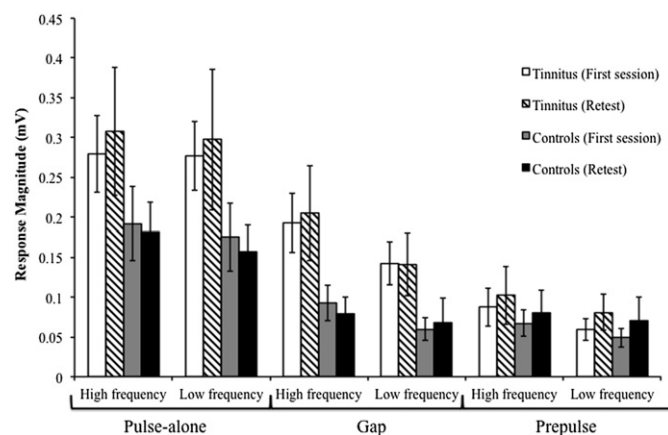
condition,  $t < 1$ . There was also a significant main effect of Stimulus type,  $F(2,60) = 42.0$ ,  $p < .001$ , as well a main effect of Frequency,  $F(1,30) = 15.2$ ,  $p < .001$ .

On retest data, there was a significant main effect of Stimulus type,  $F(2,34) = 13.9$ ,  $p < .001$ , and a main effect of Frequency,  $F(1,17) = 9.94$ ,  $p = .006$ . There was no significant group effect,  $F(1,17) = 2.08$ ,  $p = .17$ , and no other significant effect.

When comparing test–retest data on startle Magnitude, Pearson's correlations ranged from .70 to .93 for all conditions (see Table 2). There were no significant differences in magnitude scores between test and retest.

### 3.4. Percentage of inhibition

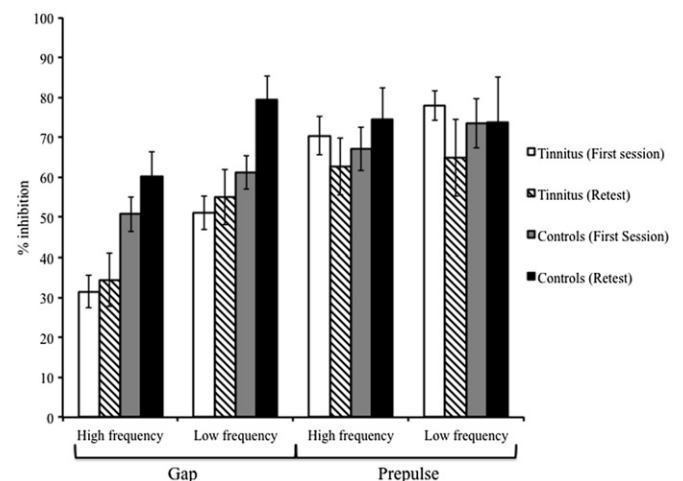
The expected three-way interaction between Group, Stimulus type and Frequency was not significant,  $F < 1$ . There was, however, a significant interaction between Group and Stimulus type,  $F(1,30) = 6.9$ ,  $p = .013$  (see Fig. 4). To follow-up on this interaction, and to more specifically address the effects of high- and low-frequency in the gap condition, a  $2 \times 2$  ANOVA was run for each condition separately (Gap and PPI) with Group (Tinnitus vs. Control) as a between-subject factor and Frequency (High vs. Low) as a within-subject factor. In the GAP condition, although the



**Fig. 3.** Startle magnitudes (SEM) for the three trial types, for each background frequency and each testing session. Startle magnitudes are higher for the tinnitus group across all conditions.

difference between groups was greater at high- than at low-frequency, the expected interaction between Group and Frequency was not significant,  $F(1,30) = 2.28$ ,  $p = .14$ . Irrespective of the frequency, the Tinnitus Group displayed significantly less inhibition than the Controls,  $F(1,30) = 8.13$ ,  $p = .008$ , whereas the groups did not differ in the Prepulse condition,  $F < 1$ . Effect size for the Group difference in the Gap condition was  $\eta^2 = .21$  (i.e., a large effect). There were also two significant main effects: Stimulus type,  $F(1,30) = 44.5$ ,  $p < .001$ , and Frequency,  $F(1,30) = 26.8$ ,  $p < .001$ .

On retest data, there was a main effect of Group, with Tinnitus showing overall less inhibition than Controls,  $F(1,17) = 5.6$ ,  $p = .030$ . The Group X Stimulus type was not significant,  $F(1,17) = 1.14$ ,  $p = .30$ . However, when looking at each Condition separately (as for the test data), the Tinnitus group once again differed significantly from Controls in the Gap condition irrespective of the frequency,  $F(1,17) = 9.23$ ,  $p = .007$ , but not in the Prepulse condition,  $F < 1$ . Effect size for the Group difference in the Gap condition was  $\eta^2 = .35$  (i.e., a very large effect). There was also a main effect of



**Fig. 4.** Percentage of inhibition (SEM) for the Gap and Prepulse trials, for each background frequency (High- and Low-), each testing session (Test and Retest) for Tinnitus ( $n = 15$ ) and Control ( $n = 17$ ) groups. Lower values in the y-axis represent lower inhibition by the gap. This plot suggests that compared to Controls, the Tinnitus group has lower inhibition in the Gap condition for high- and low-frequency background noise.

Frequency,  $F(1,17) = 10.9$ ,  $p = .004$ , and an interaction between Condition and Frequency,  $F(1,17) = 7.8$ ,  $p = .012$ .

When comparing test–retest data, % of inhibition was found to be stable for the prepulse conditions, with Pearson's correlation coefficients of .73 and .80 (see Table 2). Correlations' coefficients for the gap condition were lower with .40 and .51, and significant only for the low-frequency gap condition (not for the High-frequency). However there were no significant differences between percentage of inhibition scores at test and retest in any of the conditions.

### 3.5. Startle facilitation

The main effect of background (High-frequency, Low-frequency, Silence) was significant,  $F(2,60) = 7.6$ ,  $p = .001$ . The High-frequency noise background yielded a stronger response than silent background,  $t(31) = 3.9$ ,  $p < .001$ . The Low-frequency background also yielded a stronger response than silent background, but this difference was only marginally significant after applying Bonferroni's correction,  $t(31) = 2.4$ ,  $p = .072$ . High- and low-frequency background did not differ from one another,  $t < 1$ . There was no other significant effect.

On retest data, the effect of Background also turned out significant,  $F(2,34) = 7.9$ ,  $p = .002$ . The High-frequency background yielded a stronger response than silent background,  $t(18) = 3.7$ ,  $p < .006$ . The Low-frequency background also yielded a stronger response than silent background, but again only marginally significant after applying Bonferroni's correction,  $t(18) = 2.4$ ,  $p = .08$ . High- and Low-frequency background did not differ from one another,  $t(18) = 1.4$ ,  $p = .19$ . There was no other significant effect.

When comparing test–retest data, the test–retest reliability was very good,  $r = .93$  (see Table 2). There were no significant differences in magnitude scores between test and retest.

### 3.6. Peak latency

On latency, there was no significant main effect of, or interaction with, groups, stimulus type, and frequencies, either on test or retest data.

Test–retest reliability was moderate,  $r = .39$ ,  $p < .001$ , and there was no significant differences between test and retest,  $t(63) = -1.3$ ,  $p = .20$ .

## 4. Discussion

The main findings of this study are threefold. First, compared to control participants without tinnitus, “normal-hearing” human adults with high-frequency tinnitus displayed an impaired inhibition of the startle reflex when a gap was used as a pre-stimulus, but displayed normal inhibition with a prepulse. Second, adults with tinnitus displayed overall a stronger startle response than controls without tinnitus. Third, the new tinnitus-matching procedure used here replicated previous findings with other methods showing that the tinnitus spectrum matches the hearing loss, even when hearing is normal at standard frequencies and there is no edge frequency: tinnitus spectrum at very high frequencies matched the increased hearing thresholds. Strikingly, loudness was a very stable tinnitus parameter, with a less than one dB difference on average even after a six-month delay between testing sessions. These findings will be discussed in turn.

### 4.1. Gap inhibition deficit but normal sensorimotor gating in tinnitus

Although tinnitus was associated with a consistent and reproducible decreased gap inhibition, the deficit was not specific to

high-frequency background noise, as it was also observed in low-frequency background noise. Although the high-frequency background noise was not precisely matched to the tinnitus frequency, all participants displayed high-frequency tinnitus (predominant pitch at 16 kHz) as self-reported and confirmed with a pitch- and loudness-matching procedure. To note, the frequency of 500 Hz was virtually absent from the tinnitus percept. Yet we did not confirm our assumption that the high-frequency background noise effect on gap inhibition (centered around 4 kHz) would be more similar to the tinnitus effect than the low-frequency background noise effect (centered around 500 Hz).

The data raise the central question as to the reason why background gap deficit occurred at *both* a high- and a low-frequency in tinnitus, seemingly contradicting the animal studies showing a frequency-specific impairment, and challenging the idea that the gap paradigm may “capture” the tinnitus percept. To our knowledge, Turner et al.' (2006) seminal paper is the only one in which the tinnitus frequency was verified with an independent method, whereas gap impairment was assumed to reflect the presumed tinnitus frequency in others. Yet, in some studies, gap impairments were reported at frequencies other than the one of the presumed tinnitus frequency. For instance, Engineer et al. (2011) using a 10 kHz model (Bauer and Brozoski, 2001) reported that most of the rats displayed gap impairments at 10 kHz but also at 8 kHz. Similarly, gap impairments were reported at various frequencies in one study using salicylate (Turner and Parrish, 2008) although a gap deficit was reported only at 16 kHz by others (Yang et al., 2007; Ralli et al., 2010). Therefore, the issue of tinnitus “filling in” the gap is still unsettled, notably since in all (but a single) animal studies tinnitus frequency was not verified by an independent method and gap inhibition impairments were observed at several frequencies. Moreover in a recent review, Eggermont (2012) has further pointed out discrepancies between electrophysiological correlates of tinnitus and behavioural measures assessed by the gap startle paradigm in animals, casting doubt on the original interpretation.

### 4.2. How to reconcile the human data with previous animal reports?

The paradigm investigated herein in humans is derived from animal studies. It might be possible that discrepancies between the two models be resolved through technical or methodological improvements. For instance, it might be necessary to more precisely match the background noise with the predominant tinnitus frequency in humans; however, since tinnitus frequency is often associated with hearing loss at similar frequencies, it would also be necessary to adjust the background noise in dB SL for each individual rather than presenting a steady dB SPL level across groups. More importantly, we contend that reductionist animal studies using genetically inbred strains of animals living under fully controlled conditions (e.g. controlled sleep–wake cycles, etc.) may not capture the full array of human conditions associated with tinnitus. Several studies have shown that humans with tinnitus display sleep deprivation (Hebert and Carrier, 2007; Hebert et al., 2011), complex patterns of abnormal stress responses (Hebert and Lupien, 2007; Simoens and Hebert, 2012), emotional exhaustion and depressive symptomatology (Hébert et al., 2012, *in press*). If it were *ever possible* to expect a correspondence between animal and human responses to PPI and gap paradigms, researchers studying tinnitus in animals might have to resort to more elaborate animal models in which higher central nervous system functions would be engaged.

Although further research will be needed to evaluate their significance, our findings in human subjects suggest that the

tinnitus percept does not “fill in the gap” and therefore may not be the mechanism responsible for the gap inhibition impairment in tinnitus. Rather, they raise the intriguing possibility that the gap impairment occurring at both high- and low-frequencies might be linked to an underlying or associated tinnitus mechanism. We propose that one such mechanism may relate to an impaired structure that is part of the neural circuit involved in gap processing, namely the auditory cortex. Indeed, one key difference between the PPI and the gap circuits is that the gap requires the auditory cortex for such short durations up to 75 ms in rats (Threlkeld et al., 2008), whereas PPI does not (Ison et al., 1991; Bowen et al., 2003). In fact, the tinnitus group displayed a normal PPI response with reference to controls, suggesting a normal sensorimotor gating process and hence, an integrity of the circuits responsible for the PPI response. Therefore, we surmise that the deficit in the gap response in tinnitus might lie in impaired cortical processing. Although the precise duration values up to which a cortical involvement is required are still unknown in humans, there is good evidence that values up to 250 ms cannot be detected in patients with bilateral auditory cortical lesions (Buchtel, 1989), a value well above the one used in this study.

Abnormal cortical map reorganisation in tinnitus has been reported in human studies (Mühlnickel et al., 1998; Weisz, 2005; Bakker et al., 2011) and has been proposed as a core mechanism of tinnitus (Eggermont and Roberts, 2004). Interestingly, gap processing impairment of durations around 50 ms has also been reported in numerous animal studies using either noise trauma (Turner et al., 2006; Wang et al., 2009; Zhang et al., 2010; Engineer et al., 2011; Longenecker and Galazyuk, 2011; Middleton et al., 2011) or salicylate to induce tinnitus (Yang et al., 2007; Turner and Parrish, 2008; Ralli et al., 2010), cortical map reorganisation being an important common feature of both noise trauma and salicylate techniques (Eggermont, 2012). Therefore, our data are consistent with the notion that gap impairment might be an indirect measure of cortical map reorganisation. This hypothesis is indirectly supported by the improvement of gap impairment following the remapping of the auditory cortex (Engineer et al., 2011).

#### 4.3. Enhanced startle magnitude in tinnitus

An unexpected finding was that startle magnitude was generally stronger in tinnitus compared to controls. One explanation for this over-reactivity could be related to many other factors among which their higher levels of anxiety (Shargorodsky et al., 2010), known to be associated greater magnitude startle response (Grillon et al., 1994; Bakker et al., 2008). Another explanation, not mutually exclusive, is that even with “normal” hearing thresholds, individuals with tinnitus have abnormal coding of loudness and might therefore be more reactive to sounds than controls without tinnitus (Schaette and McAlpine, 2011). Therefore, the stronger response observed here could be an index of hyperacusis, as has been previously found in the animal literature (Ison et al., 2007; Sun et al., 2009).

#### 4.4. Psychoacoustic parameters of tinnitus: a reliable subjective measure

Our participant-oriented method to assess the psychoacoustic parameters of tinnitus replicated previous findings that reported that the predominant tinnitus frequency is usually within the hearing loss region (Norena et al., 2002; Roberts et al., 2008). Indeed, despite overall standard “normal” hearing thresholds (250–8000 Hz), tinnitus participants displayed higher thresholds than controls at very high frequencies (>11,200 Hz) and rated the

predominant tinnitus frequency within that region (~16,000 Hz). This supports the hypothesis that tinnitus is associated with some degree of peripheral hearing damage (Schaette and McAlpine, 2011) and underscores the importance of very high-frequency testing in tinnitus.

#### 4.5. Test–retest

Notably, the pitch- and loudness-matching of tinnitus were both robust and reproducible after several months. For instance, using the conservative criterion  $r^2 = .64$  for a good test–retest reliability (Kline 2000), our loudness data ( $r = .91$  or  $r^2 = .83$ ) indicate that 83% of the variance at test was accounted for by the variance at retest, with an average of nearly six months between the two testing sessions. Even though some studies have shown low correlations between tinnitus distress and loudness (Andersson, 2003; Holgers et al., 2003; Hiller and Goebel, 2007), those measures might provide important information regarding the mechanisms involved in tinnitus and should always be assessed. Finally, although the power of the retest was lower than in the first testing session presumably because of a smaller number of participants, overall all of the effects reported here were consistent and replicable through retesting of a subset of participants with an average delay of several months. We have shown that these effects are robust and propose that this is a central issue if the paradigm is to be used to measure tinnitus in the future.

### 5. Conclusion

In conclusion, this study shows a consistent deficit in gap processing in individuals with high-frequency tinnitus, at both low- and high-frequencies. Such deficit was observable both at test and retest sessions after several months of delay. Our findings suggest that the tinnitus percept is not “filling in the gap” and is unlikely to be responsible for the gap inhibition impairment. We propose that the deficit might reflect abnormal cortical auditory processing associated with tinnitus.

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