An exploratory investigation of pupillometry as a measure of tinnitus intrusiveness on a test of auditory short-term memory

Doug J.K. Barrett[1], David Souto[1], Michael Pilling[2] & David M. Baguley[3,4,5]

[1]Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK.

[2]Department of Psychology, Oxford Brookes University, Oxford, UK.

[3]Hearing Sciences, Division of Clinical Neurosciences, School of Medicine, University of Nottingham, Nottingham, UK.

[4] Nottingham NIHR Biomedical Research Centre, University of Nottingham, UK.

[5] Nottingham Audiology Services, Nottingham University Hospitals NHS Trust, Nottingham, UK.

Financial disclosures/conflict of interest: This study was funded by the University of Leicester. There are no conflicts of interest, financial, or otherwise.

The data that support the findings of this study will be openly available via the University of Leicester Research Repository.

All correspondence should be addressed to:

Doug J.K. Barrett, Department of Neuroscience, Psychology and Behaviour, University of Leicester, LE1 9HN, UK. E-mail: djkb1@le.ac.uk

Abstract

Objectives: The purpose of the current study was to investigate the potential of pupillometry to provide an objective measure of competition between tinnitus and external sounds during a test of auditory short-term memory.

Design: Twelve participants with chronic tinnitus and twelve control participants without tinnitus took part in the study. Pre-test sessions used an adaptive method to estimate listeners' frequency discrimination threshold on a test of delayed pitch discrimination for pure tones. Target and probe tones were presented at 72 dB SPL and centred on 750 Hz. ± 2 semitones with an additional jitter of 5-20 Hz. Test sessions recorded baseline pupil diameter and task related pupillary response (TEPRs) during three blocks of delayed pitch discrimination trials. The difference between target and probe tones was set to the individual's frequency detection threshold for 80% response-accuracy. Listeners with tinnitus also completed the Tinnitus Handicap Inventory (THI). Linear mixed effects procedures were applied to examine changes in baseline pupil diameter and TEPRs associated with group (Tinnitus vs. Control), block (1 to 3) and their interaction. The association between THI scores and maximum TEPRs was assessed using simple linear regression.

Results: Patterns of baseline pupil dilation across trials diverged in listeners with tinnitus and controls. For controls, baseline pupil dilation remained constant across blocks. For listeners with tinnitus, baseline pupil dilation increased on blocks 2 and 3 compared to block 1. TEPR amplitudes were also larger in listeners with tinnitus than controls. Linear mixed effects models yielded a significant group by block interaction for baseline pupil diameter and a significant main effect of group on maximum TEPR amplitudes. Regression analyses yielded a significant association between THI scores and TEPR amplitude in listeners with tinnitus.

Conclusions: Our data indicate measures of baseline pupil diameter and TEPRs are sensitive to competition between tinnitus and external sounds during a test of auditory short-term memory. This result suggests pupillometry can provide an objective measure of intrusion in tinnitus. Future research will be required to establish whether our findings generalise to listeners across a full range of tinnitus severity.

Introduction

Tinnitus is a prevalent condition (McCormack et al., 2016), often associated with substantial burden and distress, which may include anxiety, depression, and insomnia (Watts et al., 2018). This represents a very significant public health problem, and the societal costs of tinnitus are substantial: a UK estimate of tinnitus healthcare costs is £750 (~ $1,059 or ~€873) million per year (Stockdale et al., 2017). Whilst therapies to alleviate the impact of tinnitus are widely available, a cure has proved elusive (McFerran et al., 2019). One reason for this, is that at present there is no reliable biomarker or objective measure of tinnitus, so treatment studies rely on self-report measures whose subjective nature may obscure possible benefits of interventions. Therefore, the identification and verification of an objective measure of tinnitus is an urgent priority.

In the absence of an objective measure, the severity of tinnitus and its impact on listeners is assessed primarily using self-report questionnaires. These comprise subscales that evaluate distinct aspects of tinnitus, such as perceptual difficulties, emotional and cognitive distress, and intrusiveness (Kennedy et al., 2005). Intrusiveness is often defined in terms of competition between external sounds and the tinnitus percept during the perception and evaluation of auditory information (Andersson et al., 2006; Hallam et al., 1988). Hibbert and colleagues (Hibbert et al., 2020) concluded intrusiveness is dependent on tinnitus awareness, unpleasantness, and its impact on everyday activities. In the current manuscript, we use intrusiveness to describe the impact of tinnitus on capacity-limited cognitive resources and mental effort during listening, where capacity is defined as the amount of work a system can perform in a given moment (Townsend & Ashby, 1978). This impact is likely to reflect both perceptual qualities of the internal percept (i.e., loudness and pitch) and the extent to which it captures attention (Kennedy et al., 2005).

The term selective attention describes neural mechanisms that operate to prioritise relevant over irrelevant sensory input, increasing the acuity of attended information and gating access to capacity-limited processes including short-term memory (Choi et al., 2014; Gazzaley, 2011; Hillyard et al., 1998; Myers et al., 2017). Behavioural data from dichotic listening tasks and the Attentional Network Test suggests listeners with tinnitus exhibit an attentional bias towards the tinnitus percept during the encoding and the retention of external sounds (Cuny et al., 2004; Heeren et al., 2014; Roberts et al., 2013). This attentional bias may explain the absence of habituation in problem tinnitus (Hallam et al., 1988; Walpurger et al., 2003), with attention eliciting and reinforcing plastic changes in connectivity between auditory and frontal cortex, hippocampal gyri (Vanneste & De Ridder, 2012) and the limbic system (Erlandsson et al., 1992; Saunders, 2007; Ueyama et al., 2013). An attentional bias towards tinnitus is also likely to impact negatively on hearing; reducing the resources available to encode, maintain and evaluate external sounds in short-term memory. In listeners with normal hearing, the precision of auditory recall is inversely related to perceptual set size (e.g., the number of sounds in a sequence). Changes in the precision of recall for cued compared to uncued stimuli also demonstrate the role of selective attention in gating access to relevant over irrelevant sounds to short-term memory (Kumar et al., 2013). These findings have been interpreted in terms of a reciprocal relationship between the number of attended sounds and the distribution of capacity-limited resources during their encoding and maintenance (Joseph et al., 2015; Kumar et al., 2013).

The findings above demonstrate reliable associations between perceptual set size, selective attention, and the precision of recall for auditory objects. In extending this evidence to tinnitus, one can predict an association between the attentional weight assigned to tinnitus and the extent to which it competes for short-term memory resources. Barrett and Pilling (2017) tested this possibility by manipulating the locus of attention towards or away from simulated tinnitus during a delayed pitch discrimination task. In their study, listeners with normal hearing compared the pitch of two tones separated by a three second retention interval. The frequency-difference between tones was varied using a method of constant stimuli (Harris, 1948) and the slope of the resulting psychometric function was used to index the precision of recall. Tones were presented in the absence or presence of simulated tinnitus, which was presented at constant or modulated amplitude on a subset of trials. To avoid masking, the tones and simulated tinnitus were separated by a large frequency difference and participants were required to ignore or report the amplitude modulation of the tinnitus when present. The results revealed a decrease in precision when tones were presented in the presence of simulated tinnitus compared to silence. When participants were required to report the amplitude of simulated tinnitus, the decrease in precision was significantly larger than in the silent baseline condition. When participants were instructed to ignore simulated tinnitus, the reduction in precision was smaller, and did not reach statistical significance.

Barrett and Pilling's (2017) results suggest changes in the precision of auditory recall reflect competition between simulated tinnitus and task-relevant sounds during tests of short-term memory. For listeners with tinnitus, the internal percept represents an additional stimulus. The extent to which this competes for resource with external sounds, depends on whether attention is oriented towards or away from the tinnitus during listening. Competition between tinnitus and external sounds is also likely to increase the mental effort required to encode and maintain external sounds. In the psychological literature, task-evoked pupillary responses (TEPRs) have been used to index changes in cognitive-load and mental effort during tests of auditory and visual recall (Goldinger & Papesh, 2012; Pichora-Fuller et al., 2016). Early studies revealed a positive association between pupil dilation and the number of tones or digits participants had to retain during tests of auditory short-term memory (Beatty & Kahneman, 1966; Kahneman et al., 1967). Subsequent findings have revealed a close correspondence between behavioural estimates of short-term memory capacity and asymptotic pupil dilation during auditory recall (Granholm et al., 1996; Peavler, 1974) and visual change detection (Kursawe & Zimmer, 2015). Distributing attention across two, compared to a single speaker, has also been shown to elicit increases in pupil dilation over and above those associated with the degradation of speech (Koelewijn et al., 2014). These findings indicate TEPRs are sensitive to the number and the distribution of attention across sounds during encoding and maintenance in short-term memory. If problem tinnitus reflects competition between tinnitus and external sounds, differences in TEPRs may provide an objective measure of the increase in listening effort required to encode and maintain sounds during tests of auditory short-term memory.

The current study is designed to evaluate pupillometry as an objective measure of intrusiveness in tinnitus. To do this, we contrasted pupil size and TEPRs during a delayed pitch discrimination task in listeners with and without tinnitus. TEPRs are defined as phasic changes in pupil dilation relative to a baseline obtained in the absence of stimulation or task-demands (Beatty & Lucero-Wagoner, 2000), which is time-locked to stimulus onsets (or offsets) and the inferred mental operations they elicit, such as the encoding and maintenance of a sound on each trial. In addition to TEPRs, we recorded changes in tonic pupil diameter prior to the onset of each trial in the absence of auditory stimulation. Recent evidence has linked changes in tonic pupil diameter to levels or arousal, shifts in selective attention, exploratory behaviour and increases in processing-load (Bast et al., 2018; Pajkossy et al., 2017; Zénon, 2019). In tinnitus, competition between the internal percept and external sounds is likely to increase demands associated with the maintenance of task-relevant information in auditory short-term memory. Competition is also likely to increase demands associated with the maintenance of an attentional set that prioritises external sounds over blocks of trials (Maudoux et al., 2012). To control the impact of potential of perceptual differences on these processes in listeners with and without tinnitus, we measured delayed pitch discrimination accuracy for pure tones with frequencies below those associated with i) age-related sensorineural and noise-induced hearing loss (Eggermont, 2019; Jilek et al., 2014; Nicolas-Puel et al., 2002), and ii) psychoacoustic estimates of average tinnitus frequency (Ibraheem & Hassaan, 2017; Schecklmann et al., 2012; Shekhawat et al., 2014). In addition, we used an adaptive psychophysical procedure to estimate individual frequency detection thresholds to ensure the accuracy of delayed pitch discrimination was equivalent for listeners in each group. In this situation, differences in tonic pupil size and TEPRs can be attributed to an increase in the mental effort required to obtain a fixed level of accuracy during the encoding and maintenance of tone-frequency in auditory short-term memory.

Method

Participants

Fourteen participants with chronic tinnitus (TG) were recruited to the study from the local community and Leicester branch of the British Tinnitus Association Support Group. All had experienced tinnitus in one or both ears for at least six months. One participant withdrew from the study during the session, and one was excluded because of astigmatism in their right eye. Twelve participants with no history of tinnitus or neurological disorder were recruited as a control group (CG) for the study. None of the participants wore hearing aids and differences in the age of each group were not statistically significant (TG: $M = 46.5$, $SD = 12.5$. CG: $M = 43.8$, $SD = 16.4$. $t_{22} = 0.45$, $p = 0.66$, Cohen's $d = 0.18$). Approval for the study was obtained from the School of Psychology Ethics Committee at the University of Leicester. Recruitment, consent, and experimental procedures conformed to American Psychology Association ethics standards.

Apparatus

Experiments were run on an IBM PC with a 21-inch HP Trinition P1130 CRT monitor (Walnut, CA, USA) at a frame-rate of 1000 Hz and resolution of 1,280 * 1,024 pixels. Sounds were presented binaurally over headphones (HDA 200: Sennheiser Electronic Corporation, Wedemark, Germany) and stimulus presentation and timing were controlled using custom-built software in MATLAB (Mathworks, Natick, MA, USA) with Psychtoolbox (Brainard, 1997; Kleiner et al., 2007) and Palamedes (Prins, 2014) toolbox extensions. Viewing distance was fixed at 60 cm using a fixed chin rest and pupil dilation and fixation were measured using an EyeLink 1000 video-based eye tracker (SR Research Ltd., Ottawa, ON, Canada) with spatial resolution of < 0.02 degrees at a sample rate of 1000 Hz. The study was run in a dimly lit room at a constant light level for all participants.

Stimuli

Stimuli for the delayed pitch discrimination (DPD) task were pure tones. Tones were 500 milliseconds (ms) long with 10 ms cosine onset and offset ramps presented at 72 dB SPL. Target tones on each trial were centred at one of three frequencies; 750 Hz ± 2 semitones (668 & 842 Hz) with an additional jitter of ± 5 to 20 Hz to avoid consolidation in long-term memory. Probe tones were higher or lower in frequency than target tones by a variable amount (see procedure below). Trials also included white noise bursts of 500. Ms presented at 72 dB SPL. Participants viewed a uniform mid-grey screen (52 cd/m^2) with a centrally located Gabor patch subtending 1 x 1 visual degree on each trial. Gabor patches were generated by convolving a sine wave with a Gaussian window to produce a discriminable grating with the same mean luminance as the display.

Procedure

Participants completed the Tinnitus Handicap Inventory (THI: Newman, Jacobson & Spitzer, 1996) and the DPD task. The THI consists of 25 questions that assesses the impact of tinnitus on an individuals' quality of life. Responses are scored on a 4-point scale to produce an overall score between 0 and 100. Participants then undertook a calibration procedure requiring them fixate a Gabor patch presented sequentially at the centre of the screen and then 5 equidistant points on the circumference of a virtual circle (eccentricity = 5°). Gabor patches were presented at each location for 2 seconds and the calibration procedure was repeated using high (72.5 cd/m^2), mid (12.7 cd/m^2) and low (3.8 cd/m^2) luminance displays. The calibration was used to ensure pupillary responses during experimental trials fell within listeners' dynamic range. Following calibration, participants were familiarised with the DPD task (see Figure 1).

Trials on the DPD task started with a Gabor at the centre of a mid-luminance display and participants were instructed to maintain their gaze on the Gabor throughout the trial. One and a half seconds after the onset of the fixation-point, a target and probe tone were presented. Tones were separated by a silent retention interval of 2 seconds, and participants reported whether the pitch of the probe was lower or higher than the target using the “up” and “down” arrows on a standard keyboard. The number of low and high frequency probes was equal, and their order of presentation was pseudorandomised across trials. Once a response was recorded, a 500 ms burst of white noise was presented to signal the end of the trial and mask any perceptual priming associated the target and probe tones. Trials were separated by silent interval and a uniform mid luminance display for 500 ms.

During familiarisation, the difference between target and probe tones was set at 2 semitones. Participants were asked to verbalise their decisions to ensure they understood the task and could make accurate lower-higher decisions. Trials were repeated until participants made at least 10 correct responses. Following a short break, 3 blocks of the DPD task were used to estimate listener’s frequency detection thresholds (FDTs). Individual estimates were obtained using a weighted 1-up, 1-down staircase over 80 trials to calculate the frequency-difference required to discriminate between low and high probe- relative to the target-tones with 80% probability (Kaernbach, 1991). Individual FDTs were used to i) control for changes in sensory acuity associated with hearing loss or tinnitus and ii) equate the difficulty of pitch discrimination across TG and CG participants. Pupil size was not recorded during familiarisation or FDT estimation.

Following FDT estimation, participants completed 3 test blocks of 50 trials on the DPD task. The frequency-difference between target and probe tones was set at the participant’s mean 80% accuracy threshold (Δ Semitones). Pupil size and fixation location were recorded from the right eye. Pupil size (area) was tracked using EyeLink’s proprietary centroid mode, which tracks the centre of the pupil image using a centre-of-mass algorithm (Zhu et al., 1999). A square root transformation of the pupil area results in a measure of linear angle in arbitrary units that scales with pupil diameter and viewing distance (Hayes & Petrov, 2016). Each test block was preceded by a 9-point calibration sequence to ensure gaze location could be tracked accurately and participants could maintain their gaze on the central Gabor.

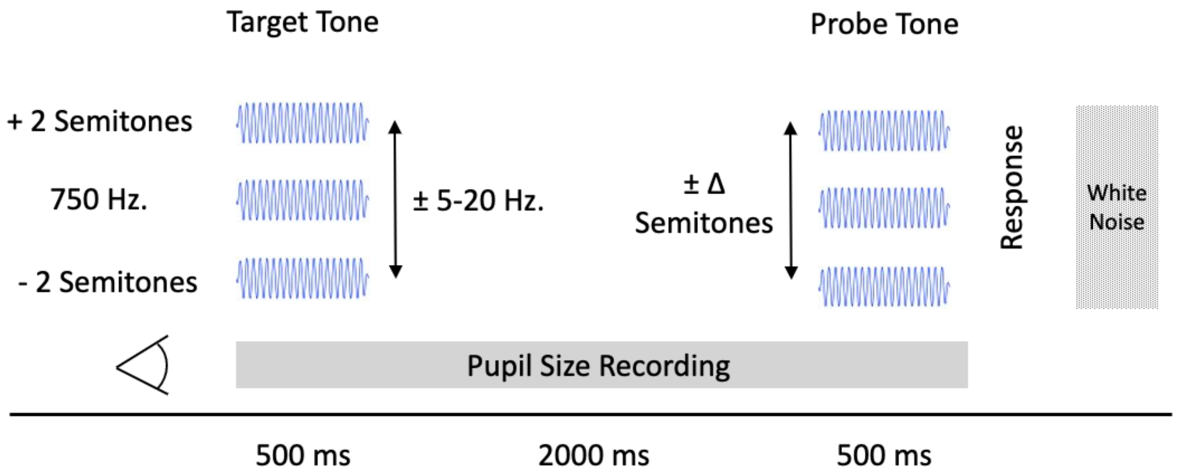

Figure 1. Illustration of the sequence of events on each trial. Changes in pupil dilation on each trial were calculated using a baseline obtained during a silent period immediately preceding the target-tone. Target-tones were 750 Hz, two semitones higher or lower, with the addition of a random jitter (5-20 Hz). Probe-tones were adjusted with an adaptive procedure (weighted 1-up, 1-down) in semitone steps.

Participant's accuracy on the test session was quantified as the proportion of correctly categorized probe-tones. Pupillary responses were pre-processed off-line for correct responses for each block of 50 trials. Errors were excluded from analyses as they could reflect poor attention and add noise to the comparison between groups. Blinks and eye movements were excluded from the data using the Eyelink 1000's default detection algorithm. Trials with missing data on 30% or more samples were also excluded from further analyses. Pupil diameter recordings on remaining trials (CG mean = 81.22%, SD = 10.81. TG mean = 71.83, SD = 18.04, $t_{22} = 1.55$, $p > 0.05$, Cohen's $d = 0.63$) were smoothed using Locally Weighted Scatterplot Smoothing (Lowess) (Cleveland, 1981) with a 10% span (i.e., 350 ms). Baseline pupil dilation was measured at a single sample before the onset of the target tone on each trial. Baseline correction is commonly achieved by subtracting average pupil dilation over a period between 100 ms and 1 second before the event of interest (Win et al., 2018). Averaging reduces the impact of blinks and outliers on baseline measurements but can also be influenced by preparatory changes in arousal and attention prior to stimulus onset (Akdoğan et al., 2016; Irons et al., 2017). To negate the potential of individual and group differences in preparatory activity on the estimation of TEPR amplitude, we used a single sample in the smoothed trace as an absolute baseline at the beginning of each trial[1]. Baseline values were subtracted from the pupil diameter from the onset of the target tone until 500 msec after the offset of the probe tone. Maximum TEPRs were calculated for the period between the onsets of the target and probe tones. Maximum TEPR and baseline values ± 3 standard deviations from individual's mean in each block were excluded as outliers.

Results

Self-Report and Behavioural Data

Mean THI scores in the tinnitus group ranged from 4 to 36 (*Mean* = 19.7, *SD* = 7.7, *Median* = 22). This represents a relatively mild level of subjective tinnitus severity in our sample. Table 1 presents summary statistics for estimated FDTs and accuracy on the DPD task by group and block during the test sessions. Differences between CG and TG listeners on FDTs were small (*M* = 0.016 semitones) and did not reach statistical significance (t_{22}= 0.04, *p* > 0.95, Cohen's *d* = 0.02). To analyse potential differences in the accuracy of DPD across groups, the proportion of correct responses for each participant were subject to a general linear mixed-effects analysis (GLME) with a binomial link function. Group (CG vs. TG), Block (1, 2 & 3) and their interaction were modelled as fixed-effects. Participant was modelled as a random-effect, to control for individual differences in the intercept of the regression equation (Baayen et al., 2008). CG accuracy in block 1 was used as the reference and sliding contrasts were defined using the MASS package in R (Venables, 2002). This yielded a non-significant difference between CG and TG listeners (*ß* = 0.11, *SE* = 0.29, *p* > 0.05). The difference between blocks 1 and 3 (*ß* = 0.35, *SE* = 0.13, *p* < 0.05) was statistically significant, but the difference between blocks 1 and 2 was not (*ß* = 0.23, *SE* = 0.0.12, *p* > 0.05). Group by Block interactions for blocks 2 (*ß* = 0.04, *SE* = 0.23, *p* > 0.05) and 3 (*ß* = 0.21, *SE* = 0.27, *p* > 0.05) did not reach statistical significance. The results indicate comparable frequency detection thresholds and levels of accuracy on the DPD task for CG and TG listeners. Table 1 presents descriptive statistics for FDTs and accuracy on the DPD. Table 5 presents GLME statistics for accuracy by Group and Block.

---

[1] Tonic and TEPR amplitude measured using a single sample and mean over 100ms as the baseline produced equivalent results, suggesting both methods are similarly robust to pre-stimulus variability in pupil dilation.

Table1. Mean frequency detection threshold (FDT) and proportion of correct higher or lower probe-tone responses for tinnitus and control participants by block

		Proportion Correct		
Group	FDT (semitones)	Block 1	Block 2	Block 3
Control Group	0.61 (0.45)	0.88 (0.33)	0.85 (0.34)	0.92 (0.28)
Tinnitus Group	0.62 (0.39)	0.86 (0.35)	0.83 (0.38)	0.88 (0.33)

Pupillometry

Pupil diameter during the calibration procedure was averaged across fixations for each level of display luminance and subject to a linear mixed-effects (LME) analysis with group, display luminance and their interaction modelled as fixed-factors. Participant was modelled as a random-effect to control for individual differences in the intercept of the regression equation (Baayen et al., 2008). Mid luminance displays were used as the reference and sliding contrasts were defined using the MASS package in R. The MLE on pupil dilation yielded a significant increase in high ($ß$ = -3.94, SE = 1.06, $t > 1.96$) and decrease in low ($ß$ = -6.70, SE = 1.06, $t > 1.96$) compared to mid luminance displays. Differences between groups ($ß$ = 3.56, SE = 3.45, $t < 1.96$) and Group by Display Luminance interactions for high ($ß$ = -0.91, SE = 1.50, $t < 1.96$) and low ($ß$ = 0.13, SE = 1.50, $t < 1.96$), compared to mid luminance displays were not significant. These results reveal similar luminance driven changes in pupil diameter in CG and TG listeners. Pupil sizes for mid luminance displays also fell within the dynamic range of listeners in both groups (see Table 2).

Table 2. Mean pupil diameter by Group and Display Luminance during initial calibration. Standard deviation in parenthesis.

	Mean Pupil Diameter	
	CG	TG
High Luminance Display	31.48 (3.49)	34.13 (7.45)
Mid Luminance Display	35.43 (4.56)	38.99 (9.18)
Low Luminance Display	42.09 (6.24)	45.78 (12.07)

Table 3. Statistical effects of Group, Display Luminance and Group * Display Luminance interactions on pupil diameter during calibration.

	Mean Pupil Diameter		
	ß	*SE*	*t*-value
Intercept	35.42	2.44	14.52
Group	3.56	3.45	1.03
M - H Lum.	-3.94	1.06	*3.72
L - M Lum.	6.70	1.06	*6.28
Group * M - H Lum.	-0.91	1.50	-0.61
Group * L - M Lum.	-0.13	1.50	0.08

H = high, M = mid and L = low. Lum = display luminance. Random effect for participants' variance = 53.97, SD = 7.35. * Statistically significant effects on pupil diameter ($|t|$ value > 1.96).

Due to technical issues, pupil dilation failed to record on one block of the DPD for two CG and four TG participants. Data for 2 blocks for these participants and 3 blocks for the remainder were subject to analyses. Figure 2 plots mean baseline-corrected TEPRs for blocks 1 to 3. To contrast tonic pupil dilation and listening effort across groups, mean baseline pupil diameter and maximum TEPR for each participant were subject to separate LME analyses. Group (CG vs. TG), Block (1, 2 & 3) and their interaction were modelled as fixed-effects and participant as a random-effect. Block 1 was used as the reference and sliding contrasts were defined using the MASS package in R. Table 4 presents descriptive statistics and Table 5 the estimated coefficients for the LME analyses of tonic pupil dilation and maximum TEPRs.

The LME on baseline pupil diameter yielded a non-significant difference between TG and CG listeners ($ß = 2.36$, $SE = 2.90$, $t < 1.96$). Comparisons between blocks revealed a significant increase on blocks 2 ($ß = 0.92$, $SE = 0.16$, $t > 1.96$) and 3 ($ß = 0.84$, $SE = 0.16$, $t > 1.96$) compared to block 1. Estimated coefficients for Group by Block 2 ($ß = 1.15$, $SE = 0.31$, $t > 1.96$) and 3 ($ß = 2.20$, $SE = 0.32$, $t > 1.96$) interactions were also significant. Post hoc analyses revealed significant increases in baseline pupil diameter in TG listeners on blocks 2 ($ß = 1.50$, $t = 6.57$, $p < 0.001$) and 3 ($ß = 1.94$, $t = 8.26$, $p < 0.001$) compared to block 1. Differences in CG listeners on blocks 2 ($ß = -0.35$, $t = 1.60$, $p > 0.05$) and 3 ($ß = 0.26$, $t = 1.20$, $p > 0.05$) compared to 1 did not reach statistical significance. These results indicate baseline pupil dilation across blocks was consistent in CG listeners. Baseline pupil dilation among TG listeners in contrast, increased significantly on the last two blocks of testing.

The MLE on TEPRs revealed a significantly higher maximum pupil dilation for TG compared to CG listeners ($\beta = 0.84$, $SE = 0.32$, $t > 1.96$). Estimated coefficients for the difference between blocks 2 ($\beta = -0.03$, $SE = 0.9$, $t < 1.96$) and 3 ($\beta = 0.05$, $SE = 0.09$, $t < 1.96$) compared to 1 did not reach statistical significance. Group by block 2 ($\beta = -0.07$, $SE = 0.17$, $t < 1.96$) and 3 ($\beta = -0.24$, $SE = 0.18$, $t < 1.96$) interactions were also non-significant. These results indicate baseline corrected TEPRs were significantly larger among TG than CG participants across all blocks of testing. The lack of any significant group or by block interactions indicates differences between CG and TG listeners in TEPR amplitude were relatively constant (see Table 4). To investigate the relationship between TEPRs and subjective measures of tinnitus, we calculated a simple regression with THI scores the predictor and the mean of participants' maximum TEPR across blocks the outcome. A significant regression equation was obtained ($F_{1,10} = 16.15$, $p < 0.05$) with an adjusted R^2 of 0.58. This indicates that for every unit increase in THI, maximum pupil dilation in TG listeners increased by 0.8 arbitrary units compared to baseline.

Table 4. Mean baseline pupil diameter (PD) and maximum TEPRs in Blocks 1 to 3 for Control (CG) and Tinnitus (TG) participants.

	Mean Baseline PD (SD)		Max TEPR (SD)	
	CG	TG	CG	TG
Block 1	36.09	38.44	1.63	2.32
	(7.01)	(8.81)	(1.59)	(2.27)
Block 2	36.29	39.94	1.62	2.31
	(5.93)	(9.24)	(1.56)	(2.24)
Block 3	35.71	40.34	1.62	2.23
	(5.38)	(8.55)	(1.82)	(2.10)

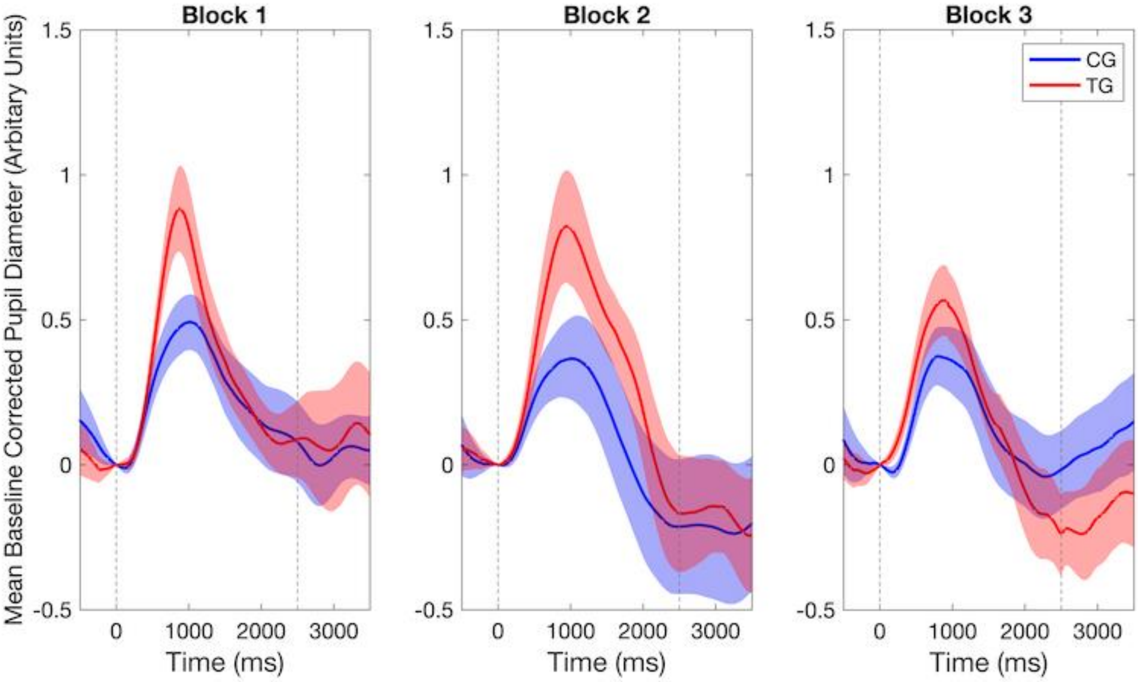

Figure 2 Mean baseline corrected pupil dilation for Control (CG) and Tinnitus (TG) groups by time and block in arbitrary units. Vertical dotted lines denote the offset and onset of the probe and target tones respectively. These data are baseline corrected grand average pupil diameter and are distinct from the trial-by-trial baseline and maximum TEPRs subject to analyses and listed in Table 5.

Table 5. Statistical effects of Group, Block and Group * Block interactions on accuracy, baseline pupil diameter and maximum TEPR during test trials.

	Accuracy (Proportion of correct higher or lower responses)		
	ß	*SE*	*z*-value
Intercept	1.98	0.15	*13.55
Group 1 - 2	-0.11	0.29	0.38
Block 2 - 1	-0.23	0.12	1.95
Block 3 - 1	0.35	0.13	*2.67
Group * Block 2 - 1	-0.04	0.23	0.16
Group * Block 3 - 1	-0.21	0.27	0.80
	Baseline Pupil Diameter		

	ß	*SE*	*t*-value
Intercept	37.17	1.45	*25.60
Group 1 - 2	2.36	2.90	0.81
Block 2 - 1	0.92	0.16	*5.88
Block 3 - 1	0.84	0.16	*5.22
Group * Block 2 - 1	1.15	0.31	*3.68
Group * Block 3 - 1	2.20	0.32	*6.86
	Mean Maximum TEPR		
	ß	*SE*	*t*-value
Intercept	2.24	0.15	*14.05
Group 1 - 2	0.83	0.32	*2.63
Block 2 - 1	-0.03	0.09	0.39
Block 3 - 1	-0.04	0.09	0.52
Group * Block 2 - 1	-0.07	0.17	0.43
Group * Block 3 - 1	-0.24	0.18	1.34

Accuracy: Random effect for participant's variance = 0.33, SD = 0.57. Baseline pupil diameter: Random effect for participants' variance = 50.32, SD = 7.09. Maximum TEPR: Random effect for participant's variance = 0.52, SD = 0.72. * Significant effects ($|z| \geq 1.96$) and ($|t| \geq 1.96$).

Discussion

The aim of the current study was to evaluate the use of pupillometry as an objective index of intrusiveness in tinnitus. To do this, we compared baseline pupil diameter and TEPRs in listeners with chronic tinnitus to age-matched controls without tinnitus during a delayed pitch discrimination task. Frequency differences between target and probe tones were titrated using an adaptive procedure to equate the perceptual difficulty of discrimination across listeners with and without tinnitus. Our results reveal significantly larger TEPRs among listeners with tinnitus compared to age-matched controls. TEPRs for TG and CG listeners diverged during the presentation of the target tone, with the mean group differences peaking approximately 800 ms after its presentation before returning to baseline levels before the onset of the probe tone. Regressing the maximum amplitude of TEPRs with THI scores for listeners with tinnitus, also revealed a significant positive association between subjective reports of tinnitus-disruption and an objective measure of listening effort during a test of auditory short-term memory. In addition to group differences in TEPRs, our data revealed divergent patterns of baseline pupil diameter across blocks in listeners with and without tinnitus. For CG listeners, mean baseline or “tonic” pupil diameter remained constant across blocks of trials. For TG listeners, tonic pupil diameter was significantly larger on blocks two and three than the initial block of testing. These findings demonstrate tinnitus-specific changes in i) phasic reactivity within trials and ii) tonic pupil size across trials.

The results above suggest tinnitus contributes measurable effects on tonic pupil size and reactivity. These effects were obtained for sounds that produced equivalent levels of behavioural accuracy across participants, reducing the potential contribution of tinnitus-related changes in perceptual acuity to differences in mental effort during the maintenance of pure tones. In listeners without tinnitus, TEPR amplitude is positively associated with the number of sounds (Kahneman et al., 1967) or sound sources (Koelewijn et al., 2014) during tests of perception and short-term memory. Task-related increases in phasic pupil dilation have been attributed to an increase in cognitive load, or the mental effort required to encode and maintain sounds over short periods of time (Goldinger & Papesh, 2012; Pichora-Fuller et al., 2016). The increase in TEPR amplitude among TG listeners in our study, is consistent with the prediction that competition between tinnitus and external sounds increases listening effort during tests of auditory short-term memory (Barrett & Pilling, 2017). The level of this competition is likely to reflect attentional mechanisms, which determine the distribution of cognitive resources across internal and external precepts during hearing (Cuny et al., 2004; Kumar et al., 2013; Maudoux et al., 2012; Roberts et al., 2013). In addition to the phasic changes indexed by TEPRs, differences in the magnitude of baseline pupil diameter in TG compared to CG listeners may also reflect attentional processes that operate over blocks of trials. Task related changes in tonic pupil size have been associated with demands on short-term memory (Peysakhovich et al., 2017), levels of uncertainty (Zénon, 2019) and shifts between focussed and exploratory states of attention (Pajkossy et al., 2017). A recent study by Unsworth and Robinson (2016), associated high baseline pupil size with distractibility during a psychomotor vigilance task and elevated levels of intrinsic alertness and sustained attention during a test of vigilance (Unsworth et al., 2020). In the presence of tinnitus, maintaining accuracy on the DPD task in our study requires the maintenance of an attentional set that prioritises external sounds over consecutive blocks of trials. The increase in baseline pupil diameter observed in TG listeners on blocks 2 and 3, may reflect the temporal dynamics of this process and provide an objective measure of tinnitus-related fluctuations in arousal, cognitive-load and attentional set during tests of auditory short-term memory. Further research will be required to establish the diagnostic sensitivity of changes in baseline pupil diameter to competition between tinnitus and external sounds. Our results, however, suggest measures of tonic pupil size and phasic reactivity have the potential to provide complementary information about the impact of tinnitus on listening effort and attentional control during trials and across blocks of testing.

Our results suggest pupillometry holds promise as an objective measure of tinnitus effects. To date, we know of only one other study that has used pupillometry to investigate the impact of tinnitus on listening effort. Juul Jensen and colleagues (Juul Jensen et al., 2018) used a speech-in-noise task to contrast pupil dilation in a sample of hearing-impaired listeners with and without tinnitus. The accuracy of participant's responses was used to equate signal to noise ratios for all listeners at two levels of speech intelligibility; 50% and 95%, and maximum TEPR amplitudes were compared in the tinnitus and control groups at each level of intelligibility. In contrast to our own findings, differences in TEPR amplitudes between the tinnitus and control groups did not reach statistical significance. A further comparison using Growth Curve Analyses to estimate the best-fitting cubic polynomial for TEPRs, revealed a significant *decrease* in pupil dilation among listeners with tinnitus compared to controls. This direction of this effect is opposite to the increase in TEPRs that we observed and is inconsistent with the hypothesis that competition between tinnitus and external sounds elicits an increase in effort during tests of auditory perception and short-term memory.

One explanation for the difference between Juul Jensen et al.'s (2018) result and our own, is that pupillometric measures of listening effort are sensitive to task-demands. Speech recognition is a cumulative process, which involves cognitive resources during the integration and interpretation of sensory input. In addition to auditory short-term memory, report-accuracy depends on linguistic factors, such as lexical similarity, word frequency, and the listener's vocabulary and experience (Kuchinsky et al., 2012). Phasic decreases in pupil size have been observed during high presentation-rates in alternative forced choice tests (Poock, 1973), and during digit span tasks when sequence length exceeds individual's short-term memory (Johnson et al., 2014). Juul Jensen and colleagues reported significantly higher levels of fatigue among listeners with tinnitus compared to controls, suggesting task-difficulty and listener engagement may have contributed to the reduction in phasic pupil diameter in their study. Our stimuli comprised tones at a set level of discriminability that were presented in the absence of noise. Comparing delayed pitch-discrimination accuracy provides a direct test of auditory short-term memory that is independent of linguistic processes. Recording pupillary responses during baseline and retention periods also provides an index of internal processes that operate in the absence of external auditory stimulation. In this situation, group differences in pupillometry can be attributed to the impact of tinnitus on post-perceptual processes, such as the retention and evaluation of information in short-term memory. Differences in the stimuli and the cognitive processes under test, therefore, caution against direct comparison between our own and Juul Jensen et al.'s (2018) results, while providing insights into the task-attributes that are likely to influence the magnitude and direction TEPRs to competition between tinnitus and external sounds. These include selecting tasks designed to isolate specific cognitive functions (i.e., short-term memory) and optimising task difficulty to maximise engagement and minimise fatigue (Murphy et al., 2011; Zénon, 2019).

In addition to differences in the stimuli and task, other factors that may affect the sensitivity of pupillometry to tinnitus include its severity and the incidence of comorbid hearing loss. In our sample, tinnitus-severity was mild, and an important question for future studies is whether group differences in pupillometry generalise to listeners who report higher levels of tinnitus severity. Tinnitus is often preceded by hearing loss and the pitch of the internal percept often correspond to frequency region with the greatest loss (Norena et al., 2002; Schecklmann et al., 2012). To date, only a few studies have investigated the impact of hearing loss on pupil reactivity, and these have produced mixed results (Zekveld et al., 2018). In the current study, tones for the DPD task were selected to fall below frequencies commonly affected by sensorineural hearing loss and tinnitus (Ibraheem & Hassaan, 2017; Nicolas-Puel et al., 2002; Shekhawat et al., 2014). This was done to exclude the impact of perceptual masking of tones by tinnitus on pupil responses or any reduction in tone discriminability associated with hearing impairment. Measuring auditory thresholds and extending our method to include frequencies that target individuals' hearing loss and tinnitus frequency, is likely to provide valuable information about the way sensory impairment and perceptual masking interact with cognitive processes to influence pupil reactivity on tests of short-term memory. The current exploratory results, however, provide preliminary evidence that changes in tonic and phasic pupil size can be used to measure the impact of tinnitus on listening effort and sustained attention on a test of auditory short-term memory. Building on this finding will require studies with larger samples that are representative of the clinical population with a primary complaint of troublesome tinnitus. This should include classifying tinnitus in terms of both aetiology and severity, as well as information about treatments. Developing robust pupillometric measures, is also likely to require a more nuanced understanding of the neural mechanisms that mediate task-related changes in tonic and phasic pupil reactivity and their relationship to other factors that contribute to individual's cognitive and psychological responses to tinnitus. Integrating this understanding with tests that target cognitive processes most susceptible to competition between tinnitus and external sounds, has the potential to provide clinicians an objective measure of severity and treatment efficacy in listeners with tinnitus.

Data Availability

Summary behavioural and pupillometry data are available at the University of Leicester's Research Repository.

Acknowledgments

All authors contributed equally to this work. D.B., M.P. and D.B. contributed to the design of the study. D.B. developed the stimuli and ran the experimental sessions; D.S. contributed software for recording pupil size and removing artefacts; D.B. authored the main paper. All authors discussed the results and implications and commented on the manuscript at all stages. We would like to thank participants from the Leicester branch of the British Tinnitus Association Support Group and wider community. We also thank two anonymous reviewers for their helpful and constructive comments.

References

Akdoğan, B., Balcı, F., & van Rijn, H. (2016). Temporal expectation indexed by pupillary response. *Timing & Time Perception, 4*(4), 354-370.

Andersson, G., Jüris, L., Classon, E., Fredrikson, M., & Furmark, T. (2006). Consequences of suppressing thoughts about tinnitus and the effects of cognitive distraction on brain activity in tinnitus patients. *Audiology and Neurotology, 11*(5), 301-309.

Baayen, R. H., Davidson, D. J., & Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *Journal of memory and language, 59*(4), 390-412.

Barrett, D. J., & Pilling, M. (2017). Evaluating the precision of auditory sensory memory as an index of intrusion in tinnitus. *Ear and hearing, 38*(2), 262-265.

Bast, N., Poustka, L., & Freitag, C. M. (2018). The locus coeruleus–norepinephrine system as pacemaker of attention–a developmental mechanism of derailed attentional function in autism spectrum disorder. *European Journal of Neuroscience, 47*(2), 115-125.

Beatty, J., & Kahneman, D. (1966). Pupillary changes in two memory tasks. *Psychonomic Science, 5*(10), 371-372.

Beatty, J., & Lucero-Wagoner, B. (2000). The pupillary system. *Handbook of psychophysiology, 2*(142-162).

Brainard, D. H. (1997). The psychophysics toolbox. *Spatial vision, 10*(4), 433-436.

Choi, I., Wang, L., Bharadwaj, H., & Shinn-Cunningham, B. (2014). Individual differences in attentional modulation of cortical responses correlate with selective attention performance. *Hearing research, 314*, 10-19.

Cleveland, W. S. (1981). LOWESS: A program for smoothing scatterplots by robust locally weighted regression. *American Statistician, 35*(1), 54.

Cuny, C., Norena, A., El Massioui, F., & Chéry-Croze, S. (2004). Reduced attention shift in response to auditory changes in subjects with tinnitus. *Audiology and Neurotology, 9*(5), 294-302.

Eggermont, J. J. (2019). *The auditory brain and age-related hearing impairment*. Academic Press.

Erlandsson, S. I., Hallberg, L. R., & Axelsson, A. (1992). Psychological and audiological correlates of perceived tinnitus severity. *Audiology, 31*(3), 168-179.

Gazzaley, A. (2011). Influence of early attentional modulation on working memory. *Neuropsychologia, 49*(6), 1410-1424.

Goldinger, S. D., & Papesh, M. H. (2012). Pupil dilation reflects the creation and retrieval of memories. *Current directions in psychological science, 21*(2), 90-95.

Granholm, E., Asarnow, R. F., Sarkin, A. J., & Dykes, K. L. (1996). Pupillary responses index cognitive resource limitations. *Psychophysiology, 33*(4), 457-461.

Hallam, R., Jakes, S., & Hinchcliffe, R. (1988). Cognitive variables in tinnitus annoyance. *British Journal of Clinical Psychology, 27*(3), 213-222.

Harris, J. D. (1948). Discrimination of pitch: suggestions toward method and procedure. *The American journal of psychology, 61*(3), 309-322.

Hayes, T. R., & Petrov, A. A. (2016). Mapping and correcting the influence of gaze position on pupil size measurements. *Behavior Research Methods, 48*(2), 510-527.

Heeren, A., Maurage, P., Perrot, H., De Volder, A., Renier, L., Araneda, R., Lacroix, E., Decat, M., Deggouj, N., & Philippot, P. (2014). Tinnitus specifically alters the top-down executive control sub-component of attention: evidence from the attention network task. *Behavioural brain research, 269*, 147-154.

Hibbert, A., Vesala, M., Kerr, M., Fackrell, K., Harrison, S., Smith, H., & Hall, D. A. (2020). Defining Symptom Concepts in Chronic Subjective Tinnitus: Web-Based Discussion Forum Study. *Interactive journal of medical research, 9*(1), e14446.

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 353*(1373), 1257-1270.

Ibraheem, O. A., & Hassaan, M. R. (2017). Psychoacoustic characteristics of tinnitus versus temporal resolution in subjects with normal hearing sensitivity. *International archives of otorhinolaryngology, 21*(2), 144-150.

Irons, J. L., Jeon, M., & Leber, A. B. (2017). Pre-stimulus pupil dilation and the preparatory control of attention. *PLoS One, 12*(12), e0188787.

Jilek, M., Šuta, D., & Syka, J. (2014). Reference hearing thresholds in an extended frequency range as a function of age. *The Journal of the Acoustical Society of America, 136*(4), 1821-1830.

Johnson, E. L., Miller Singley, A. T., Peckham, A. D., Johnson, S. L., & Bunge, S. A. (2014). Task-evoked pupillometry provides a window into the development of short-term memory capacity. *Frontiers in psychology, 5*, 218.

Joseph, S., Kumar, S., Husain, M., & Griffiths, T. D. (2015). Auditory working memory for objects vs. features. *Frontiers in neuroscience, 9*, 13.

Juul Jensen, J., Callaway, S. L., Lunner, T., & Wendt, D. (2018). Measuring the impact of tinnitus on aided listening effort using pupillary response. *Trends in hearing, 22*, 2331216518795340.

Kaernbach, C. (1991). Simple adaptive testing with the weighted up-down method. *Perception & psychophysics, 49*(3), 227-229.

Kahneman, D., Beatty, J., & Pollack, I. (1967). Perceptual deficit during a mental task. *Science, 157*(3785), 218-219.

Kennedy, V., Chéry-croze, S., Stephens, D., Kramer, S., Thai-van, H., & Collet, L. (2005). Development of the International Tinnitus Inventory (ITI): a patient-directed problem questionnaire. *Audiological Medicine, 3*(4), 228-237.

Kleiner, M., Brainard, D., & Pelli, D. (2007). What's new in Psychtoolbox-3?

Koelewijn, T., Shinn-Cunningham, B. G., Zekveld, A. A., & Kramer, S. E. (2014). The pupil response is sensitive to divided attention during speech processing. *Hearing research, 312*, 114-120.

Kuchinsky, S. E., Vaden Jr, K. I., Keren, N. I., Harris, K. C., Ahlstrom, J. B., Dubno, J. R., & Eckert, M. A. (2012). Word intelligibility and age predict visual cortex activity during word listening. *Cerebral cortex, 22*(6), 1360-1371.

Kumar, S., Joseph, S., Pearson, B., Teki, S., Fox, Z., Griffiths, T., & Husain, M. (2013). Resource allocation and prioritization in auditory working memory. *Cognitive neuroscience, 4*(1), 12-20.

Kursawe, M. A., & Zimmer, H. D. (2015). Costs of storing colour and complex shape in visual working memory: Insights from pupil size and slow waves. *Acta Psychologica, 158*, 67-77.

Maudoux, A., Lefebvre, P., Cabay, J.-E., Demertzi, A., Vanhaudenhuyse, A., Laureys, S., & Soddu, A. (2012). Auditory resting-state network connectivity in tinnitus: a functional MRI study. *PLoS One, 7*(5), e36222.

McCormack, A., Edmondson-Jones, M., Somerset, S., & Hall, D. (2016). A systematic review of the reporting of tinnitus prevalence and severity. *Hearing research, 337*, 70-79.

McFerran, D. J., Stockdale, D., Holme, R., Large, C. H., & Baguley, D. M. (2019). Why is there no cure for tinnitus? *Frontiers in neuroscience, 13*, 802.

Murphy, P. R., Robertson, I. H., Balsters, J. H., & O'connell, R. G. (2011). Pupillometry and P3 index the locus coeruleus–noradrenergic arousal function in humans. *Psychophysiology, 48*(11), 1532-1543.

Myers, N. E., Stokes, M. G., & Nobre, A. C. (2017). Prioritizing information during working memory: beyond sustained internal attention. *Trends in cognitive sciences, 21*(6), 449-461.

Nicolas-Puel, C., Faulconbridge, R. L., Guitton, M., Puel, J.-L., Mondain, M., & Uziel, A. (2002). Characteristics of tinnitus and etiology of associated hearing loss: a study of 123 patients. *The international tinnitus journal, 8*(1), 37-44.

Norena, A., Micheyl, C., Chéry-Croze, S., & Collet, L. (2002). Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. *Audiology and Neurotology, 7*(6), 358-369.

Pajkossy, P., Szőllősi, Á., Demeter, G., & Racsmány, M. (2017). Tonic noradrenergic activity modulates explorative behavior and attentional set shifting: Evidence from pupillometry and gaze pattern analysis. *Psychophysiology, 54*(12), 1839-1854.

Peavler, W. S. (1974). Individual differences in pupil size and performance. In *Pupillary dynamics and behavior* (pp. 159-175). Springer.

Peysakhovich, V., Vachon, F., & Dehais, F. (2017). The impact of luminance on tonic and phasic pupillary responses to sustained cognitive load. *International Journal of Psychophysiology, 112*, 40-45.

Pichora-Fuller, M. K., Kramer, S. E., Eckert, M. A., Edwards, B., Hornsby, B. W., Humes, L. E., Lemke, U., Lunner, T., Matthen, M., & Mackersie, C. L. (2016). Hearing impairment and cognitive energy: The framework for understanding effortful listening (FUEL). *Ear and hearing, 37*, 5S-27S.

Poock, G. K. (1973). Information processing vs pupil diameter. *Perceptual and Motor Skills, 37*(3), 1000-1002.

Prins, N. (2014). Kingdom, FAA (2009). Palamedes: Matlab routines for analyzing psychophysical data

Roberts, L. E., Husain, F. T., & Eggermont, J. J. (2013). Role of attention in the generation and modulation of tinnitus. *Neuroscience & Biobehavioral Reviews, 37*(8), 1754-1773.

Saunders, J. C. (2007). The role of central nervous system plasticity in tinnitus. *Journal of communication disorders, 40*(4), 313-334.

Schecklmann, M., Vielsmeier, V., Steffens, T., Landgrebe, M., Langguth, B., & Kleinjung, T. (2012). Relationship between audiometric slope and tinnitus pitch in tinnitus patients: insights into the mechanisms of tinnitus generation. *PLoS One, 7*(4), e34878.

Shekhawat, G. S., Searchfield, G. D., & Stinear, C. M. (2014). The relationship between tinnitus pitch and hearing sensitivity. *European Archives of Oto-Rhino-Laryngology, 271*(1), 41-48.

Stockdale, D., McFerran, D., Brazier, P., Pritchard, C., Kay, T., Dowrick, C., & Hoare, D. J. (2017). An economic evaluation of the healthcare cost of tinnitus management in the UK. *BMC health services research, 17*(1), 1-9.

Townsend, J., & Ashby, F. (1978). Methods of modeling capacity in simple processing systems In Castellan J & Restle F (Eds.), Cognitive theory (Vol. 3, pp. 200–239)

Ueyama, T., Donishi, T., Ukai, S., Ikeda, Y., Hotomi, M., Yamanaka, N., Shinosaki, K., Terada, M., & Kaneoke, Y. (2013). Brain regions responsible for tinnitus distress and loudness: a resting-state FMRI study. *PLoS One, 8*(6), e67778.

Unsworth, N., Miller, A. L., & Robison, M. K. (2020). Individual differences in lapses of sustained attention: Ocolumetric indicators of intrinsic alertness. *Journal of Experimental Psychology: Human Perception and Performance, 46*(6), 569.

Vanneste, S., & De Ridder, D. (2012). The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. *Frontiers in systems neuroscience, 6*, 31.

Venables, W. R. (2002). BD (2002). Modern Applied Statistics with S. *New York: Springer Science & Business Media, 200*, 183-206.

Walpurger, V., Hebing-Lennartz, G., Denecke, H., & Pietrowsky, R. (2003). Habituation deficit in auditory event-related potentials in tinnitus complainers. *Hearing research, 181*(1-2), 57-64.

Watts, E. J., Fackrell, K., Smith, S., Sheldrake, J., Haider, H., & Hoare, D. J. (2018). Why is tinnitus a problem? A qualitative analysis of problems reported by tinnitus patients. *Trends in hearing, 22*, 2331216518812250.

Zekveld, A. A., Koelewijn, T., & Kramer, S. E. (2018). The pupil dilation response to auditory stimuli: current state of knowledge. *Trends in hearing, 22*, 2331216518777174.

Zénon, A. (2019). Eye pupil signals information gain. *Proceedings of the Royal Society B, 286*(1911), 20191593.

Zhu, D., Moore, S. T., & Raphan, T. (1999). Robust pupil center detection using a curvature algorithm. *Computer methods and programs in biomedicine, 59*(3), 145-157.