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Caractérisation et objectivation de l'acouphène subjectif chronique idiopathique

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Cette thèse intitulée :

Caractérisation et objectivation de l'acouphène subjectif chronique idiopathique

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RÉSUMÉ

Objectif: Cette thèse avait pour objectif principal la mise en oeuvre et la validation de la faisabilité, chez l'humain, du paradigme de modulation du réflexe acoustique de sursaut par un court silence (GPIAS) afin de l'utiliser comme mesure objective de l'acouphène. Pour ce faire, trois expériences ont été réalisées. L'expérience 1 avait pour objectif de valider l'inhibition du réflexe de sursaut par un court silence chez des participants humains normo-entendants (sans acouphène) lors de la présentation d'un bruit de fond centré en hautes et en basses fréquences afin de déterminer les paramètres optimaux du paradigme. L'expérience 2 avait pour objectif de valider la précision et la fidélité d'une méthode de caractérisation psychoacoustique de l'acouphène (appariement en intensité et en fréquence). Finalement, l'expérience 3 avait pour objectif d'appliquer le paradigme d'objectivation de l'acouphène par le réflexe de sursaut à des participants atteints d'acouphènes chroniques en utilisant les techniques développées lors des expériences 1 et 2. **Méthodologie :** L'expérience 1 incluait 157 participants testés dans l'une des conditions de durée du court silence (5, 25, 50, 100, 200 ms) et dans l'un des deux paradigmes (court silence à l'intérieur du bruit de fond ou suivant celui-ci) à l'aide de bruits de fond en hautes et en basses fréquences. L'expérience 2 incluait deux groupes de participants avec acouphène, l'un musicien (n=16) et l'autre sans expérience musicale (n=16) ainsi qu'un groupe de simulateur sans acouphène (n=18). Ils tous ont été évalués sur leur capacité d'appariement en fréquence et en intensité de leur acouphène. Les mesures ont été reprises chez un sous-groupe de participants plusieurs semaines plus tard. L'expérience 3 incluait 15 participants avec acouphène et 17 contrôles évalués à l'aide du paradigme d'inhibition du réflexe de sursaut à l'aide d'un court silence (GPIAS). Les paramètres psychoacoustiques de l'acouphène ont également été mesurés. Toutes les mesures ont été reprises plusieurs mois plus tard chez un sous-groupe de participants. **Résultats** : Expérience 1 : le paradigme d'inhibition du réflexe acoustique de sursaut par un court silence est applicable chez l'humain normo-entendant. Expérience 2 : les mesures psychoacoustiques informatisées de l'acouphène incluant l'appariement en fréquence et en intensité sont des mesures précises et fidèles du percept de l'acouphène. Expérience 3 : un déficit d'inhibition au paradigme du GPIAS a été retrouvé chez le groupe de participants avec acouphène pour les bruits de fond en hautes et en basses fréquences au test et au retest. Les mesures d'appariement en fréquence ont révélé un acouphène dont la fréquence prédominante était d'environ 16 000 Hz chez la plupart des participants. **Discussion** : Il est possible d'appliquer le paradigme d'inhibition du réflexe acoustique de sursaut par un court silence à des participants humains atteints d'acouphène, tel qu'il est utilisé en recherche animale pour « objectiver » la présence d'acouphène. Toutefois, le déficit d'inhibition mesuré n'est pas spécifique à la fréquence de l'acouphène lorsque validé à partir des données d'appariement psychoacoustique. Nos résultats soulèvent des questions quant à l'interprétation originale du paradigme pour détecter la présence d'un acouphène chez les animaux.

Mots-clés: Acouphène, Réflexe acoustique de sursaut, Psychoacoustique, Appariement en fréquence, Appariement en intensité, Gap-Startle, Near-Gap, Gap-following, Startle-inhibition, Diagnostic

ABSTRACT

Objective: The main objective of this thesis was the implementation and validation of applying the gap prepulse inhibition of the acoustic startle reflex (GPIAS) paradigm in humans, in order to objectively measure tinnitus. To do this, three experiments were carried out. Experiment 1 was designed to validate the inhibition of the acoustic startle reflex by using a short gap within high and low frequency narrowband noise in normal hearing humans (without tinnitus) to determine the optimal paradigm parameters. Experiment 2 was designed to validate the accuracy and the test-retest fidelity of a tinnitus psychoacoustic characterization method (intensity and frequency matching). Finally, Experiment 3 applied the GPIAS paradigm to participants with chronic tinnitus using the techniques developed in experiments 1 and 2. **Methods:** Experiment 1 included 157 participants tested with only one gap duration (5, 25, 50, 100, 200 ms) and with one of the two paradigms (gap imbedded in the background noise or following it) including high and low frequencies background noise. Experiment 2 included two groups of participants with tinnitus, one group consisting of musicians (n=16) and one group without musical experience (n=16). A third group consisted of adults who were instructed to simulate having tinnitus (n = 18). Tinnitus pitch and intensity matching abilities were assessed for all participants. A subgroup of participants was retested several weeks later. Experiment 3 included 15 participants with tinnitus and 17 controls assessed with the GPIAS. The psychoacoustic parameters of tinnitus were also measured. A subgroup of participants was retested several weeks later. **Results**: Experiment 1: the GPIAS is applicable in humans with normal hearing. Experiment 2: psychoacoustic measurements of tinnitus frequency and intensity using a computerized matching procedure produced precise and accurate measurements of the tinnitus percept. Experiment 3: an inhibition deficit was found using the GPIAS paradigm in the tinnitus group for background noise of high and low frequency compared to the control group, at test and retest. The frequency matching measurements revealed a 16,000 Hz tinnitus predominant frequency for most tinnitus participants. **Discussion:** It is possible to apply the gap prepulse inhibition of the startle reflex paradigm on human participants with tinnitus, as used in animal research to "objectify" the presence of tinnitus. However, the inhibition deficit found in the tinnitus group was not specific to their tinnitus frequency. This was validated by psychoacoustic tinnitus pitch matching. Our results question the original interpretation of the GPIAS paradigm for objectifying the presence of tinnitus.

Keywords: Tinnitus, Startle reflex, Psychoacoustic, Pitch matching, Intensity matching, Gap-Startle, Near-Gap, Gap-Following, Startle-inhibition, Diagnostic

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LISTES DES ABBRÉVIATIONS

Ag/AgCl: Silver Metal / Silver Chloride
ANOVA: Analysis of Variance
ANSI: American National Standard Institute
ASR : Acoustic Startle Reflex
BDI-II: Beck Depression Inventory Second Edition
CFI : Canadian Foundation Innovation
CI: Confidence Interval
cm: Centimeters
CSST : Commission de la santé et de la sécurité au travail
dB : Decibel
dB(A): Decibel with using the A-weighting frequency curve
EMG : Electromyographic
FRQS : Fonds de Recherche Québec Santé
GABAA: Gamma-Aminobutyric Acid
GPIAS: Gap-Prepulse Inhibition of the Acoustic Startle
HL : Hearing Level
Hz : Hertz
IR : Inhibition résiduelle
IRSST: Institut de recherche Robert-Sauvé en santé et en sécurité du travail du Québec
ISI : Inter-Stimulus-Interval
ITI : Inter-Trial-Interval
K channels: Potassium channels
kHz : Kilohertz
ms : Milliseconds
min: Minutes
mm: Millimeters
mV ou uV: microvolts
η^2 : Partial eta-square
n.s. : Non-Significant
NSERC: Natural Sciences and Engineering Research Council of Canada
p: P-value
PPI: Prepulse Inhibition
RMS: Root Mean Square
s: Seconds
SD: Standard Deviation
SEM: Standard Error of the Mean
SL : Sensation Level
SPL : Sound Pressure Level
SS: Startle Sound
THQ: Tinnitus Handicap Questionnaire
VAS: Visual Analog Scale
WCBO : Worker Compensation Board of Ontario

Cette thèse est dédiée à tous ceux que le silence a quittés ...

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1. INTRODUCTION

1.1 QU'EST-CE QUE L'ACOUPHÈNE?

1.1.1 Définition et prévalence

L'acouphène est défini comme la perception d'un son dans l'oreille ou dans la tête sans présence de source sonore externe (Jastreboff, 1990). Lorsque les sons entendus proviennent d'une source interne située à l'intérieur du corps (p. ex. rythme cardiaque, circulation sanguine, etc.), ce type d'acouphène est dénommé « objectif » (Bento, Sanchez, Miniti, & Tedesco-Marchesi, 1998; De Ridder, et coll. 2010; Forte, Turner, & Liu, 1989; Sismanis, Stamm, & Sobel, 1994). Toutefois, lorsque les sons entendus ne proviennent d'aucune source interne ou externe au corps, ces acouphènes sont appelés « subjectifs ». Les acouphènes subjectifs sont généralement décrits par les patients comme un bruit, un sifflement, un bourdonnement à une oreille, aux deux oreilles ou dans la tête (Meikle & Taylor-Walsh, 1984; Stouffer & Tyler, 1990) sans toutefois qu'il soit possible d'enregistrer un signal sonore. La temporalité des acouphènes subjectifs est parfois définie comme transitoire ou chronique (Gilles et coll., 2012). Les acouphènes subjectifs transitoires sont généralement décrits comme des sons qui apparaissent de manière spontanée ou à la suite d'un évènement traumatique et disparaissent sans recours à des traitements après quelques secondes, minutes, heures et mêmes jours. Les acouphènes subjectifs chroniques font référence aux acouphènes continus qui se prolongent sur une longue période de temps, généralement 6 mois ou plus. La prévalence de l'acouphène subjectif dans la population générale est estimée entre 10 à 20% et ce,

dans la plupart des pays du monde (pour une revue des études épidémiologiques: Hoffman & Reed, 2004; Sanchez, 2004). Au Québec, la prévalence de ce trouble est estimée à 12,9% des Québécois (Paré & Levasseur, 2001). De plus, des études ont démontré qu'elle pouvait atteindre 50% chez une population de travailleurs exposés au bruit (Axelsson & Sandh, 1985; McShane, Hyde, & Alberti, 1988; Mrena, Ylikoski, Makitie, Pirvola, & Ylikoski, 2007). En effet, il est connu que la perte auditive est un important facteur de risque de l'acouphène (Chung, Gannon, & Mason, 1984; Sindhusake et coll., 2003). L'exposition au bruit étant l'une des principales causes de surdité (Rabinowitz, 2000), il est fort envisageable que les populations atteintes de surdité liée à l'exposition au bruit en milieu de travail soient plus à risque d'acouphène. Cette relation n'est pourtant pas directe: bien que toute personne étant atteinte d'acouphène possède un certain degré de perte auditive ou de dommage auditif (mesurable ou non par audiométrie), une certaine proportion de patients atteints de surdité ne développeront jamais d'acouphène (Hoffman & Reed, 2004). La prévalence de l'acouphène est également plus élevée chez les personnes plus âgées, chez les fumeurs, les hypertendus, les personnes atteintes de troubles auditifs, les personnes exposées aux bruits au travail ou durant leurs loisirs et les personnes atteintes de troubles anxieux (Shargorodsky, Curhan, & Farwell, 2010).

1.1.2. Comorbidités : l'acouphène un problème sérieux

L'acouphène jugé incommodant et dérangeant au point de nuire significativement à la vie quotidienne est estimé entre 1 et 2% de la population générale (Axelsson & Ringdahl, 1989; Johansson & Arlinger, 2003). Au Québec, ce pourcentage atteint 1,3% soit 78 000 Québécois (Paré & Levasseur, 2001). Les comorbidités connues associées

à l'acouphène incluent: une grande détresse psychologique (Langguth, Kleinjung, et coll., 2007; Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011), des troubles du sommeil (Hébert & Carrier, 2007; Hébert, Fullum, & Carrier, 2011), des difficultés de perception de la parole (Huang et coll., 2007), de l'hypersensibilité auditive (Hébert, Fournier, & Norena, 2013) et du stress (Hébert, Paiement, & Lupien, 2004). Pour un adulte sur 100, l'ampleur de la détresse liée à l'acouphène serait telle qu'elle empêcherait l'individu de vivre une vie normale (Vio & Holme, 2005). Certains cas de suicide lié à la présence d'acouphène extrêmement dérangeant ont également été rapportés (Pridmore, Walter, & Friedland, 2012). La prévalence d'acouphène *incommodant* est également plus élevée chez certaines populations, notamment chez les travailleurs québécois exposés au bruit dont la prévalence est estimée à 10% soit 10 fois plus que dans la population générale (Michel et coll., 2014).

1.1.3 Un fardeau économique

Le fardeau économique de l'acouphène sur la société a récemment été évalué dans une étude réalisée aux Pays-Bas (Maes, Cima, Vlaeyen, Anteunis, & Joore, 2013). Le coût sociétal de l'acouphène a été jugé comme substantiel et estimé à 6,8 milliards d'Euros en 2009, ce qui représente trois fois plus de coûts que ceux associés aux troubles de la personnalité limite (van Asselt, Dirksen, Arntz, & Severens, 2007) et deux fois plus que ceux associés aux maux de dos (Lambeek et coll., 2011). L'acouphène représente également un poids financier important pour certaines organisations gouvernementales notamment les anciens combattants et les organismes de santé et sécurité au travail. Par exemple, les paiements de prestations d'invalidité pour les acouphènes et la perte auditive offertes par le département américain des Anciens Combattants (VA) ont dépassé 1,2

milliards de dollars en 2009 et continuent d'augmenter (Yankaskas, 2013). Les projections les plus récentes estiment que les prestations atteindront 2,75 milliards de dollars en 2016 (American Tinnitus Association, 2013). L'indemnisation offerte au personnel militaire est exclusivement basée sur la déclaration de bonne foi de la présence de l'acouphène par le militaire (Yankaskas, 2013). L'apparition de l'acouphène suivant une exposition au bruit en milieu de travail a également des répercussions sur les demandes d'indemnisation des travailleurs auprès des organismes de santé et sécurité au travail. En effet, une étude réalisée à partir de la base de données du "Worker Compensation Board of Ontario" (WCBO) a examiné cette prévalence (McShane, et coll., 1988) : sur un échantillon de près de 3 466 demandes d'indemnisation pour perte auditive, la moitié (49.8%) soulignait la présence d'acouphène. La WCBO offre jusqu'à 2% d'indemnisation supplémentaire aux personnes atteintes d'acouphène continuel sur le pourcentage total de déficience permanente accordée, ce qui peut représenter des milliers de dollars par personne. Au Québec, la Commission de la santé et de la sécurité au travail (CSST) couvre des tests auditifs supplémentaires (~400$ pour une évaluation auditive), des masqueurs d'acouphène (~1200$ par masqueur) et plusieurs autres thérapies selon certains critères (~90$/heure). Les indemnisations pour acouphène reposent présentement sur un formulaire envoyé à la CSST par l'audiologiste ou par l'oto-rhino-laryngologiste sans qu'aucune évaluation de l'acouphène soit requise.

1.1.4 Conclusions

En somme, la prévalence élevée de l'acouphène dans la population générale, les comorbidités importantes affectant les personnes sévèrement atteintes et le fardeau financier que représente l'acouphène pour la société permettent de considérer

l'acouphène comme un problème de santé publique important. Toutefois, il n'existe actuellement aucune mesure objective fiable de la présence de l'acouphène, ne laissant donc que des mesures subjectives et les récits des patients pour pouvoir l'évaluer. Il y a donc consensus à travers la communauté scientifique sur l'importance primordiale de mettre au point une mesure objective du phénomène. Cette mesure est essentielle à l'élaboration d'un diagnostic fiable, d'un suivi adéquat de la progression du trouble, et d'une mesure du succès de différents traitements et approches. L'état actuel des connaissances sur les mesures de l'acouphène chez l'humain et l'animal est présenté dans les sections suivantes.

1.2 MESURES DE L'ACOUPHÈNE CHEZ L'HUMAIN

1.2.1 Rapports du patient

Les patients éprouvent beaucoup de difficultés à rapporter et décrire leur acouphène. Cette caractérisation est difficile puisqu'elle s'appuie sur l'expérience du patient et du contexte dans lequel il évolue. Les résultats de deux études réalisées dans deux états bien distincts des États-Unis auprès de centaines de patients atteints d'acouphène sont fort révélateurs à ce sujet (Meikle & Taylor-Walsh, 1984; Stouffer & Tyler, 1990). Ces deux études consistaient à demander au participant d'apposer une étiquette à leur acouphène. Ainsi l'étiquette « vague de l'océan » était fréquemment rapportée par les patients qui habitaient la côte ouest des États-Unis vivant près de l'océan Pacifique en Orégon (Meikle & Taylor-Walsh, 1984), alors que celle-ci n'était pas rapportée par les patients vivant sur les plaines américaines de l'Iowa (Stouffer &

Tyler, 1990). Inversement, l'étiquette « son de criquet » était rapportée avec une fréquence plus importante par ceux qui vivaient sur les plaines américaines. Le contexte semble donc être un facteur déterminant dans la description de l'acouphène. Cette difficulté à caractériser et décrire des sons par les patients atteints d'acouphène n'est pas limitée à la seule description de l'acouphène, mais inclut également les sons externes non familiers. Ainsi, lorsque l'on demande à des patients d'émettre une étiquette sur différents sons purs de faible intensité, mais audible, plusieurs éprouvent une grande difficulté à effectuer la tâche (Wahlström & Axelsson, 1995). En effet, une proportion importante de patients appose l'étiquette de « bruit » à la présentation de « sons purs ». Le rapport du patient est une partie essentielle de l'évaluation clinique de l'acouphène (Henry, Zaugg, & Schechter, 2005). Toutefois, considérant les influences de l'expérience et du contexte sur celui-ci, il semble important que cette mesure soit jointe à d'autres afin d'établir le meilleur portrait clinique possible.

1.2.2 Mesures psychoacoustiques

L'acouphène peut également être mesuré à l'aide de différentes techniques psychoacoustiques. En effet, il est possible d'estimer la fréquence et l'intensité de l'acouphène perçu par un patient en utilisant différentes techniques qui permettent d'apparier leur perception à des sons externes variant en fréquence et en intensité. Le niveau minimum de masquage est une autre mesure psychoacoustique qui permet de déterminer le niveau minimum d'intensité requis pour qu'un bruit masque tout juste l'acouphène. Finalement, l'inhibition résiduelle est la quatrième et dernière mesure psychoacoustique qui permet, dans certains cas, de faire disparaître ou diminuer l'intensité de l'acouphène pendant quelques secondes à quelques minutes.

1.2.2.1 Appariement en fréquences

Les premières études psychoacoustiques réalisées afin d'estimer la tonalité de l'acouphène utilisaient une méthode de choix forcé ou d'ajustement (Burns, 1984; Henry, Fausti, Flick, Helt, & Ellingson, 2000; Henry, Flick, Gilbert, Ellingson, & Fausti, 2001; Henry, Rheinsburg, & Ellingson, 2004; Karatas & Deniz, 2011; König, Schaette, Kempter, & Gross, 2006; Martines et coll., 2010; Mitchell, Vernon, & Creedon, 1993; Moore, Vinay, & Sandhya, 2010; Nageris, Attias, & Raveh, 2010; Newman, Wharton, Shivapuja, & Jacobson, 1994; Pan et coll., 2009; Penner & Bilger, 1992; Penner & Klafter, 1992; Penner & Saran, 1994; Savastano, 2008; Schecklmann et coll., 2012; Shekhawat, Searchfield, & Stinear, 2014; Tyler & Conrad-Armes, 1983b; Vernon & Meikle, 2003; Ward & Baumann, 2009). La technique de choix forcé consiste essentiellement à présenter deux sons de fréquences différentes au participant et de lui faire choisir laquelle, parmi ces deux fréquences, correspond le mieux à la tonalité de son acouphène. Une fois le choix réalisé, la fréquence choisie est conservée puis présentée de nouveau, mais cette fois-ci avec une nouvelle fréquence de comparaison. Le choix final est obtenu lorsque la fréquence choisie est la même et ce, peu importe la fréquence de comparaison présentée ou lorsqu'un certain critère de constance est atteint (Tyler & Conrad-Armes, 1983b). La méthode d'ajustement consiste à faire varier la fréquence d'un son pur présenté de manière continue afin de l'apparier à la fréquence prédominante de l'acouphène (Tyler & Conrad-Armes, 1983b). Généralement, cette technique implique l'utilisation d'un bouton de réglage ou d'un oscilloscope afin de faciliter le changement en continu de la fréquence par le participant. Ces premières études ont permis de démontrer que la fréquence prédominante de l'acouphène est fréquemment située à

l'intérieur des fréquences qui sont atteintes par la perte auditive. Toutefois, la fidélité test-retest de ces deux méthodes s'est avérée faible comprenant une grande variabilité entre les résultats obtenus au test et ceux au retest (Henry, et coll., 2000; Henry, et coll., 2001; Mitchell, et coll., 1993; Nageris, et coll., 2010). Pour cette raison, l'appariement en fréquence n'est pas une mesure clinique recommandée et, de ce fait, est peu utilisé pour mesurer l'efficacité des traitements lors d'essai clinique (Langguth, Goodey, et coll., 2007).

Une nouvelle méthode centrée sur le patient a été utilisée dans de nombreuses recherches récentes (Heijneman, de Kleine, Wiersenga-Post, & van Dijk, 2013; Kay, Searchfield, Coad, & Koyabashi, 2008; Moffat et coll., 2009; Noreña, Micheyl, Chéry-Croze, & Collet, 2002; Roberts, Moffat, Baumann, Ward, & Bosnyak, 2008; Roberts, Moffat, & Bosnyak, 2006; Sereda et coll., 2011; Weisz, Hartmann, Dohrmann, Schlee, & Norena, 2006; Zhou, Henin, Long, & Parra, 2011). Cette technique appelée cotation d'appréciation (ou « likeness rating ») consiste en une échelle de 0 à 10 d'appréciation (0 = ne correspond pas du tout à mon acouphène à 10 = correspond parfaitement à mon acouphène) et permet au participant de coter chaque son présenté de 0.25 à 16 kHz par pas de demi-octave. La majorité des sons sont présentés à trois reprises et couvrent presque l'entièreté du champ fréquentiel audible humain. De plus, cette technique permet de déterminer la contribution respective de chacune des fréquences qui composent l'acouphène plutôt que de devoir choisir la fréquence dominante comme dans la technique du choix forcé ou celle d'ajustement. La résultante permet d'obtenir un « spectre » de l'acouphène dans lequel il est possible d'observer l'ensemble des fréquences qui le composent en plus de déterminer la ou les fréquences prédominantes (p.

ex. celle dont la cote est la plus élevée). Cette technique a d'ailleurs permis d'établir une relation directe entre le spectre fréquentiel de l'acouphène et la perte auditive (Noreña, et coll., 2002). En effet, les fréquences qui composent le spectre de l'acouphène sont en miroir de la perte auditive (Kay, et coll., 2008; Noreña, et coll., 2002; Roberts, et coll., 2008; Roberts, et coll., 2006; Sereda, et coll., 2011; Zhou, et coll., 2011) et ce, même lorsque les seuils auditifs cliniques standards sont dans les limites de la normale (Weisz, et coll., 2006). Cette technique permet au clinicien d'évaluer la concordance entre la perte auditive et les fréquences constituant l'acouphène. Considérant que cette technique présente des sons dont la fréquence varie par pas de demi-octave, la précision fréquentielle pourrait être insuffisante pour bien caractériser la fréquence prédominante de l'acouphène comparativement à une technique d'ajustement. Une étude comparative de la précision fréquentielle entre ces deux techniques s'avère essentielle. De plus, une seule étude évaluant la fidélité test-retest de la technique « cotation d'appréciation » a été effectuée et a démontré des résultats mitigés : de très faibles corrélations pour les fréquences faiblement cotées et des corrélations très fortes pour les fréquences dont les cotations étaient élevées (Roberts, et coll., 2008).

1.2.2.2 Appariement en intensité

Il est possible d'apparier l'intensité perçue de l'acouphène à celle d'un son externe. La technique consiste à présenter un son pur et à varier son niveau sonore jusqu'à l'obtention d'un niveau semblable à celui de l'acouphène (Henry, et coll., 2000; Henry et coll., 2009; Henry, et coll., 2004; Penner, 1988; Penner & Bilger, 1992; Penner & Klafter, 1992; Penner & Saran, 1994; Roberts, et coll., 2008). Certaines techniques sont dirigées par l'expérimentateur qui contrôle l'intensité du son présenté et demande au

patient de lui indiquer lorsque le niveau correspond à celui de son acouphène. D'autres techniques permettent plutôt au patient de contrôler par lui-même le niveau sonore, généralement par un bouton de réglage. La plupart des études ont démontré que le niveau mesuré varie généralement entre 5 à 10 dB au-dessus du seuil auditif (dB SL) (Hallam, Jakes, Chambers, & Hinchcliffe, 1985; Newman, et coll., 1994; Tyler & Conrad-Armes, 1983a, 1983b). Il n'y aurait qu'une faible corrélation entre le niveau mesuré en dB SL et le niveau subjectif rapporté par le patient (Andersson, 2003). Certaines études ont démontré une très bonne fidélité test-retest des mesures d'appariement en intensité : des différences inférieures à 5 dB entre les mesures obtenues au test et au retest ont été démontrées après quelques jours (Henry, et coll., 2009; Henry, et coll., 2004; Mitchell, et coll., 1993; Roberts, et coll., 2008) jusqu'à quelques mois (Nageris, et coll., 2010). D'autres études ont toutefois démontré une plus grande variabilité dans la fidélité test-retest (Burns, 1984; Henry, et coll., 2000; Henry, Rheinsburg, Owens, & Ellingson, 2006; Penner, 1983; Penner & Bilger, 1992). Les différentes techniques utilisées ainsi que des différences au niveau des critères de sélection des participants pourraient expliquer une partie de ces différences. L'appariement en intensité est pour le moment peu utilisé pour l'évaluation de l'acouphène ainsi que pour le suivi de sa progression en clinique.

1.2.2.3 Niveau minimum de masquage

Le niveau minimum de masquage constitue le niveau d'intensité minimale requis pour tout juste masquer la perception de l'acouphène à l'aide d'un bruit. Similaire à l'appariement en intensité, le niveau sonore du bruit peut être contrôlé par l'expérimentateur ou par le patient. Tout particulièrement en clinique et parfois en recherche, un bruit à bande large est utilisé comme stimulus masquant (Henry, et coll.,

2005). Toutefois, les bruits masquants dont les fréquences centrales sont proches de celles de la perte auditive sont plus efficaces à masquer l'acouphène (Mitchell, 1983) et requièrent une intensité en dB SL moindre que lorsqu'elles ne sont pas comprises dans le son masquant (Roberts, et coll., 2008). Cette mesure est parfois utilisée afin de valider l'acceptation par le patient de certaines thérapies sonores notamment les générateurs de bruit. En effet, plus le niveau minimum de masquage est similaire au niveau obtenu lors de l'appariement en intensité de l'acouphène, plus les chances sont élevées que le patient bénéficie d'une thérapie sonore (Vernon, 1992). De plus, cette mesure est parfois utilisée afin de valider l'efficacité d'un traitement lors d'essai clinique (Davis, Paki, & Hanley, 2007).

1.2.2.4 Inhibition résiduelle

L'inhibition résiduelle (IR) permet de supprimer temporairement l'acouphène. La profondeur de la suppression peut être totale (l'acouphène est disparu) ou partielle (l'intensité a diminuée) et sa durée peut varier de quelques secondes à quelques heures (Roberts, 2007). La technique consiste à présenter de manière continue, de 30 secondes à une minute, un bruit dont le niveau se situe à 10 décibels au-dessus du niveau minimum de masquage. Le type de bruit a une incidence importante sur la profondeur et la durée de la suppression. En effet, plus la fréquence centrale d'un bruit à bande étroite se rapproche de celle de l'acouphène, plus le bruit sera efficace à supprimer celui-ci et à prolonger la durée de la suppression (Roberts, et coll., 2008; Roberts, et coll., 2006). L'inhibition résiduelle permet une suppression totale ou partielle chez environ 70 à 80% des personnes atteintes d'acouphène, mais augmente parfois l'intensité de l'acouphène chez certains rares individus (Henry & Meikle, 2000; Roberts, et coll., 2008; Vernon &

Meikle, 2003). Cette technique pourrait servir à départager les patients pouvant bénéficier de traitement par stimulation acoustique de ceux pour qui ce type de traitement serait contre-indiqué. Les paramètres de profondeur et de durée pourraient également servir de prédicteur du succès d'une telle thérapie. Aucune étude à ce jour n'a examiné ces applications cliniques. L'inhibition résiduelle ne constitue pas un traitement en soi. En effet, même lorsque la technique d'IR est répétée de manière journalière pendant deux semaines, aucun changement n'est noté au spectre de l'acouphène ainsi qu'aux paramètres de profondeur et de durée de l'inhibition (Roberts, et coll., 2008). L'évaluation de la fidélité test-retest sur une période de deux à trois semaines a démontré une stabilité moyenne pour la profondeur (*r* moyen = .6) et pour la durée (*r* moyen = .4) de l'inhibition (Roberts, et coll., 2008).

1.2.3 Questionnaires

Les questionnaires et les échelles visuelles analogues sont utilisés de manière routinière en audiologie clinique ainsi qu'en recherche afin de mesurer la perception subjective du patient incluant la détresse, le dérangement et le handicap ressenti, ainsi que l'impact sur la qualité de vie (Henry, et coll., 2005). Il existe plus d'une douzaine de questionnaires évaluant l'impact de l'acouphène sur différentes sphères de la vie du patient :

- Tinnitus Handicap Questionnaire (THQ) (Kuk, Tyler, Russell, & Jordan, 1990)
- Tinnitus Reaction Questionnaire (TRQ) (Wilson, Henry, Bowen, & Haralambous, 1991)
- International Tinnitus Inventory (ITI) (Kennedy et coll., 2005)

- Tinnitus Handicap Inventory (THI) (Newman, Jacobson, & Spitzer, 1996)
- Tinnitus Handicap/Support Scale (TH/SS) (Erlandsson, Hallberg, & Axelsson, 1992)
- Subjective Tinnitus Severity Scale (STSS) (Halford & Anderson, 1991)
- Tinnitus Cognitions Questionnaire (TCQ) (Wilson & Henry, 1998)
- Tinnitus Coping Style Questionnaire (TCSQ) (Budd & Pugh, 1996)
- Tinnitus Problems Questionnaire (TPQ) (Tyler & Baker, 1983)
- Tinnitus Questionnaire (TQ) (Hallam, Jakes, & Hinchcliffe, 1988)
- Tinnitus Severity Index (TSI) (Meikle, Vernon, & Johnson, 1984)
- Tinnitus Severity Scale (TSS) (Sweetow & Levy, 1990)
- Tinnitus Functionnal Index (TFI) (Meikle et coll., 2012)

Les questionnaires les plus utilisés sont le THQ, le THI, le TQ et le TRQ. Ces quatre questionnaires possèdent une cohérence interne élevée (Alpha de Cronbach entre 0.91 et 0.96) et une validité de surface importante obtenue par une validation croisée à l'aide d'autres questionnaires similaires (J.J. Eggermont, 2012). La fidélité test-retest est également élevée pour l'ensemble de ces questionnaires (r = .88 à .94) (J.J. Eggermont, 2012). Le THI, le TRQ, le THQ, et le STSS ont tous été validés en langue française (France) (Ghulyan-Bédikian, Paolino, Giorgetti-D'Esclercs, & Paolini, 2010; Meric, Pham, & Chéry-Croze, 1996, 1997, 2000). Notons que le seul questionnaire validé en français québécois est le Tinnitus Handicap Inventory (Bolduc, Désilets, Tardif, & Leroux, 2014).

1.2.4 Échelle visuelle analogue

Les échelles visuelles analogues (VAS) sont utilisées en complémentarité aux questionnaires (Henry, et coll., 2005). Elles consistent en une ligne continue d'un nombre de centimètres exacts (ex. : 10 cm) et permettent aux chercheurs ainsi qu'aux cliniciens d'évaluer différents aspects subjectifs de l'acouphène du patient. Les deux extrémités de la ligne continue représentent les deux extrémités d'un même concept. Par exemple, à la question « Quelle est l'intensité générale de votre acouphène ? », l'extrémité gauche de la ligne sera « Très faible » et l'extrémité droite sera « Très fort ». Cette technique permet de choisir les aspects voulant être mesurés tels que l'intensité, le désagrément, l'attention portée à l'acouphène, etc. Toutefois, les résultats obtenus au VAS sont corrélés de manière importante avec les résultats obtenus aux questionnaires de handicap ou de détresse suggérant qu'ils mesurent, du moins en partie, le même concept (Figueiredo, Azevedo, & Oliveira Pde, 2009). Leur utilisation doit être judicieuse afin d'optimiser la recherche d'information nouvelle et de maximiser le temps d'expérimentation ou d'évaluation clinique.

1.2.5 Conclusions

En résumé, les mesures de l'acouphène chez l'humain incluent le rapport descriptif du patient, les mesures psychoacoustiques d'appariement en fréquence, en intensité, le niveau minimum de masquage et l'inhibition résiduelle ainsi que des mesures de questionnaires et d'échelles visuelles analogues. Bien qu'essentiel, le rapport du patient est influencé par son expérience et le contexte. Les mesures psychoacoustiques permettent entre autres de quantifier le percept entendu par le patient. Toutefois, la

validation des techniques psychoacoustiques actuelles est insuffisante pour permettre le diagnostic de l'acouphène, suivre la progression du trouble ainsi que d'évaluer l'efficacité des traitements. L'aspect psychologique de l'acouphène peut être évalué grâce à des questionnaires validés ainsi que par l'utilisation d'échelles visuelles analogues. Considérant que les aspects psychologiques (détresse, anxiété, etc.) liés à l'acouphène et les paramètres psychoacoustiques du percept (intensité, fréquence, etc.) ne sont que très faiblement corrélés (Balkenhol, Wallhäusser-Franke, & Delb, 2013; Tyler & Conrad-Armes, 1983a), toute étude désirant évaluer l'efficacité d'un traitement devrait inclure l'ensemble de ces mesures afin d'évaluer l'impact subjectif et perceptif du traitement.

1.3 MESURES DE L'ACOUPHÈNE CHEZ L'ANIMAL

1.3.1 La recherche animale et ses modèles

Depuis la fin des années 80 et le début des années 90, la recherche animale en acouphène a connu un essor important et a contribué de manière spectaculaire à l'avancement des connaissances sur les changements neurophysiologiques associés à l'acouphène. Elle a, par ailleurs, permis l'élaboration de différentes théories sur les mécanismes de génération. Il est possible d'induire de l'acouphène chez la plupart des espèces animales (souris, rats, cochons d'Inde, hamsters, chats) grâce à différentes techniques d'induction dont notamment l'injection de salicylate ou de médicaments ototoxiques ainsi que par traumatisme sonore (Eggermont & Roberts, 2014; Hayes, Radziwon, Stolzberg, & Salvi, 2014; von der Behrens, 2014). En effet le salicylate, qui est l'ingrédient actif de l'aspirine, permet à de fortes concentrations d'induire de

l'acouphène chez l'animal et l'humain. Cette induction était même utilisée à une certaine époque par les médecins afin de déterminer la dose optimale d'aspirine à prescrire à un patient : « Augmenter jusqu'à l'apparition de l'acouphène puis diminuer légèrement la dose » (Day et coll., 1989; Mongan, Kelly, Nies, Porter, & Paulus, 1973). L'acouphène est également un effet secondaire fréquent lors de l'utilisation de médicaments ototoxiques notamment en oncologie (cisplatine, carboplatine) afin de traiter différentes formes de cancer ou encore en médecine traditionnelle pour le traitement des infections (aminoglycosides) (Dille et coll., 2010). L'étude de l'acouphène chez l'animal offre une panoplie d'avantages méthodologiques comparativement à celle chez l'humain. Elle permet, entre autres, d'utiliser des techniques invasives (ex : électrodes implantés, enregistrement de cellule nerveuse individuelle), elle permet un contrôle de la génétique de la population étudiée et de l'étiologie de l'acouphène (von der Behrens, 2014). Par contre, le même inducteur n'aura pas le même effet chez tous les animaux d'une même race ou d'une même espèce. Ainsi, tout comme chez l'humain, le même traumatisme sonore peut engendrer de l'acouphène chez un individu et non chez l'autre. Les animaux étant dans l'incapacité de rapporter verbalement la présence d'un acouphène, les chercheurs doivent se rabattre sur des techniques indirectes afin de l'objectiver (Hayes, et coll., 2014; von der Behrens, 2014). Les sections suivantes présentent les différentes techniques utilisées par les chercheurs utilisant des sujets expérimentaux animaux.

1.3.2 Paradigme de conditionnement classique

Les premiers chercheurs à élaborer et valider un paradigme de conditionnement afin d'objectiver la présence d'acouphène chez l'animal ont été Pawel Jastreboff et ses collaborateurs (1988). La technique consistait à entraîner des rats privés d'eau à ne boire

qu'en présence de bruit de fond. Les rats étaient donc conditionnés à ne plus boire en présence de silence : lorsque le bruit de fond s'éteignait, les rats qui continuaient à boire recevaient des décharges électriques. Cette technique de conditionnement était répétée jusqu'à ce que le comportement souhaité, soit ne pas boire en présence de silence, était intégré et stable sur plusieurs séances. Les chercheurs utilisaient la mesure du nombre de lichettes («lick» en anglais) afin de déterminer si le comportement était intégré : le nombre de lichettes devait diminuer significativement en présence de silence. Une fois ce niveau atteint, Jastreboff et ses collaborateurs ont utilisé l'administration de salicylate afin d'induire de l'acouphène aux rats. Le même paradigme était par la suite repris, mais cette fois sans présence de décharges électriques. Chez les rats ayant reçu le salicylate, le nombre de lichettes ne diminuait plus en présence de silence comparativement aux rats contrôles. Selon les auteurs, cette différence entre les deux groupes était indicative de la présence de l'acouphène. En effet, seuls les rats ayant reçu le salicylate persistaient dans leurs comportements (lichettes) en présence de silence.

D'autres paradigmes de conditionnement suivant les mêmes principes de base ont par la suite été développés (pour une revue des différentes techniques: Hayes, et coll., 2014; von der Behrens, 2014). De manière générale, l'animal est toujours entraîné à répondre au silence de façon différente (boire, manger, etc..) que lorsqu'il est en présence de bruit (sons purs, bruits centrés en fréquence, bruits à bande large). Lorsque le comportement conditionné est acquis par l'animal, les chercheurs induisent l'acouphène et mesure de nouveau les comportements de l'animal à l'aide du paradigme utilisé lors du conditionnement. Une différence dans le comportement de l'animal en présence de silence est interprétée comme signalant la présence de l'acouphène. De manière générale,

les techniques de conditionnement requièrent beaucoup de temps afin d'entraîner de manière appropriée le comportement des animaux. De plus, plusieurs techniques s'appuient sur des comparaisons de groupes, et non sur des données individuelles, pour déterminer la présence de l'acouphène. L'extinction rapide du comportement conditionné est un autre inconvénient important lorsque le décours temporel de l'apparition de l'acouphène (de l'apparition à la chronicisation) doit être évalué.

1.3.3 Le paradigme d'inhibition du réflexe de sursaut par un court silence ou « GPIAS »

Récemment, une nouvelle mesure objective de l'acouphène ne requérant aucun conditionnement a été proposée chez le rat à l'aide d'un paradigme adapté du réflexe acoustique de sursaut (acoustic startle reflex) (Turner et coll., 2006). Ce réflexe consiste, entre autres, en une réponse du nerf facial suite à un bruit soudain, inattendu et d'intensité élevée (Koch, 1999). Il est modulé par l'insertion d'un bruit de plus faible intensité ("Pré-pulse") quelques millisecondes avant le son causant le sursaut. En effet, le "Pré-pulse" diminue l'amplitude de la réponse via un filtrage sensorimoteur (Figure 1). Ce phénomène a été abondamment étudié par la mesure du clignement de l'oeil chez l'humain (Blumenthal et coll., 2005).

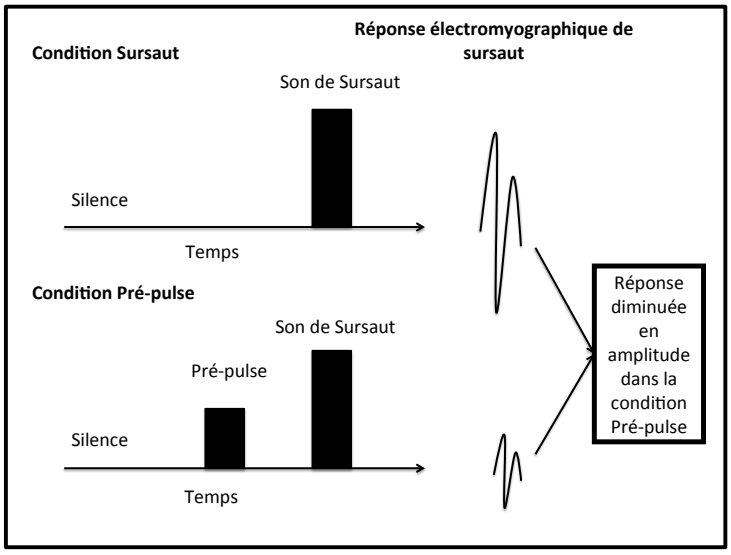

Figure 1. Paradigme d'inhibition de la réponse acoustique de sursaut par le pré-pulse. Lorsqu'un son de sursaut est présenté seul dans le silence, la réponse électromyographique mesurée est grande. Toutefois, lorsque le son de sursaut est précédé par un son d'amplitude plus faible quelques millisecondes avant le son de sursaut, la réponse électromyographique associée sera réduite comparativement à la condition sans pré-pulse.

Cette technique d'inhibition du réflexe de sursaut a été adaptée chez le rat : un court silence est introduit à l'intérieur d'un bruit de fond continu quelques millisecondes avant le bruit de sursaut (Cranney, Cohen, & Hoffman, 1985; Ison, 1982). Chez les rats avec audition normale, le silence produit le même effet que le Pré-pulse, c'est-à-dire qu'il inhibe le son de sursaut (voir figure 2).

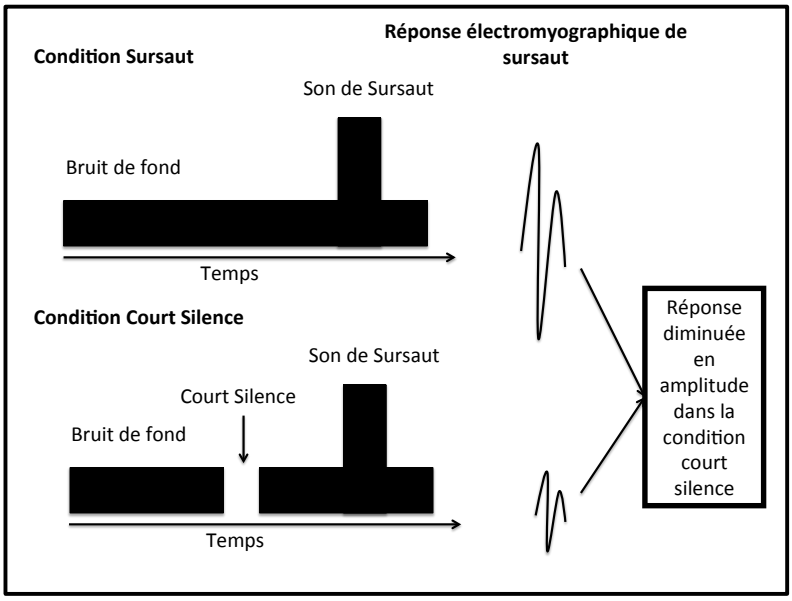

Figure 2. Paradigme d'inhibition de la réponse acoustique de sursaut par un court silence. Lorsqu'un son de sursaut est présenté seul dans un bruit de fond, la réponse électromyographique mesurée est grande. Toutefois, lorsque le son de sursaut est précédé d'un court silence quelques millisecondes avant le son de sursaut, la réponse électromyographique associée sera réduite comparativement à la condition sans court silence.

Toutefois, chez les rats à qui l'on a induit de l'acouphène soit par injection de salicylate (Yang et coll., 2007) soit par traumatisme sonore (Engineer et coll., 2011) l'inhibition causée par le court silence est réduite ou absente (voir figure 3) et ce, en présence d'une audition normale.

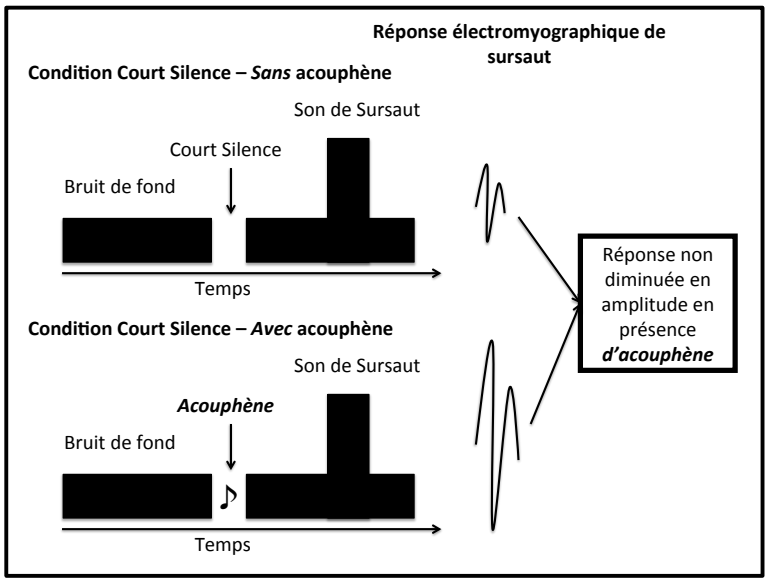

Figure 3. Paradigme d'inhibition de la réponse acoustique de sursaut par un court silence appliqué à l'acouphène. Lorsque le son de sursaut est précédé d'un court silence quelques millisecondes avant le son de sursaut, la réponse électromyographique associée sera réduite comparativement à la condition sans court silence, ce qui n'est plus le cas en présence d'acouphène.

De plus, cette absence d'inhibition serait spécifique à la fréquence de l'acouphène: plus la fréquence centrale du bruit de fond serait similaire à celui de l'acouphène présumé, plus l'absence d'inhibition serait grande. Turner et collaborateurs (2006) ont comparé chez les mêmes rats traumatisés acoustiquement les résultats obtenus à l'aide du paradigme d'inhibition du réflexe de sursaut par un court silence à ceux obtenus à l'aide d'un paradigme de conditionnement classique. En effet, les rats ont été exposés unilatéralement à un bruit de bande étroite centré à 16 kHz à une intensité de 116 dB SPL pendant une heure, une procédure connue pour engendrer un déplacement temporaire des seuils auditifs et de l'acouphène à 10 kHz (Bauer & Brozoski, 2001). À la suite de cette

procédure, les rats ont été testés à l'aide des deux paradigmes sur plusieurs semaines. Les résultats obtenus au paradigme de GPIAS ont démontré une diminution significative de l'inhibition seulement pour les rats qui ont été traumatisés acoustiquement. De plus, cette réduction d'inhibition est spécifique au bruit de fond utilisant une bande étroite centré à 10 kHz et non pour celui de 16 kHz ou encore celui utilisant un bruit à bande large. L'absence d'inhibition spécifique au bruit de fond de 10 kHz est interprétée par les auteurs comme une démonstration de la présence d'un acouphène à 10 kHz chez les rats ayant subi l'induction. De plus, les résultats obtenus avec la technique de conditionnement classique ont permis d'inférer que la fréquence de l'acouphène était bel et bien de 10 kHz. Cette technique consistait à entraîner les rats à appuyer sur un levier pour manger seulement durant des périodes de bruits de différentes fréquences centrales et d'arrêter lorsque les bruits étaient éteints. Seuls les rats ayant subi un traumatisme acoustique appuyaient de manière plus fréquente sur le levier en présence d'un silence comparativement aux rats contrôles, et ce, seulement en présence d'un bruit de fond de 10 kHz. La validation croisée de la technique du GPIAS par le conditionnement classique a permis aux auteurs de renforcer leur interprétation du GPIAS à savoir que l'acouphène « remplirait » le silence, et empêcherait ainsi ce dernier d'inhiber le son de sursaut. Cette technique prometteuse permettrait donc une mesure objective de la fréquence ou des fréquences composant l'acouphène sans avoir à recourir à des techniques de conditionnement. Toutefois, aucune autre étude n'a encore répliqué ces résultats. L'application de cette technique chez l'humain pourrait permettre de confirmer les résultats obtenus chez le rat et valider l'interprétation des auteurs.

1.4 OBJECTIF DE LA THÈSE

L'objectif principal de la thèse est d'implémenter et de valider la faisabilité, chez des participants humains contrôles et avec acouphène, le paradigme de modulation du réflexe acoustique de sursaut par un court silence (GPIAS) déjà utilisé chez les rats, afin de l'utiliser comme mesure objective de l'acouphène chez l'humain. Pour ce faire, trois expériences ont été réalisées.

L'expérience 1 avait pour objectif de valider l'inhibition du réflexe de sursaut par un court silence chez des humains contrôles (sans acouphène) lors de la présentation d'un bruit d'un fond centré en hautes et en basses fréquences, ce qui n'avait jamais été démontré. Une étude a démontré que l'inhibition du réflexe de sursaut pouvait être produite par un court silence de 25 ms inséré à l'intérieur d'un son pur continu de 1000 Hz (Lane, Ornitz, & Guthrie, 1991). Une autre étude a démontré une augmentation de l'inhibition lors de l'utilisation de courts silences d'une durée d'une à dix millisecondes insérés dans un bruit à bande large. Cependant, ces auteurs ont utilisé une tape sur le glabelle pour déclencher le réflexe plutôt qu'un son fort et inattendu (Ison & Pinckney, 1983). Puisque la durée du court silence dans l'étude de Turner et collaborateurs (2006) est de 50 ms et que nous voulons appliquer ce même modèle chez l'humain, il est important de connaître la relation « durée du silence-inhibition » afin de déterminer si la valeur de 50 ms produit suffisamment d'inhibition chez l'humain et si cette durée est la plus appropriée pour l'application à des personnes avec acouphène. En effet, l'inhibition doit être suffisamment importante pour éviter un effet plancher, mais non complète afin d'éviter la saturation (effet plafond). Cette étude permettra donc de déterminer les paramètres optimaux pour l'utilisation du paradigme chez les humains avec acouphène.

De plus, aucune des deux études susmentionnées n'a démontré la spécificité fréquentielle de cet effet (s'il existe une différence entre hautes et basses fréquences).

Par la suite, l'expérience 2 avait pour objectif de caractériser de manière précise l'acouphène à l'aide de différentes mesures psychoacoustiques informatisées (appariement en fréquence et en intensité). Cette information était capitale pour l'expérience 3, puisque la réduction ou l'absence d'inhibition du réflexe de sursaut ne devait se produire que lorsque le bruit de fond était centré sur la fréquence proche de celle de l'acouphène; il était donc essentiel de pouvoir déterminer les caractéristiques fréquentielles de ce dernier.

Finalement, l'expérience 3 avait pour objectif de valider la présence de l'acouphène chez des personnes atteintes à l'aide du paradigme d'inhibition du réflexe de sursaut par un court silence similaire à celui employé chez le rat. Le potentiel de cette technique est immense : si elle s'avère applicable à l'humain et est corroborée par les mesures psychoacoustiques d'appariement en fréquence et en intensité, elle pourrait devenir une mesure essentielle au diagnostic de la présence de l'acouphène, permettre un suivi adéquat de la progression du trouble, et devenir la mesure de référence du succès de différents traitements et approches.

1.4.1 Les trois *hypothèses* proposées afin de répondre à l'objectif principal de la thèse :

1) L'absence ou la réduction de l'inhibition du réflexe de sursaut par un court silence devrait être observable chez des participants humains avec acouphène, comparativement à des participants contrôles sans acouphène.

2) L'acouphène n'entraînerait une absence ou une réduction d'inhibition que lorsque le bruit de fond est centré sur la fréquence proche de celle de l'acouphène.

3) Le degré d'inhibition du réflexe de sursaut lors de la présentation du silence devrait être corrélé avec l'intensité subjective de l'acouphène rapportée par le participant.

1.5 APPROCHES MÉTHODOLOGIQUES

1.5.1 Expérience 1

L'expérience 1 avait comme objectif de valider la présence d'inhibition du réflexe acoustique de sursaut suite à la présentation de différentes durées de court silence chez l'humain. Les objectifs poursuivis étaient de:

1) déterminer la durée optimale du silence pouvant générer une inhibition du réflexe (5 ms, 25 ms, 50 ms, 100 ms ou 200 ms).

2) déterminer s'il existe une différence d'inhibition selon la fréquence centrale du bruit de fond utilisé (hautes fréquences vs basses fréquences). Ce deuxième objectif secondaire est important puisque si l'inhibition est similaire, peu importe la fréquence du bruit de fond dans la population normale, mais diffère dans la population clinique atteinte d'acouphène, nous pourrions utiliser une mesure intra-sujet pour démontrer la présence de l'acouphène en plus des comparaisons de groupe.

1.5.2 Expérience 2

Après avoir démontré, dans l'expérience 1, la présence d'inhibition du réflexe acoustique de sursaut par la méthode du court silence chez des sujets jeunes normaux, et avoir déterminé la durée optimale du silence pour l'inhibition, l'objectif de l'expérience 2 était de valider une méthode de caractérisation psychoacoustique de l'acouphène. Cette mesure était essentielle à la réalisation des hypothèses 2 et 3 de ce projet de recherche. En effet, la deuxième hypothèse de ce projet de recherche stipule que l'acouphène n'entraînerait une absence ou une réduction d'inhibition que lorsque le bruit de fond était centré sur la fréquence proche de celle de l'acouphène. Il était donc impératif de mesurer de manière efficace ces paramètres psychoacoustiques afin de tester cette hypothèse. De plus, la troisième hypothèse de ce projet propose une corrélation entre le degré d'inhibition du réflexe de sursaut et l'intensité subjective de l'acouphène. Il était donc essentiel de bien mesurer ce paramètre afin de tester cette hypothèse. Par ailleurs, quatre objectifs secondaires ont été poursuivis lors de cette étude :

1) Déterminer si les mesures d'appariement en intensité et en fréquence sont sensibles et spécifiques à la présence de l'acouphène.

2) Reproduire les résultats des études qui ont démontré les liens entre la perte auditive et le spectre fréquentiel de l'acouphène.

3) Évaluer la fidélité test-retest des mesures d'appariement en fréquence et en intensité de l'acouphène.

4) Évaluer l'influence de l'expérience musicale sur les capacités d'appariement en fréquence et en intensité de l'acouphène.

1.5.3 Expérience 3

L'expérience 3 avait pour objectif d'appliquer le paradigme d'objectivation de l'acouphène par le réflexe de sursaut à des participants atteints d'acouphène utilisant les techniques développées lors de l'expérience 1 et l'expérience 2 ; elle a permis de répondre aux hypothèses soulevées au départ.

EXPÉRIENCE 1

The gap-startle paradigm to assess auditory temporal processing: bridging animal and human research

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Abstract

The gap-prepulse inhibition of the acoustic startle (GPIAS) paradigm is the primary test used in animal research to identify gap detection thresholds and impairment. When a silent gap is presented shortly before a loud startling stimulus, the startle reflex is inhibited and the extent of inhibition is assumed to reflect detection. Here we applied the same paradigm in humans. One hundred and fifty seven normal-hearing participants were tested using one of five gap durations (5, 25, 50, 100, 200 ms) in one of the following two paradigms: gap-*Embedded* in, or gap-*Following*, the continuous background noise. The duration-inhibition relationship was observable for both conditions but followed different patterns. In the gap-*Embedded* paradigm, GPIAS increased significantly with gap duration up to 50 ms and then more slowly up to 200 ms (trend only). In contrast, in the gap-*Following* paradigm, significant inhibition −different from 0− was observable only at gap durations from 50 to 200 ms. The finding that different patterns are found depending on gap position within the background noise is compatible with distinct mechanisms underlying each of the two paradigms.

Key words: Startle, Temporal processing, Prepulse inhibition, Gap-Startle, Hearing, Gap-Prepulse inhibition of the Acoustic startle reflex (GPIAS), Gap-*Embedded*, Gap-*Following*.

Introduction

Temporal processing is a major property of the mammalian auditory system thought to be critical in speech perception and sound localization. In animals, one of the most often-used techniques to assess temporal acuity is the acoustic gap-startle paradigm. The acoustic startle reflex is a primitive reflex that consists of contraction of the major muscles of the body following a loud and unexpected sound (Koch, 1999). This reflex is reduced when preceded by a silent gap embedded in a soft background noise or tone, a technique also known as gap-prepulse inhibition of the acoustic startle (GPIAS). The investigation of auditory temporal resolution capacity by this technique involves short silent gaps of various durations as pre-stimuli, with the assumption that the amount of inhibition produced by the gap reflects detection, or temporal processing. A consistent finding is that the percentage of inhibition of the startle reflex increases as the gap duration increases (Allen, Schmuck, Ison, & Walton, 2008; Barsz, Ison, Snell, & Walton, 2002; Bowen, Lin, Merrit, & Ison, 2003; Cranney, Cohen, & Hoffman, 1985; Dean, Sheets, Crofton, & Reiter, 1990; Harbin & Berg, 1983; Ison, Allen, Rivoli, & Moore, 2005; Ison & Bowen, 2000; Ison, O'Connor, Bowen, & Bocinea, 1991; Ison & Pinckney, 1983).

Human studies using the gap-startle paradigm are scant (Cranney, Hoffman, & Cohen, 1984; Fournier & Hébert, 2013; Harbin & Berg, 1983; Ison & Pinckney, 1983; Lane, Ornitz, & Guthrie, 1991). Only two studies have reported increased reflex inhibition with increasing gap duration (Harbin & Berg, 1983; Ison & Pinckney, 1983). Using the gap-startle paradigm with a shock to the forehead to elicit the startle reflex, Ison and Pinckney (1983) estimated a threshold of 5 ms. Using a psychophysical gap

detection task in the same subjects, the estimated threshold was 5.4 ms. This finding led authors to suggest that gap-startle detection thresholds and psychophysical gap detection share neural mechanisms.

Harbin and Berg (1983) used the gap-startle paradigm for gap durations of 10 to 120 ms to compare young to older adults. The startle reflex was elicited by an airpuff stimulation. Increased inhibition with increasing gap durations from 10 to 80 ms was found for young adults but with a sudden decrease at 120 ms. No interpretation was provided for this surprising finding: If inhibition provided by the gap-startle paradigm reflects perceptual detection then why would a 120 ms gap provide less inhibition than an 80 ms gap? Also, does inhibition decrease or increase for values greater than 120 ms?

The present study aims to determine the duration-inhibition relationship of very short (5 ms) up to long gap durations (200 ms) using the gap-startle inhibition paradigm with auditory stimulation only. In addition, since gaps embedded in a noise background (hereafter gap-Embedded) and gaps following a noise background (hereafter gap-Following) yield different patterns of results in animal studies (Hickox & Liberman, 2014; Ison et al., 1991; Threlkeld, Penley, Rosen, & Fitch, 2008), both types of gaps were used with the assumption that they would not produce the same inhibition patterns. More specifically, differences in inhibition patterns should be observable for gap durations <50 ms, since Gap-*Embedded* of longer durations have been suggested to be processed by the brainstem, similarly to Gap-*Following* (Threlkeld et al., 2008).

Another aspect that was examined here is the frequency specificity of the inhibition using high- and low-frequency pre-stimuli (background and prepulse). One

animal study (Hoffman & Searle, 1967) and one human study (Cranney et al., 1984) found no effect of background frequency on acoustic startle inhibition (broadband and narrow-band noises in Hoffman & Searle 1967; 1 or 2.5 kHz pure tones in Cranney et al. 1984). Yet two human studies found greater inhibition for white noise prepulse compared to a tone (Blumenthal & Berg, 1986; Wynn, Dawson, & Schnell, 2000). Also, we Fournier & Hébert (2013) reported more inhibition of the GPIAS using a low-frequency (centered around 500 Hz) compared to a high-frequency narrow-band noise (centered around 4 kHz). The effect of low- and high- frequency background noises will be re-examined here.

Methods

Participants:

One hundred and seventy-six participants (mostly students at Université de Montréal) were recruited through word of mouth and paper ads. Inclusion criteria included having hearing thresholds ≤ 30 dB HL at any frequency between 250 Hz and 4 kHz in either ear as assessed by a standard clinical procedure. Exclusion criteria were uncontrolled medical conditions (e.g. hypertension, diabetes), middle and/or outer ear pathology and heavy smokers (>10 cigarettes/day) (Kumari, Cotter, Checkley, & Gray, 1997). Participants who were non-responsive to the acoustic startle (N=17, see below) and participants with noisy EMG (N=2) were excluded. The final sample totaled 157 participants who were assigned to one of the following ten groups based on gap durations (5, 25, 50, 100, or 200 ms) and gap types (Gap either *Embedded* or *Following)* (see Figure 1). Sociodemographic characteristics of all groups are presented in Table I. 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.

Insert Table I here

Materials and Procedure:

Startle stimuli and task

A schematic view of Startle with background noise (Pulse-alone), Gap-*Embedded* or Gap-*Following,* Startle in silence (Pulse-alone) and Prepulse trials are shown in Figure 1. Startle trials consisted of startle noises (50 ms broadband noise bursts set at 105 dBA SPL with near-instantaneous rise and fall time <1 ms) preceded by either a low- or high-frequency continuous background noise set at 65 dB(A). The low-frequency background noise was centered at 500 Hz (200-1200 Hz) and high-frequency background noise at 4 kHz (3.5-4.5 kHz). Gap-*Embedded* trials were similar to startle trials, except that a silent gap of 5, 25, 50, 100 or 200 ms was inserted between two segments of background noise with a constant inter-stimulus interval of 120 ms before the startle noise producing stimulus onset asynchrony (SOA) of 125, 145, 170, 220 and 320 ms, respectively. Gap-*Following* trials were similar except that the different silent gaps were following the end of the background noise producing different inter-stimulus intervals of 5, 25, 50, 100, 200 ms, equivalent to stimulus onset asynchrony (SOA). Prepulse trials were either low- or high- frequency 50 ms noise bursts set at 65 dB(A) presented in silence, 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 maximize inhibition (Braff et al., 1978). 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). All stimuli 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.

EMG measures

Eyeblink activity was measured using 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 a IMac running the Acqknowledge 4.1 software connected to a Biopac MP150 system (Biopac Systems, Inc., Santa Barbara, CA) using the following settings: ×1000 amplification, 90-500 Hz bandpass filter, RMS transformation, A/D conversion at 1 kHz. The stimulus presentation system was coupled to a Fireface sound card (RME, Haimhausen, Germany) hosted by a PC computer. Startle noise presentation was synchronized with eyeblink activity recording via a square-wave trigger signal to precisely determine the window of responses for magnitudes and latencies of the eyeblink (see Data processing below).

Procedure

Participants were instructed to sit quietly in a soundproof booth, refrain from moving and listen to the sounds presented binaurally via closed dynamic headphones DT 770 Pro/250 while watching a white cross projected on a dark screen. The test session began with a 2 min acclimatization period consisting of a high-frequency background noise of 65 dB(A) that ended with four pulse-alone stimuli for habituation before the beginning of block 1. The task consisted of three blocks. In the first block, 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 a 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 the experimenter to monitor participants' drowsiness or lack of attention. There were 70 stimuli, lasting for a total duration of about 25 min.

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 occurrences were very few (2.7%) 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 transformed 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, which 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 (N=17). Percentage of inhibition was calculated for each condition (gaps 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). Latency facilitation was calculated for each condition (gaps or prepulse) using the following formula: Latency facilitation = (pulse-alone latency) - (gap/prepulse) latency. Data for each trial type were averaged for each background noise (high, low, silence) for each participant. For percentage of inhibition, data above two standard deviations from the group mean were replaced by the average value of the appropriate group for each trial type, gap duration and background noise (total of 4.9%).

Statistical Analyses

The effects of gap duration and gap type on percentage of inhibition were assessed by a 5 X 2 X (2) mixed ANOVA with Gap duration (5, 25, 50, 100, 200 ms) and Gap type (Gap-*Embedded* or Gap-*Following*) as between-subject factors, and Frequency (High vs. Low) as within-subject factor. Similar ANOVAs were run on latency facilitation, magnitude and latency of the startle-alone, and percentage of inhibition and latency facilitation of

the prepulse. Significant interactions were followed up by appropriate ANOVAs, t-tests or Sheffe's Post-hoc comparisons. 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 reported *p* values are corrected values. Greenhouse-Geiser degrees of freedom were used to evaluate significance and are reported when sphericity assumptions were violated.

Results

Effects of Gap duration and Gap type on **Percent (%) inhibition**

Figure 2 displays % inhibition for all gap durations across high and low frequencies. The expected two-way interaction between Gap duration (5, 25, 50, 100, 200) and Gap Type (*Embedded* or *Following* the noise) was significant $F(4,147)=5.1$, $p=.001$, $\eta^2 =0.12$. There was also a significant interaction between Frequency and Gap Type $F(1,147)=8.8$, $p=.004$, $\eta^2 =0.06$ and Frequency and Gap duration $F(4,147)=2.8$, $p=.027$, $\eta^2 =0.07$. For Gap-*Embedded,* overall % inhibition was greater for Low (54%) than for High (44%) Frequency, $F(1,79)= 10.8$, $p=.002$, $\eta^2 = .12$. There was also a main effect of Gap duration $F(4,79)= 9.5$, $p<.001$, $\eta^2 =.33$. For the Gap-*Following,* there was only a main effect of Gap duration, $F(4,68)= 30.5$, $p<.001$, $\eta^2 =0.64$. No effect involving frequency was found here, p=.29.

For the Gap-*Embedded* condition, 5 ms gaps produced significantly less inhibition (24,2%) than 50 (56,1%), 100 (55,8%), and 200 (72%) ms, but not less than 25 ms (36,8%), and the latter differed significantly only from 200 ms gaps (see Table II). The lower limit of the 99% confidence interval (CI) for each gap duration was calculated to

assess differences from 0% inhibition, that is, no inhibition (see Table IV). All gap durations produced significant measurable inhibition that was different from 0%.

For the Gap-*Following* condition, both 5 (-7,7%) and 25 (13,4%) ms gaps produced significantly less inhibition than 50 (50,2%), 100 (72,2%), and 200 (61,6%) ms. Percent inhibition did not differed significantly between 5 and 25 ms (see Table II). However, the lower limit of the 99% confidence interval did include 0% for 5 and 25 ms gap durations, meaning that 5 and 25 ms gaps did not produce significant inhibition (see Table IV).

In summary, in the Gap-*Embedded* condition all gap durations produced significant and increasing inhibition whereas in the Gap-*Following* only gaps ≥50 ms produced significant and similar inhibition.

Figure 2

Table II

Effects of Gap duration and Gap type on **Latency facilitation**

Figure 3 displays latency facilitation for all gap durations and gap types. The expected two-way interaction between Gap duration (5, 25, 50, 100, 200) and Gap type (Embedded or following the noise) was significant $F(4,147)=5.68$, $p<.001$, $\eta^2 =0.13$. Only main effects of Gap durations were found in the Gap-*Embedded,* $F(4,79)= 5.36$,

p=.001, η^2 =.21, and Gap-*Following,* $F(4,68)= 3.83$, $p=.007$, η^2 =0.18, conditions. Sheffé's post hoc comparisons showing group differences between Gap durations are presented in Table III.

For the Gap-*Embedded* condition, 50 ms gaps significantly produced less latency facilitation than 100 and 200 ms. The lower limit of the 99% confidence interval (CI) for each gap duration confirmed that only 100 and 200 ms gap durations produced significant measurable latency facilitation different from 0 ms.

A different scenario was found for the Gap-*Following* condition, with the 50 ms gap producing significantly more latency facilitation than 5 ms and 25 ms (the latter was marginally significant). Consistent with amplitudes, the lower limit of the 99% confidence interval (CI) for each gap duration confirmed that only 50, 100 and 200 ms gap durations produced significant latency facilitation.

Figure 3

Table III

Table IV

Magnitude and latency of the startle sound: **Control condition**

A 5 x 2 X (2) mixed ANOVA was performed on Startle stimuli to ensure that all groups responded in a similar way. For Magnitude, there was only a significant main effect of frequency $F(1,147)=8.53$, $p=.004$, $\eta^2 =.06$ with greater startle reactivity in high-frequency (213 uV) than low-frequency (199 uV) background. When comparing the startle magnitude in high- or low-frequency background to startle magnitude in silence with paired-sample t-tests, startle in silence was significantly lower (140 uV) than high-frequency $t(74)= 6.4$, $p<.001$ and low- frequency background $t(74)= 5.3$, $p<.001$. No main effect of gap duration ($F<1$) or gap type ($F<1$), nor interaction between these two factors ($F<1$), was significant. For Latency, there were no main effects or interactions. The mean latency was 61 ms.

Percent of inhibition and latency facilitation of the prepulse: **Control condition**

A 5 x 2 X (2) mixed ANOVA was performed to ensure that all groups had similar sensorimotor gating abilities. For % inhibition, there was a significant main effect of frequency $F(1,147)=5.3$, $p=.023$, $\eta^2 =.04$ with more inhibition for the lower frequency (78.8%) compared to high-frequency (75.4%) prepulse. There was also a main effect of gap duration $F(4,147)=2.7$, $p=.033$, $\eta^2 =.07$. There was only one significant difference of the order of 14% between 50 ms and 100 ms ($p=.009$ by Sheffé's comparisons). For latency facilitation, there were no main effects or interactions.

Gap vs. Prepulse

Comparisons between % inhibition of the prepulse vs the gap condition for each group (paired-sample t-tests) revealed that prepulse produced more inhibition than any Gap

duration (5, 25, 50, 100, 200) and Gap type (*Embedded* or *Following*), with the exception of 200 ms in the Gap-*Embedded* condition, with which it did not differ significantly (See Table V).

Table V

Discussion

Herein, we report the important finding that patterns of startle reflex % inhibition and latency facilitation in relation to silent gaps of various durations differed substantially depending on gap position within the background noise (*i.e*., embedded *versus* following), suggestive of distinct mechanisms underlying each of the two paradigms.

For the gap *embedded* within background noise paradigm, inhibition of the startle reflex increased with gap durations of up to 50 ms. These results are consistent with previous animal (Cranney et al., 1985; Ison, 1982; Ison et al., 1991; Threlkeld et al., 2008) and human studies (Harbin & Berg, 1983; Ison & Pinckney, 1983) employing various types of background (tone or noise) and startle stimuli (tone, white noise, noise burst, airpuff, shock to the forehead) (See Supplementary Table) suggesting that such factors − modality and type of stimulus− exert only minor influences on the pattern of inhibition and, conceptually, that a commonality in GPIAS exists across species. The startle reflex inhibition-gap duration relationship from very short to protracted duration was such that statistically significant increments occurred up to 50 ms whereas there was only a trend for further inhibition between 50 ms, 100 ms and 200 ms. Similar patterns have been reported using a wide range of gap durations with rapid maximum inhibition

occurring at approximately 50 ms (80 ms, Cranney et al.; 40 ms, Harbin & Berg; 30 ms, Threlkeld et al.).

In contrast, the gap-*Following* paradigm did not produce any significant inhibition at 5 and 25 ms gap durations, lying within the 99% confidence interval of no inhibition. However, inhibition values from 50 to 200 ms gap durations were of similar magnitudes as to the ones determined using the Gap-*Embedded* paradigm, with 50% inhibition at 50 ms, 72% at 100 ms and 62% at 200 ms. These findings, reported herein for the first time in humans, are consistent with previous animals studies (Bowen et al., 2003; Ison & Allen, 2003; Ison & Allen, 2012; Ison et al., 1991). One possible line of interpretation for the discrepancy between the two paradigms at 50 ms gap duration (or lower) might be related to the fact that in the Gap-*Following* paradigm, only a single cue (*i.e*., gap onset) is available compared to double cues in the Gap-*Embedded* paradigm (*i.e*., gap onset and offset), thereby making – in the latter - the gap more perceptible and more efficient as an inhibitor of the startle. Moreover, increasing the duration between a gap's offset and onset increases the inhibition in a way similar to a phenomenon observed in prepulse studies: increasing either the separation between two clicks, or increasing the duration of a single prepulse, increases the inhibition up to values of approximately 50 ms, a phenomenon called temporal summation (Blumenthal, 1995). Conversely, gap offsets at 125 and 145 ms SOA could be seen as interfering with the effectiveness of the gap onset at 120 ms: the offset of the gap could exert a negative influence on the inhibition driven by the onset, as an onset cue produce more inhibition than a gap-embeded (offset-onset) of a few milliseconds at similar onset ISI. Accordingly, auditory cortex deactivation studies have shown that GPIAS was diminished for gap durations ≤ 50 ms in gap-

Embedded but not in gap-Following noise, suggesting the involvement of cortical neural substrates in the former (Ison et al., 1991; Threlkeld et al., 2008) and the possibility of brainstem involvement in the latter. Cortical involvement is supported by experimental data showing that auditory cortical neurons respond to the gap offset with a characteristic burst of spikes (termed the gap termination response) presumed to be a neural correlate of brief gap detection (Eggermont, 1999; Recanzone, Engle, & Juarez-Salinas, 2011). Moreover, a recent study has shown that gap detection (as measured by GPIAS) appears to be processed by interneurons that allow ongoing comparisons between pre− and post−gap spiking activity (Weible et al., 2014). Interestingly, this ongoing comparison held for gap duration ≤ 25 ms, but not for 50 ms. Possibly then, gaps ≤ 25 ms embedded in a background noise could be processed as a whole rather than consisting of distinct features such as offsets and onsets. If this were not the case, then cortical deactivation would not have any effect on gap startle inhibition since both offsets and onsets would be processed and inhibition would occur even without active cortical areas. Therefore, temporal summation is present in the gap-embedded for values ≤ 50 ms. For greater values, separation between the onset and offset is too large to consider the gap as a whole, and the latter is then processed by its distinct features.

Finally, another explanation for the discrepancies between the inhibition of the Gap-*embedded* and Gap-*following* condition at 5 ms and 25 ms might be the lead time or stimulus onset asynchrony (SOA) difference between the two conditions. Indeed, it is well known that the optimal lead interval range producing maximal inhibition is 60–240 ms for auditory prepulses (Graham & Murray, 1977, Braff et al 1978). By reducing the gap duration to 25 and 5 ms in the gap-following condition, we are consequently

reducing the lead times to values lower than the optimal interval range and thus jeopardizing inhibition. For the gap-embedded condition the SOA is reduced with the reduction of the gap but never less than 125 ms since the inter-stimulus-interval is fixed at 120 ms in this condition. A follow-up study should focus on the effect of lead times on GPIAS using fixed gap durations at different SOA times.

It is noteworthy that latency facilitation occurred only under conditions associated with significant % inhibition in the gap-Following paradigm, again supporting the notion that the two paradigms rely on distinct neural networks, at least at short gap duration values. Thus, latency facilitation would occur only under conditions in which inhibition is driven by brainstem mechanisms (Gap-Following: 50, 100 and 200 ms; Gap-Embedded: 100 and 200 ms). However, this proposition was not subjected to direct testing herein and further research will be needed to clarify the origin of latency facilitation.

Our results demonstrate greater inhibition of the startle reflex when low frequency prepulses are used or when gaps are embedded within a low-frequency background noise. These results are in line with our previous findings (Fournier & Hébert, 2013) but contrast with some previous human (Cranney et al., 1984) and animal (Cranney et al., 1985; Hoffman & Searle, 1967) studies that have found no effect of frequency. However these studies have used pure tones rather than narrow-band noise, the latter being more effective than pure tones to generate inhibition in a prepulse paradigm (Blumenthal & Berg, 1986; Wynn et al., 2000).

Although the noise centered around 4 kHz spanned less critical bands than the one centered around 500 Hz (two vs. 16, see Moore 2003) and thus the latter might have sounded louder than the former, it is unlikely that loudness is involved in this frequency

difference. Indeed, extant data are that *louder* background noise would be less effective in inhibiting the startle by the prepulse since it is the difference between the background noise and the prepulse level, rather than the absolute level, that is the critical factor (e.g., Blumenthal, & al., 2006). In addition, if sound level were a critical factor here, all three types of stimulus would produce similar differences, which is not the case. Furthermore, a recent study using a similar GPIAS paradigm but applied to auditory evoked potentials also demonstrated greater inhibition of components N1, N2, P2 (particularly P2) when using a 8 kHz pure tone compared to a 600 Hz one as background noise (Ku et al., 2015). These findings cannot be explained in terms of critical bands (or loudness) since pure tones presented at similar dB Sensation Level, and thus loudness levels, were used. One possible explanation to reconcile the discrepancy among studies is the size of the difference in Hertz used between the low and the high frequency stimuli. Indeed, Cranney and colleagues used very close frequencies only 1,500 Hz away from each other (1000 and 2500 Hz) compared to the present study (3,500 Hz of difference between 500 and 4,000 Hz) and the Ku and colleagues' study (7,400 Hz of difference between 600 and 8,000 Hz). The small difference in Hz might have thus been insufficient to generate a difference of inhibition between high and low frequencies.

Implications for hearing disorders

Inhibition of the acoustic startle reflex by a variety of pre-stimuli such as prepulses and gaps has been widely used in animal research to assess physiological changes within the central auditory system, notably temporal acuity related to age-related hearing loss (Barsz et al., 2002; Ison, Agrawal, Pak, & Vaughn, 1998; Swetter, Fitch, & Markus, 2010), and

modifications of auditory functions with deletion of specific genes (*e.g.* K channels) (Allen et al., 2008; Ison & Allen, 2012) or pharmacological treatment (Ison & Bowen, 2000; Leitner & Girten, 1997). Gap-prepulse inhibition of the acoustic startle (GPIAS) has become the gold standard to assess behavioral gap detection in animals. This method has been proposed as an objective measure of tinnitus in animal models (Turner et al., 2006) under the rationale that tinnitus might "fill in" the gap and thus prevent inhibition of the startle. Moreover, the lack of inhibition would be specific to the tinnitus frequency, that is, a high-frequency tinnitus would produce more GPIAS deficit (i.e., less inhibition) when the gap is embedded in a high-frequency noise background than in a low-frequency background. Since it is based on a reflex rather than costly and time-consuming conditioning, this method has been enthusiastically adopted by many as a behavioral measure of tinnitus in several animal species (for a review, see Galazyuk & Hébert, 2015). However the interpretation of the tinnitus "filling in" the silent gap has been recently challenged in human (Boyen, Baskent, & van Dijk, 2015; Campolo, Lobarinas, & Salvi, 2013; Fournier & Hébert, 2013) as well as in animal studies (Hickox & Liberman, 2014). Since tinnitus is usually in the high frequency range (~10 kHz and above in animals when assessed by operant conditioning paradigms), one reason for being cautious about interpreting a decrease in inhibition as an objective marker of tinnitus is that, as shown herein, high−frequency produce less inhibition than low−frequency background noises (also found in Fournier & Hébert, 2013). Therefore identifying the source of a decrease in inhibition between high− and low− frequency backgrounds might be difficult when criteria for a deficit are not clearly defined. Moreover, although in one study GPIAS deficits were identified in human tinnitus

participants at both low− and high− frequency background noises without precisely controlling resemblance with tinnitus frequencies (Fournier & Hébert, 2013), some studies have found normal psychophysical gap detection abilities in tinnitus subjects (Boyen et al., 2015; Campolo et al., 2013), questioning the link between GPIAS and behavioral detection abilities. In psychophysical studies conducted in normal adults without hearing disorders − similar to the participants in the present study – threshold values of ~4.19 ms were identified and the vast majority of young adults were able to detect 5 ms gaps (Giannela Samelli & Schochat, 2008; Hoover, Pasquesi, & Souza, 2015). Herein, we showed that inhibition produced by a 5 ms gap-Embedded (but not gap-Following) stimulus is ~24% and constitutes a robust measure, with a lower limit of the conservative 99% confidence interval higher than null inhibition. This is consistent with the notion that the shortest gap was indeed detected. However, tinnitus data suggest that GPIAS and psychophysical detection might not be as straightforwardly linked as previously proposed, and that additional attentional processes might be involved in the latter (Li, Du, Li, Wu, & Wu, 2009).

It is concluded that in any study using the GPIAS method, there is a necessity to consider the type of gap paradigm (Gap-*Embedded versus* Gap-*Following*) and the duration selected to establish the inhibition (or lack thereof) as fundamentally different outcomes might arise.

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Table I. Sociodemographic characteristics (standard deviation) of participants in each gap duration group (5, 25, 50, 100, 200 ms) for each gap type (-*Embedded* or –*Following*).

Gap-E*mbedded* in the background

Gap duration (ms)	5	25	50	100	200	*p-value*
Number of participants	12	12	32	15	13	
Gender: Male Female	 7 5	 8 4	 19 13	 12 3	 5 8	 n.s.
Age in years (S.D.)	22.1 (3.3)	23.7 (3.6)	23.2 (2.9)	24.7 (2.0)	24.3 (2.5)	n.s.
Education in years (S.D.)	15.6 (3.1)	16.5 (2.7)	16.8 (2.9)	16.8 (1.4)	17.4 (3.3)	n.s.

Gap-*Following* the background

Gap duration (ms)	5	25	50	100	200	*p-value*
Number of participants	12	12	14	22	13	
Gender: Male Female	 4 8	 4 8	 6 8	 7 15	 4 9	 n.s.
Age in years (S.D.)	21.8 (2.6)	21.2 (3.0)	23.6 (2.7)	24.4 (2.9)	23.3 (3.3)	n.s.
Education in years (S.D.)	16.1 (2.0)	16.1 (2.5)	16.2 (2.2)	18.0 (2.1)	16.9 (2.4)	n.s.

Table II. *Post hoc* comparisons (*p* values) of **% inhibition** between each gap duration (5, 25, 50, 100, 200 ms) for each gap type (-*Embedded* or –*Following*).

Gap-*Embedded*	5 ms	25 ms	50 ms	100 ms	200 ms
5 ms	--	--	--	--	--
25 ms	0.73	--	--	--	--
50 ms	**=.002**	0.16	--	--	--
100 ms	**0.011**	0.29	1	--	--
200 ms	**<.001**	**0.004**	0.28	0.42	--
Gap-*Following*	5 ms	25 ms	50 ms	100 ms	200 ms
5 ms	--	--	--	--	--
25 ms	0.3	--	--	--	--
50 ms	**<.001**	**0.005**	--	--	--
100 ms	**<.001**	**<.001**	0.11	--	--
200 ms	**<.001**	**<.001**	0.78	0.78	--

The *p* values in bold represent cases in which groups significantly differ from one another.

Table III. *Post hoc* comparisons (*p* values) of **latency facilitation** between each gap duration groups (5, 25, 50, 100, 200 ms) for each gap type (-*Embedded* or –*Following*).

Gap-*Embedded*	5 ms	25 ms	50 ms	100 ms	200 ms
5 ms	--	--	--	--	--
25 ms	0.91	--	--	--	--
50 ms	0.99	0.7	--	--	--
100 ms	0.16	0.66	**0.02**	--	--
200 ms	0.13	0.57	**0.016**	1.0	--
Gap-*Following*	5 ms	25 ms	50 ms	100 ms	200 ms
5 ms	--	--	--	--	--
25 ms	0.94	--	--	--	--
50 ms	**0.015**	0.13	--	--	--
100 ms	0.61	0.98	0.2	--	--
200 ms	0.35	0.83	0.67	0.97	--

The *p* values in bold represent cases in which groups significantly differ from one another.

Table IV. Lower limits of the 99% confidence intervals (% inhibition and latency facilitation) for each gap duration groups (5, 25, 50, 100, 200 ms) for each gap type (-*Embedded* or –*Following*).

	Gap-*Embedded*		Gap-*Following*	
Gap duration	% of inhibition	Latency facilitation	% of inhibition	Latency facilitation
5 ms	**7.3**	-7	-24.6	-7
25 ms	**20.0**	-4	-3.5	-4
50 ms	**45.7**	-5	**34.5**	**6**
100 ms	**40.7**	**1**	**59.7**	**1**
200 ms	**56.1**	**1**	**45.3**	**1**

Values in bold represent cases in which the lower limit of the 99% confidence interval is greater than 0, suggesting the presence of a reliable inhibition and/or latency effect.

Table V. Individual differences between % inhibition by the Prepulse (control) and Gap conditions averaged across each gap duration (5 vs. 25 vs. 50 vs. 100 vs. 200 ms) and gap type (-*Embedded* vs. –*Following*) group.

	Mean difference (%) Prepulse - Gap	Paired sample *t-test*	*p*-value
Gap-*Embedded*			
5 ms	56.5 (33.3)	t(11)=5.9	**<.001
25ms	33.1 (32.3)	t(11)=3.5	* =0.005
50 ms	11.5 (24.8)	t(31)=2.6	* =0.014
100 ms	28.3 (22.6)	t(14)=4.9	**<.001
200 ms	6.4 (15.5)	t(12)=1.5	=0.16
Gap-*Following*			
5 ms	72.1 (26.5)	t(11)=9.4	**<.001
25ms	70.9 (29.5)	t(11)=8.3	**<.001
50 ms	24.0 (20.4)	t(13)=4.4	* =0.001
100 ms	12.1 (16.4)	t(21)=3.5	* =.002
200 ms	21.5 (17.9)	t(12)=4.3	**<.001

Supplement Table, Expérience 1.

Studies	**Subjects**	**Gap Duration (ms)**	**Type of noise**	**Startle Stimulus**	**Results**
Cranney, J., Cohen, M. E., & Hoffman, H. S. (1985)	Rats	5, 10, 20, 40, 80, 320, 1280	Tone	White noise burst	Strong inhibition up to 80 ms gaps, then slower inhibition up to 320 ms
Ison, J.R. (1982)	Rats	Experiment 2: 0, 5, 10, 20 Experiment 3: 0, 1, 2, 3, 4, 5, 7, 15, 30	White noise	Tone	Strong inhibition increase up to 7 ms gaps, then slower inhibition up to 30 ms
Ison, J. R., O'Connor, K., Bowen, P. G., & Bocinea, A. (1991)	Rats	Experiment 1: 2, 4, 6, 8, 10, 15	White noise	Noise burst	Strong inhibition increase up to 6 ms gaps then stabilization of inhibition up to 15 ms
Threlkeld, S. W., Penley, S. C., Rosen, G. D., & Fitch, R. H. (2008)	Rats	2, 5, 10, 20, 30, 40, 50, 75, 100	White noise	White noise burst	Strong inhibition increase up to 30 ms gaps, gaps then stabilization (even a small decrease) of inhibition up to 100 ms
Harbin, T., J., & Berg, W. K. (1983)	Humans	10, 20, 40, 80, 120	Tone	Puff of air	Strong inhibition increase up to 40 ms gaps, then small increase up to 120 ms
Ison, J. R., & Pinckney, L. A. (1983)	Humans	0, 2, 4, 6, 8, 10	White noise	Shock on the forehead	Strong inhibition increase up to 8 ms gaps
Present Study	Humans	5, 25, 50, 100, 200	Narrow-band noise	White noise burst	Strong inhibition increase up to 50 ms gaps

Figure legends

Figure 1. A schematic view of Pulse-Alone in background noise (A), Gap-*Embedded* (B), Gap-*Following* (C), Pulse-Alone in silence (D) and Prepulse in silence (E) trials (SS = Startle Sound). Pulse-Alone trials consisted of a startle sound in either a silent or continuous noise background. Gap-*Embedded* trials consisted of a continuous noise background and a gap presented 120 ms before the Startle Sound (SS). The Gap-*Following* condition consisted of a continuous background noise and a gap of silence presented just before the Startle sound. Prepulse trials consisted of a silent background with a 50 ms prepulse presented 120 ms before the Startle Sound.

Figure 2. Percentage of inhibition (SEM) for each gap duration group (5, 25, 50, 100, 200 ms) and gap type (-*Embedded* or -*Following*).

Figure 3. Latency facilitation (SEM) for each gap duration group (5, 25, 50, 100, 200 ms) and gap type (-*Embedded* or -*Following*).

Figure 4. Percentage of inhibition (SEM) for each pre-stimulus (Prepulse, Gap-*Embedded* or -*Following*) for each frequency (High- and Low-).

Figure 1, Expérience 1.

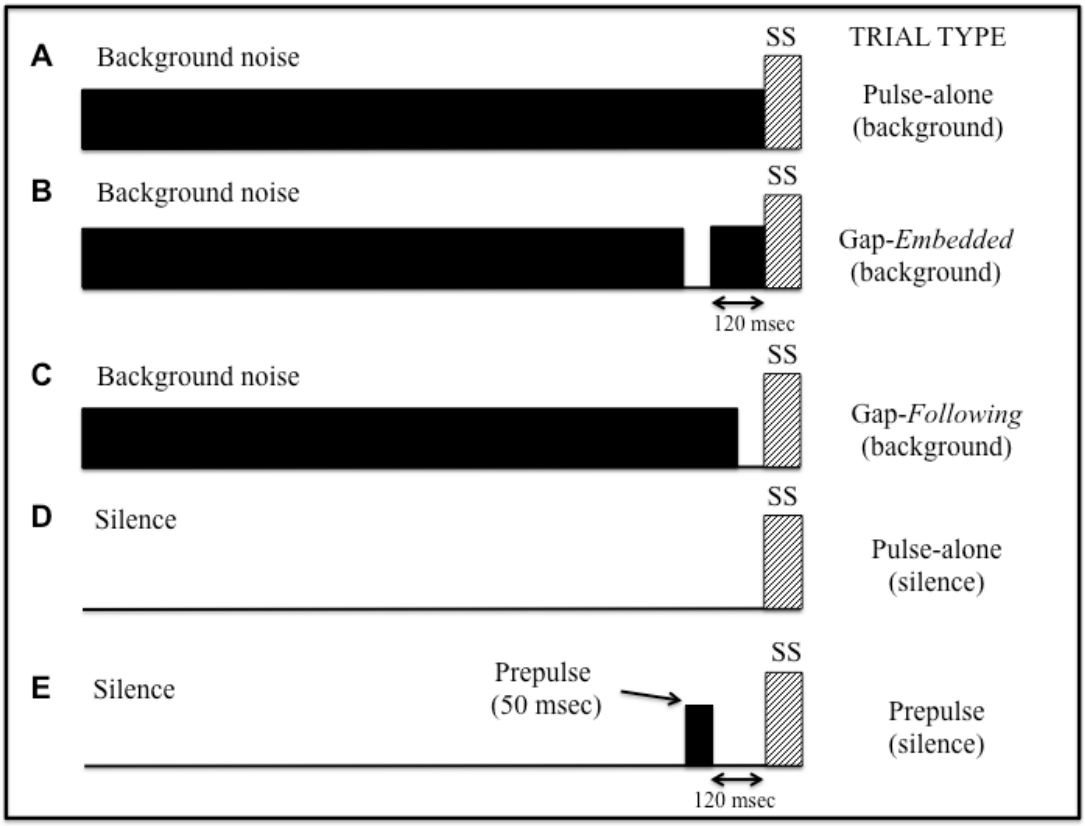


Figure 2, Expérience 1.

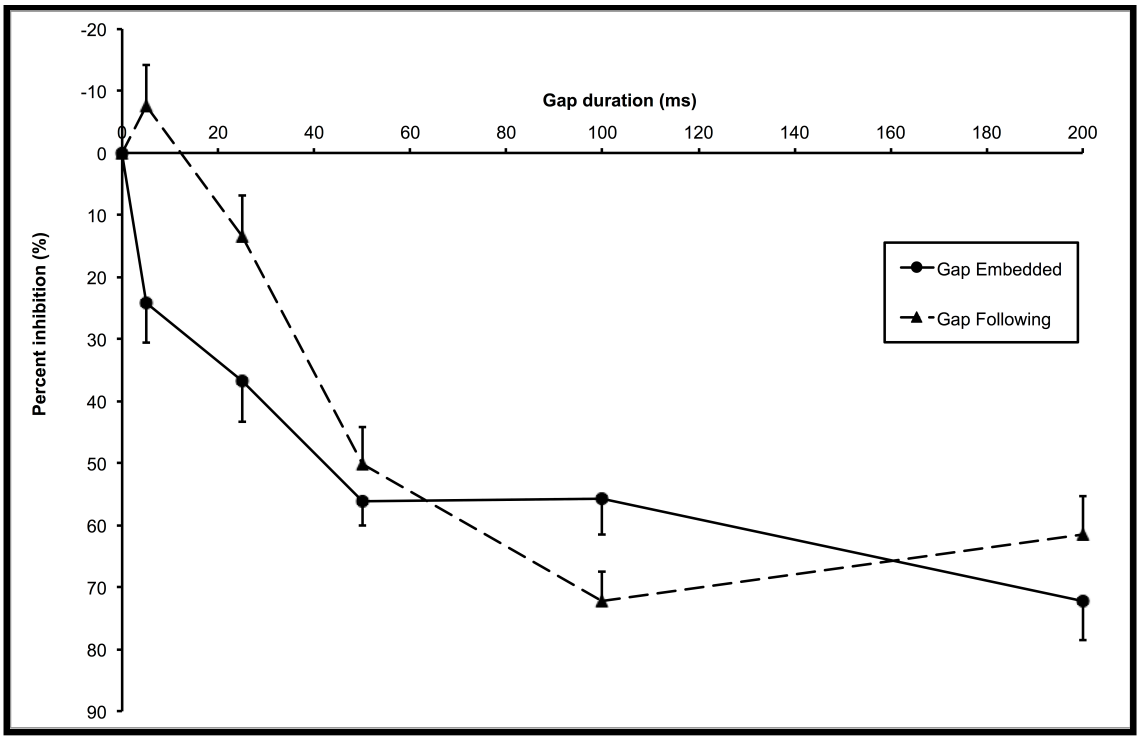
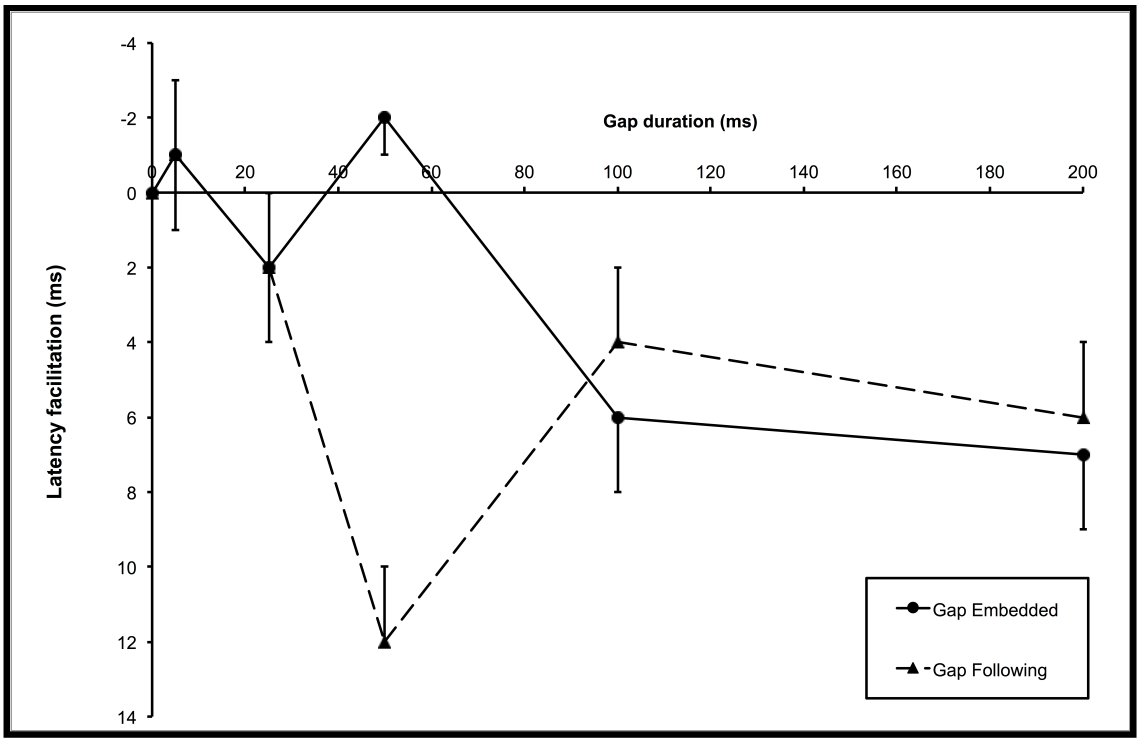


Figure 3, Expérience 1.



EXPÉRIENCE 2

Psychoacoustic Assessment to Improve Tinnitus Diagnosis

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Abstract

The diagnosis of tinnitus relies on self-report. Psychoacoustic measurements of tinnitus pitch and loudness are essential for assessing claims and discriminating true from false ones. For this reason, the quantification of tinnitus remains a challenging research goal. We aimed to: (1) assess the precision of a new tinnitus likeness rating procedure with a continuous pitch presentation method, controlling for music training, and (2) test whether tinnitus psychoacoustic measurements have the sensitivity and specificity required to detect people faking tinnitus. Musicians and non-musicians with tinnitus, and simulated malingerers without tinnitus were tested. Most were retested several weeks later. Tinnitus pitch matching was first assessed using the likeness rating method: pure tones between 0.25 to 16 kHz were presented randomly to participants who had to rate the likeness of each tone to their tinnitus, and to adjust its level from 0 to 100 dB SPL. Tinnitus pitch matching was then assessed with a continuous pitch method: participants had to match the pitch of their tinnitus by moving their finger across a touch sensitive strip, which generated a continuous pure tone from 0.5 to 20 kHz in 1 Hz steps. The predominant tinnitus pitch was consistent across the two methods for both musicians and non-musicians, although musicians displayed better external tone pitch matching abilities. Simulated malingerers rated loudness much above the other groups with a high degree of specificity (94.4%) and were unreliable in loudness (not pitch) matching from one session to the other. Retest data showed similar pitch matching responses for both methods for all participants. In conclusion, tinnitus pitch and loudness reliably corresponds to the tinnitus percept and psychoacoustic loudness matches are sensitive and specific to the presence of tinnitus.

Keywords: Tinnitus, pitch, loudness, assessment, simulated malingerers, music training, psychoacoustics

Introduction

The diagnosis of tinnitus relies exclusively on patient self-report and various subjective questionnaires (de Azevedo, Langguth, de Oliveira, & Figueiredo, 2009; El Refaie et al., 2004; Holgers et al., 2003), thus precluding objective assessment of the progression of the tinnitus percept (with time or therapeutic intervention) and identification of physiological tinnitus at an acceptable level of specificity. As a consequence, much effort has been devoted to devise psychoacoustic measures based on pitch and loudness matching.

Pitch matching

Most conventional studies on tinnitus pitch matching designed to identify a single predominant frequency (often described as tonal tinnitus) using either a forced-choice paradigm or a method of adjustment (Burns, 1984; Henry et al., 2000; Henry et al., 2001; Henry et al., 2004; Karatas & Deniz, 2011; König et al., 2006; Martines et al., 2010; Mitchell et al., 1993; Moore et al., 2010; Nageris et al., 2010; Newman et al., 1994; Pan et al., 2009; Penner & Bilger, 1992; Penner & Klafter, 1992; Penner & Saran, 1994; Savastano, 2008; Schecklmann et al., 2012; Shekhawat et al., 2014; Tyler & Conrad-Armes, 1983b; Vernon & Meikle, 2003; Ward & Baumann, 2009), show that the perceived predominant pitch falls within the frequency band of the hearing loss (Martines et al., 2010; Newman et al., 1994; Savastano, 2008; Schecklmann et al., 2012; Shekhawat et al., 2014). Because these methods have shown variable degrees of test-retest reliability (Henry et al., 2000; Henry et al., 2001; Mitchell et al., 1993; Nageris et al., 2010) pitch matching is generally not deemed a good parameter for treatment outcome (Langguth et al., 2007). Recent studies used a patient-directed approach with a likeness rating scale

(Fournier & Hébert, 2013; Heijneman et al., 2013; Kay et al., 2008; Moffat et al., 2009; Noreña et al., 2002; Roberts et al., 2008; Roberts et al., 2006; Sereda et al., 2011; Weisz et al., 2006; Zhou et al., 2011) in which the participants rate the likeness of every frequency (0.25 to 16 kHz by half octave steps) to their tinnitus, thereby defining a tinnitus spectrum. The likeness rating method showed that tinnitus is composed of a wide frequency bandwidth mirroring the hearing loss region (Heijneman et al., 2013; Kay et al., 2008; Moffat et al., 2009; Noreña et al., 2002; Roberts et al., 2008; Sereda et al., 2011; Zhou et al., 2011) even when no hearing loss is found at standard audiometric frequencies (0.25 to 8 kHz) (Fournier & Hébert, 2013; Weisz et al., 2006). However, it remains unclear whether the likeness rating technique, which involves a discrete mode of presentation, can provide an accurate estimate of the predominant pitch compared to when only one pitch is matched, such as in the continuous pitch paradigm proposed herein. A first goal of this study was to introduce a new patient-directed tinnitus likeness rating procedure and compare its precision with a continuous pitch presentation method, while controlling for participants' musical expertise. Moreover, we conducted test-retest trials to establish the method's reproducibility.

Loudness matching

When tinnitus loudness is estimated by adjusting the volume of a single external pure tone to the loudness of the predominant tinnitus pitch, it usually ranges from 5 to 15 dB Sensation Level, or dB SL, even though patients subjectively describe their tinnitus as being very loud (Hallam et al., 1985; Newman et al., 1994; Tyler & Conrad-Armes, 1983a). Some studies have shown good loudness test-retest reliability over a period ranging from several days (Henry et al., 2000; Henry et al., 1999; Henry et al., 2009;

Henry et al., 2004; Mitchell et al., 1993; Roberts et al., 2008) to several months (Fournier & Hébert, 2013; Nageris et al., 2010) with less than 5 dB difference between sessions, whereas other studies have reported greater variability (Burns, 1984; Henry et al., 2006; Penner & Bilger, 1992), putting into question the validity of this measure for tinnitus diagnosis and follow-up. Herein, we investigate the proposition that the assessment of frequency likeness ratings over the entire frequency span will increase the reliability of loudness judgments by providing participants with several opportunities to judge tinnitus loudness.

Differentiating true from false tinnitus

There is currently no measure that discriminates true from false claims of tinnitus at an adequate level of specificity. Since the economical burden of tinnitus to society is substantial (Maes et al., 2013), it is surprising that very few studies have attempted to address whether psychoacoustic measures such as pitch and loudness are effective criteria for detecting tinnitus simulation (Henry et al., 2009; Henry et al., 2013; Henry et al., 2006; Jacobson et al., 2000). Regarding pitch matching, studies reported lower tinnitus pitch matches for simulated malingerers, that is, participants instructed to pretend that they had tinnitus (Henry et al., 2009; Henry et al., 2013; Henry et al., 2006). Regarding loudness matching, studies reported *lower* dB SL matches (Henry et al., 2006), *higher* dB SPL but *no different* dB SL (Henry et al., 2009), or *higher* dB SL matches for simulated malingerers (Jacobson et al., 2000). Low frequency loudness matches were found to be the most predictive value for the presence or absence of tinnitus (Henry et al., 2013). A final goal was therefore to examine whether pitch and loudness tinnitus matching can detect people without tinnitus.

Summarizing our method and objectives, we used a new participant-directed likeness rating method to match tinnitus pitch and loudness over a wide frequency spectrum (from 0.25 to 16 kHz). We tested two groups of tinnitus participants with different levels of musical training (musicians and non-musicians), as well as a group of simulated malingerers who feigned tinnitus, and we compared external pitch matching ability performances across groups. Predominant tinnitus pitch obtained with the likeness ratings was compared to a method using a single continuous pitch. Pitch and loudness ratings at the predominant tinnitus pitch were used as predictors to address participants' sensitivity and specificity for tinnitus presence or absence. Finally, test-retest reliability was assessed after a delay of several months to test for reproducibility of findings, stability of the tinnitus percept, and suitability for treatment outcome.

Methods

Participants

A total of 50 participants were recruited through newspaper and online ads, and word of mouth. They were either musicians (n=16) or non-musicians (n=16) with tinnitus, or tinnitus simulated malingerers (n=18), that is, individuals without tinnitus instructed to simulate this sound perception with the intention of convincing the experimenter that they have tinnitus. Simulated malingerers had to have had previous experience of transient tinnitus, lasting no longer than one day and not in the month prior to the testing so that they could rely on this past experience to fake tinnitus. Musicians were selected on the criterion of having at least three years of formal musical training (mean= 10 years ± 5.5); otherwise, they were considered as non-musicians (mean= 0.13 year ± 0.5). Tinnitus in both groups had to be continuously present for at least six months

(mean for musicians = 10.6 ± 7 years; mean for non-musicians = 11.3 ± 11 years). Exclusion criteria were having more than a moderate hearing loss at any standard audiometric frequency in either ear (>55 dB HL for 0.25 to 8 kHz), uncontrolled medical conditions, outer and middle ear pathology, or heavy smoking (> 10 cigarettes/day). The participant's relevant sociodemographic characteristics are summarized in Table I (A). Overall, at standard frequencies (0.25 to 8 kHz) non-musicians had higher hearing thresholds in the right ear than did simulated malingerers but not than musicians. Non-musicians had also higher thresholds than did musicians and simulated malingerers in the left ear, but the last two did not differ. At very high frequencies (9 to 16 kHz), non-musicians had higher thresholds than did both musicians and simulated malingerers, and the last two also differed from one another. More than half of the participants in each group - nine musicians, nine non-musicians, and ten simulated malingerers - were retested some weeks later (mean of 25 weeks ± 13). All tinnitus participants confirmed that their tinnitus was essentially unchanged across sessions. Relevant sociodemographic characteristics of the retest participants are summarized in Table I (B). Overall, hearing thresholds were significantly higher for both musicians and non-musicians than for simulated malingerers.

The study has been approved by the Ethical Committee of Université de Montréal and all participants gave their written informed consent.

Materials and Procedure

Hearing test

Hearing detection thresholds were assessed monaurally from 0.25 to 8 kHz in each ear in half-octave steps by a clinical audiologist using the standard modified Hughson-Westlake up-down procedure (Schlauch & Nelson, 2009) with a AC-40 clinical audiometer (Interacoustics, Assens, Denmark) and ER-3A insert earphones (Aero Compagny Auditory Systems, Indianapolis, IN, USA). In addition, very high-frequency thresholds (9 to 16 kHz) were also assessed monaurally in each ear using Sennheiser HDA-200 supra-aural headphones (Sennheiser electronic GmbH & Co., Wedemark, Germany). The audiometric equipment was calibrated in a soundproof booth using the ANSI S3.6-2004 standard norms. An otoscopic examination was performed before each hearing test to rule out earwax compaction or middle ear infection.

Tinnitus matching with the likeness rating method

The likeness rating method (described in Fournier & Hébert, 2013) is a custom-made program running under Max/MSP software (Cycling 74, San Francisco, USA) controlling a visual interface implemented in a computer touchscreen (Élo TouchSystems, Menlo Park, CA). Stimuli were one-second pure tones ranging from 0.25 to 16 kHz (the same frequencies as in the hearing test) generated by a Fireface sound card (RME, Haimhausen, Germany) and presented binaurally using closed dynamic headphones "DT 770 Pro/250" (Beyerdynamic, Heilbronn, Germany). Participants sat in a soundproof booth in front of the touchscreen and initiated the presentation of a pure tone by pressing a green button ("Play") on the screen (Figure 1). They first rated the likeness of the tone

to their tinnitus pitch on a Likert-type scale where 0 = does not match my tinnitus at all and 10 = perfectly matches my tinnitus. 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 gauge that increased and decreased the sound level in 1 dB steps, from 0 to 100 dB SPL. The program allowed participants to play each pure tone as many times as needed. When pitch and loudness matches were done, participants pressed a red button ("Next") to initiate the following trial. Each specific pure tone was presented three times in a pseudo-random order such that no two identical frequencies were presented in a row. Two pure tones of 600 Hz and 5 kHz were presented before and served as practice trials. Headphones were calibrated before each session with a SoundPro SE/DL sound level meter using a QE-4170 microphone model (Quest Technologies, Oconomowoc, Wis., USA) and an EC-9A 2cc ear coupler (Quest Electronics, Oconomowoc, Wis., USA).

Tinnitus matching with the slider method

The slider method, described in a previous study (Hutchins & Peretz, 2012) was used to validate the precision of the likeness rating method and involved tinnitus pitch matching using a continuous pitch presentation. Responses were made on a simple device called a slider, two superposed touch-sensitive strips, with the ability to sense pressure and position (Infusion System, Montreal, Canada). These 50 cm strips were mounted on a hard surface, inset between two plastic bars. The slider sent a 10-bit midi signal to indicate the position of the participant's finger presses that was converted into a sine wave by Max/MSP. The frequency of the slider's output was determined by the position of the participant's finger press, such that lower tones were created by pressing on the

slider's left side, and higher tones by pressing on the slider's right side. The range of the slider was fixed for each individual trial, but could be changed between trials. The frequency associated with each position of the slider was based on an exponential curve, such that octaves and semitones were always equidistant in both directions (similar to how tones are arranged on a piano). Although the slider's output is fundamentally quantized by the position, in practice the 1024 available positions are so close together (~.5 mm per position) that the resulting frequency output is perceived as changing continuously when the finger moves between positions. Participants heard the tones generated by a Fireface sound card through DT 770 Pro headphones, and the sound level was adjusted at a comfortable level for each participant by the experimenter.

Participants initiated the tinnitus matching trials by pressing the space bar on a keyboard, and they were asked to use the slider to match the pitch of their tinnitus. There were three trials of tinnitus matching, with each trial subdivided into three different rounds (see Figure 2). In the first round, the range of the slider was set between 500 Hz and 20 kHz, to capture the entire possible range of a participant's tinnitus. Participants were instructed to find the pitch on the slider that best matched their tinnitus, and to save their final response and initiate the following round by pressing the space bar. In the second round, the range was limited to two octaves around the final tone chosen in round one, which was centered on the slider, and participants were again instructed to find the best match for their tinnitus. Once this was chosen, the range in the third round was limited to one octave around the final tone chosen in round two, and the tone was once again centered on the slider. This procedure was intended to allow participants to match

their tinnitus pitch as specifically as possible, up to 1 Hz precision, while still giving the entire range to draw from.

Pitch matching abilities assessment

Using the slider, the ability to match pitches to external tones was assessed. Target tones were set at 0.5 kHz, 2 kHz, 6 kHz, and 14 kHz, to cover most of the range of typical hearing, and were played a sine wave as well. The task began when the participant pressed the space bar on a keyboard. The target tone was played continuously through DT 770 Pro headphones, and participants were instructed to match it as closely as possible on the slider. The target tone was turned off while the slider was being pressed, to avoid using beating or acoustical dissonance as cues, but it was turned back on when the participants removed their finger from the slider. This was done so that the participants never needed to remember the pitch and matching was not impaired by poor pitch memory skills or interference from tinnitus pitch. Participants were told that they could take as long as they liked to match the target. When they had done so, participants saved their final response by pressing the space bar and initiated the next trial. This pitch matching ability task included 20 tones presentation, using five examples of each target such that no two identical tones were presented in a row. The slider's total range was one octave during each trial, with the upper and lower boundaries randomly chosen such that the target tone would fall in the middle two thirds of the slider. Thus, participants did not have any cues from prior trials where the target tone would be located on the slider. Furthermore, pure tones of 0.25 kHz, 4 kHz, 1 kHz, 8 kHz, and 12 kHz were previously used as practice trials for the matching task before the target tones were presented. Finally, the loudness of the tone was adjusted to a comfortable level for each participant

by the experimenter.

Visual analog scales

Five visual analog scales (VAS) of tinnitus annoyance (usually, now), loudness (usually, now), as well as attention spent usually on tinnitus were used. The scales were 100 mm horizontal lines with the left and right extremes labeled, respectively, "no annoyance at all" and "very annoying", for all five scales.

Procedure

After hearing threshold assessment, tinnitus matching methods were conducted in a counterbalanced order among groups and between test sessions (test vs. retest). The slider method always began with the pitch matching ability assessment to familiarize the participants with the slider. Participants were asked to provide repeatable tinnitus matching responses to the best of their ability. Simulated malingerers were not instructed to use any particular method to provide consistent responses during matching. All measures were taken in a soundproof booth at the BRAMS (Eckel Industries, Morrisburg, Ontario, Canada). The validated French version of the Tinnitus Handicap Questionnaire (THQ) (Kuk et al., 1990; Meric, Pham, & Chéry-Croze, 1997) and the visual analog scales were given in a random order before psychoacoustics tasks. The likeness rating method took 20-30 minutes and the slider method took no longer than 15 minutes.

Data processing and Statistical Analysis

For the likeness rating method, the mode for each frequency for each participant was used (or the median when the mode failed to reveal a single rating value). Tinnitus

loudness matching (in dB SPL) at each frequency was averaged. When participants in a trial rated the likeness of the pure tone as 0, the loudness value of that trial was removed from further analysis. The loudness was converted in sensation level (dB SL), that is, the difference between the sound pressure level of tinnitus loudness matching and the sound pressure level of the best hearing threshold shift between left and right ears. The predominant frequency of the tinnitus spectrum was defined as the frequency with the highest likeness rating score and the tinnitus loudness was set as the sensation level value at this frequency. If more than one highest rating value was reported, the predominant tinnitus pitch was averaged between the frequencies corresponding to the lowest and highest rating values across the frequency span and the mean loudness value of those frequencies.

For the slider method, the predominant tinnitus pitch corresponded to the mean frequency matched in round three of each trial. The ability to match pitch to external tones was assessed by the differences in cents between the target tone and matched frequency. Due to his elevated hearing thresholds at 14 kHz, one participant could not match this target tone and was excluded from pitch matching analyses (n = 15) at this frequency. Pitch information obtained for the external pitch matching task with the slider was converted to semitones so that meaningful comparisons could be made between different trials. Because responses in both pitch and tinnitus matching tended to consist of multiple instances of discrete tones, the pitch of the final discrete tone produced during each trial was taken as the primary measurement. In the external pitch matching task, the absolute value of the error of the final response (the pitch of final response minus the pitch of target tone) was used to avoid sharp and flat errors cancelling out. Final

responses for each target tone were considered accurate if the pitch was within 50 cents (1/2 semitone) of the target, a criterion validated in other experiments (Hutchins & Peretz, 2012; Hutchins, Roquet, & Peretz, 2012).

Hearing thresholds were averaged separately for standard frequencies (0.25 to 8 kHz) and for very high frequencies (9 to 16 kHz) for each ear. Pitch and loudness matches and pitch matching ability were assessed as within-subjects factors by a mixed ANOVA between groups. When interactions involving groups were significant, Tukey post-hoc tests were conducted. The test-retest reliability between sessions was assessed using mixed ANOVAs with Group as the between-subject factor, Frequency and Session (Test/Retest) as the within-subject factors. When interactions involving session were significant, repeated-measure ANOVAs and paired sample t-tests were conducted. Pearson product-to-moment correlations were also used to assess within-trial reliability. Binary logistic regression was used to assess sensitivity and specificity of the psychoacoustic measures. The dependent variable was the presence of tinnitus irrespective of musicianship (Tinnitus/No tinnitus). Predictor variables were the two predominant pitches (the two highest likeness rating scores) and loudness match at these predominant frequencies. Statistical analyses were performed with SPSS 18.0 for Windows (Chicago, IL, USA).

Results

Tinnitus pitch matching using the likeness ratings

A significant two-way interaction between Frequency and Group was found [$F(30,705)=2.07$; $p=.001$]. Musicians and non-musicians rated the pitch of their tinnitus

very similarly, differing only for 16 kHz (means of 3 and 7, respectively, p=.019), whereas simulated malingerers rated lower frequencies as being more like their tinnitus (see Figure 3 and 4) than did musicians (at 0.5 kHz, 1.5 kHz, 2 kHz, and 6 kHz, all p values between .029 and .005) and non-musicians (at 0.5 kHz, 0.75 kHz, 1.5 kHz, and 2 kHz, all p values between .039 and .007). At retest, only the main effect of Frequency [F(15,375)=50.78; p<.001] was significant.

For the likeness rating reliability, the three-way interaction between Session (Test vs. Retest), Frequency and Group was marginally significant [F(30,375)=1.49; p=.050]. This was due to a significant difference between the two sessions at 11.2 kHz for musicians (p=.047 by paired sample t-tests) (see Table 2).

Tinnitus loudness matching using the likeness ratings

A significant two-way interaction between Frequency and Group was also found [F(30,705)=2.16; p<.001]. Simulated malingerers rated the loudness of their tinnitus much higher than did both musicians and non-musicians at all frequencies except 0.25 kHz (all p values between .004 and <.001 by post-hoc tests) (see Figure 3). From 0.25 to 16 kHz, the mean tinnitus loudness was 4 ± 2 dB SL for musicians, 3 ± 2 dB SL for non-musicians, and 28 ± 2 dB SL for simulated malingerers. There was no significant difference between musicians and non-musicians. Retest data showed a main Group effect [F(2,25)=9.36; p=.001]. Again simulated malingerers rated loudness much higher than did the musicians (p=.001) and non-musicians (p=.008) (mean = 18 ± 3 dB SL). Musicians and non-musicians did not differ in their loudness matches, with means of 1 ± 3 dB SL and 4 ± 3 dB SL, respectively, from 0.25 to 16 kHz.

For loudness matching reliability, an interesting result emerged. The three-way interaction between Session, Frequency, and Group was significant [$F(30,375)=1.99$; $p=.002$]. Two-way ANOVAs were conducted separately for the three groups. For simulated malingerers, a significant interaction between Session and Frequency was found [$F(15,135)=3,49$; $p<.001$]. Simulated malingerers' loudness ratings differed from test to retest at all frequencies from 6 to 16 kHz ($p<.05$ for paired-sample t-tests) (see Table II). This was not the case for musicians and non-musicians, whose mean loudness test-retest ratings were stable at all frequencies except for musicians at frequency 4 kHz (hence the three-way interaction).

Predominant tinnitus pitch and loudness with the likeness ratings

Table III summarizes the results of the predominant tinnitus pitch and its loudness for the three groups at test (Table III, A) and retest (Table III, B). Tinnitus predominant pitch differed between groups ($p=.002$) only at the first test session. Non-musicians rated their tinnitus pitch slightly higher than did musicians (means = 14.2 kHz and 10.3 kHz, respectively, $p=.027$) and simulated malingerers (mean = 8.9 kHz, $p=.001$), but simulated malingerers and musicians did not differ ($p=.58$). Loudness at the predominant tinnitus pitch differed between groups for both test sessions ($p<.001$). Simulated malingerers rated the tinnitus loudness much higher than did musicians and non-musicians at both test (mean differences = 27.5 and 37.5 dB SL, respectively, both $p<.001$ by post-hoc comparisons) and retest (mean differences = 23.7 and 20.5 dB SL, respectively, $p<.001$ and $p=.003$).

Loudness ratings, not pitch, predict tinnitus malingering

When loudness at the two predominant tinnitus pitches was used as a predictor of the presence or absence of tinnitus, the model was very successful (R^2 = 0.752, overall percentage = 94.0%), correctly identifying 93.8% of tinnitus participants (i.e., sensitivity, n=30), while correctly rejecting 94.4% of participants without tinnitus (i.e., specificity, n=17). The model was much less successful (R^2 = 0.163, overall percentage = 70.0%) when using the two predominant tinnitus pitches, correctly identifying 90.6% of tinnitus participants (i.e., sensitivity, n=29), while correctly rejecting only 33.3% of participants without tinnitus (i.e., specificity, n=6). At retest, better predictive values were again found for tinnitus loudness than pitches (R^2 = .693 vs. .243, overall percentages of 84.6 vs. 73.1%), with sensitivity of 93.8% (vs. 87.5%) and specificity of 70.0% (vs. 50.0%).

Tinnitus matching using the slider method

A mixed ANOVA between Tinnitus matching trials (3) and Group was performed, and a main Group effect was found [F(2,47)= 6,40; p=.003]. Results were similar to those obtained with the likeness ratings at both test and retest: at test non-musicians described a mean pitch higher than musicians (with means of 13.5 ± 3.0 kHz and 9.6 ± 5.2 kHz, respectively, p=.049 by post-hoc comparisons) and than simulated malingerers (mean = 8.0 ± 5.2 kHz, p=.003), but there was no significant difference between musicians and simulated malingerers (see table IV, A). At retest, no significant main effects or interactions were found (see table IV, B). For pitch matching reliability, there was no interaction between sessions; however, a main effect of Group was significant [F(2,25)=3,95; p=.032]. For both sessions, non-musicians had a mean tinnitus pitch

higher than did simulated malingerers (with means of 13.9 ± 1.5 kHz and 10.0 ± 4.6 kHz, respectively, p=.025, by post-hoc comparisons). Table V shows the inter-trials reliability between the groups at test (Table V, A) and retest (Table V, B). All groups were consistent in their responses of tinnitus pitch in both sessions (all rs > .80, p<.010).

Predominant tinnitus pitch does not differ from one method to the other

The predominant tinnitus pitch between the two matching methods was compared using paired sample t-tests. Results are displayed in Table IV for each group for both sessions. The mean tinnitus pitch differences were not significant for musicians, non-musicians and simulated malingerers at test (Table IV, A) or at retest (Table 4B).

No difference between tonal and noise tinnitus types

The psychoacoustic characteristics (predominant pitch, loudness) and the psychological aspects (VAS and THQ) of tinnitus were compared between tinnitus reported as "tonal" and "noise" types using paired sample t-tests and ANOVA. Simulated malingerers were not included in this analysis. Results are shown in Table VI. Pitch and loudness at the predominant pitch and the distress measured through VAS and THQ scores did not differ between the two subgroups. The number of predominant frequencies tended to be higher by 1 in noise tinnitus than in tonal tinnitus, but the difference did not reach significance.

Tinnitus percept does not correlate with VAS or THQ

Table VII shows the correlations among all VAS, the THQ, and psychoacoustic predominant pitch and loudness at the predominant pitch for tinnitus participants.

Simulated malingerers were not included in this analysis. All VAS, including loudness, were highly correlated with THQ scores, but not with psychoacoustic pitch and loudness.

Ability to match pitch to external tones

Figure 5 shows differences between target and matched frequencies using the slider for musicians, non-musicians, and simulated malingerers. Since variability among musicians' responses was as much as 74 times smaller than within the two other groups and Levene's test for homogeneity of variances was significant for all target tones (all *p*s<.001), non-parametric Kruskal-Wallis and Mann-Whitney U tests were used to test group differences for each target tones. Differences among groups were significant for all four target tones (all *p*s between <.001 and .015). Musicians were better to match target tones than were non-musicians at all frequencies (all *p*s between <.001 and .008) and than simulated malingerers at all frequencies except 14 kHz (*p*s between .002 and .004, *p*=.13 for 14 kHz). Non-musicians and simulated malingerers did not differ from one another at any frequency (all *p*s between .07 and .72). Overall, the mean difference in cents was 7.8 (SEM: 17.5) for musicians compared to 76 (SEM: 18.1) for non-musicians - almost ten times greater than musicians - and 59 (SEM: 16.5) for simulated malingerers. At retest, differences among groups were significant at all target tones except 14 kHz (all *p*s between .003 and .05; *p*= .57 at 14 kHz). Musicians differed from non-musicians and simulated malingerers at all frequencies except 14 kHz (all *p*s between .002 and .05; *p*s= .69 and .23 at 14 kHz, respectively). Again, non-musicians and simulated malingerers did not differ from one another at any frequency (all *p*s between .12 and .69). At retest, the mean difference in cents was 6.7 (SEM: 16.5) for musicians compared to 51.9 (SEM: 16.5) for non-musicians and 36.2 (SEM: 16.5) for simulated malingerers.

Discussion

Herein, we reported several novel findings in support of the psychoacoustic assessment of tinnitus for tinnitus diagnosis and characterization.

Psychoacoustic assessment improves tinnitus diagnosis

Using a participant-directed likeness rating method to match tinnitus pitch and loudness over a wide frequency spectrum (from 0.25 to 16 kHz), we found that musicians and non-musicians rated the pitch of their tinnitus very similarly, with low likeness ratings in the low frequencies rising slowly towards the highs. Likewise, musicians and non-musicians rated the SL loudness of their tinnitus no differently over the whole frequency span and in the SL range usually described (< 5 dB SL). In sharp contrast, even relying on their past −though fleeting− experience of tinnitus, simulated malingerers rated their tinnitus as being composed of lower pitches and at a much higher loudness than did tinnitus participants over the entire range of frequencies except 0.25 kHz. Our findings support and extend previous findings showing lower pitch matches (Henry et al., 2009; Henry et al., 2006) and higher loudness in SL (Jacobson et al., 2000) in simulated malingerers but contradict those reporting lower loudness or no difference between tinnitus and no-tinnitus participants (Henry et al., 2009; Henry et al., 2013; Henry et al., 2006). The robustness of our data was further corroborated, however, by a retest session that took place six months on average after the first session, compared to less than a month in previous studies (Henry et al., 2009; Henry et al., 2006; Jacobson et al., 2000; Mitchell et al., 1993). While reliability of pitch matching was similar in the three groups, loudness reliability was excellent among musicians and non-musicians but much less reliable among simulated malingerers. It is striking that the last group's loudness rating

were different from test to retest over a broad range of frequencies, especially those in the very high frequencies, which are not routinely assessed during audiological testing. This finding highlights the importance of assessing frequencies above 8 kHz for tinnitus diagnosis and puts forth the potential value of loudness as a parameter to distinguish individuals simulating tinnitus from those who genuinely have tinnitus.

Tinnitus pitch identification

One important question addressed here was whether the likeness rating method could allow the extraction of one predominant tinnitus pitch that provides an advantage over no constraint on pitch selection. Predominant tinnitus pitch using the likeness ratings was higher in non-musicians than both musicians and simulated malingerers. This is unsurprising since non-musicians displayed slightly elevated ultra high frequency thresholds and tinnitus pitch is usually in the frequency band region of hearing loss (Fournier & Hébert, 2013; Noreña et al., 2002; Roberts et al., 2008; Zhou et al., 2011). Use of the slider yielded essentially the same results: non-musicians rated their tinnitus pitch as higher than both musicians and simulated malingerers, with no difference between the latter two. Strikingly the comparison between these two extremely different methods indeed yielded no significant tinnitus pitch differences for any of the groups, therefore supporting the strength of the likeness rating method in extracting a predominant tinnitus pitch. Similar to what has been described in previous studies (Roberts et al., 2008; Sereda et al., 2011), it is remarkable that participants who reported noise tinnitus were able to identify a predominant pitch. Given that tonal tinnitus comprises a bandwidth that can be wider than noise tinnitus (Roberts et al., 2008; Sereda et al., 2011), the relevance of distinguishing "tonal" from "noise" tinnitus becomes

questionable. More detailed differences among tinnitus spectra, such as type of hearing loss, may be more relevant to distinguishing subgroups of tinnitus patients (Heijneman et al., 2013).

Our data emphasize the appropriateness of the likeness rating method for assessing the tinnitus pitch of participants notwithstanding their musical backgrounds. Our study is the first to assess whether musical training could improve the assessment of tinnitus pitch. Indeed, although musicians were able to match external sine waves within a few cents, all three groups were consistent at matching their tinnitus pitch.

Tinnitus predictors

One of the most novel finding of this study is that when predominant pitch and loudness are extracted from the likeness ratings and compared as predictors for the presence of tinnitus, it is the loudness, not the pitch, that has the greatest predictive value. Psychoacoustic loudness at the predominant pitch is therefore a sensitive and a specific measure of the tinnitus percept. This was shown here redundantly by the fact that simulated malingerers rated higher loudness levels at many frequencies, and evinced loudness (not pitch) unreliability from test to retest, especially in the very high frequency range. These results contradict a previous study (Henry et al., 2013), which found lower loudness matches sensation level as sensitive factor of tinnitus absence. If loudness is rated greater and less reliably from one session to the next, clinicians may have an indication that tinnitus is not present. Therefore, implementing a likeness rating method similar to the touchscreen in clinical practice could potentially be a tool for discriminating tinnitus sufferers from malingerers. In 30 minutes of testing, the

experimenter is able to measure both tinnitus pitch and loudness and to report whether loudness matching is consistent with real tinnitus or simulation. If there is doubt, a retest would confirm greater loudness matches. Finally, unreliability between the test and retest would provide a third opportunity to detect simulated tinnitus, especially at very high frequencies.

Perspective: Tinnitus percept versus distress

Predictably, widely used visual analog scales or handicap questionnaires were not correlated to psychoacoustic parameters of tinnitus, a finding consistent with previous studies that found that visual analog scales are correlated with mood and distress rather than actual loudness in SL (Andersson, 2003). We therefore propose that psychoacoustic loudness should constitute an essential and complementary measure of tinnitus. In this regard, the literature on pain, to which tinnitus is often compared, is enlightening. The largely independent encoding, modulation (Kunz, Lautenbacher, LeBlanc, & Rainville, 2012), and brain networks for (Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999) sensory (pain intensity) and affective (pain unpleasantness) dimensions of pain suggest that it is a multidimensional response system that differentially encode both qualities. Furthermore, psychological interventions involving emotions (such as the cognitive behavioural therapy) modulates perceived pain unpleasantness more than perceived intensity of pain (Rainville, Bao, & Chretien, 2005), whereas therapies involving distraction seem to modulate more directly perceived intensity of pain and not mood (Villemure & Bushnell, 2002, 2009). If we transfer this analogy to tinnitus, this means that sensory (percept) and affective (distress) dimensions of tinnitus would be separable. The lack of correlations between psychoacoustic loudness and distress shown in our

study (and previous ones (Hiller & Goebel, 2006, 2007)), and evidence showing separable brain networks of tinnitus psychoacoustic loudness and distress, although still scarce (Balkenhol, Wallhäusser-Franke, & Delb, 2013), are both consistent with this idea. The implication is that interventions modulating mood, such as cognitive behavioral therapy, would act on the unpleasantness of tinnitus, which seems to be the case (Cima et al., 2012; Hesser, Weise, Westin, & Andersson, 2011), whereas therapies that modulate attention, such as noise generators or neuromodulators of attention (see Roberts, Husain, & Eggermont, 2013), would act mainly on tinnitus percept. One study has shown that alprazolam, a benzodiazepine that binds to $GABA_A$ receptors, significantly reduced both tinnitus psychoacoustic loudness (3.6 dB on average) and loudness on a 10-point visual analog scale (1.5 point on average) after 12 weeks (Johnson, Brummett, & Schleuning, 1993). The systematic assessment of both tinnitus percept and distress would make the field progress by identifying which therapies act on distress only, both distress and percept, or percept only. The answer to this question has important implications about the underlying mechanisms of tinnitus and those involved in treatment efficacy.

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Author Contributions

Conceived and designed the experiments : S. Hébert S. Hutchins PF. Performed the experiments : CEB. Analyzed the data : CEB PF S. Hébert S. Hutchins. Wrote the manuscript : CEB PF S. Hébert S. Hutchins.

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Table I: Demographic characteristics (standard deviation) of musicians with tinnitus, non-musicians with tinnitus and simulated malingerers, at test (A) and retest (B).

A	**Musicians**	**Non-musicians**	**S.malingerers**	***p*-Value**
N	16	16	18	
Sex (Male/Female)	13/3	9/7	7/11	.014
Age in years	33 (9.9)	43 (8.5)	23 (2.0)	<.001
Education level in years	19 (3.2)	17 (2.2)	17 (1.9)	n.s.
Tinnitus like (Tonal/Noise)	11/5	13/3	14/4	n.s.
Tinnitus ear (Left/Right/Central)	3/1/12	1/1/14	1/4/13	n.s.
THQ Handicap Total Score in %	17.4 (12.6)	34.5 (17.2)	43.3 (21.4)	<.001
PTA Standard left ear	8.9 (1.7)	16.3 (1.7)	4.2 (1.6)	<.001
PTA Standard right ear	9.1 (1.6)	14.5 (1.6)	3.9 (1.5)	<.001
PTA VH left ear	19.7 (3.8)	34.0 (3.8)	3.1 (3.6)	<.001
PTA VH right ear	20.3 (3.8)	35.9 (3.8)	5.0 (3.6)	<.001
B	**Musicians**	**Non-Musicians**	**S.malingerers**	***p*-Value**

N	9	9	10	
Sex (Male/Female)	8/1	5/4	4/6	.033
Age in years	37 (10.5)	41 (8.2)	23 (2.0)	<.001
Education level in years	20 (3.8)	17 (1.6)	18 (2.4)	n.s.
Tinnitus like (Tonal/Noise)	5/4	7/2	8/2	n.s.
Tinnitus ear (Left/Right/Central)	1/1/7	1/0/8	0/2/8	n.s.
THQ Handicap Total Score in %	14.4 (8.6)	33.4 (17.3)	39.9 (23.9)	.012
PTA Standard left ear	9.4 (2.1)	11.3 (2.1)	5.8 (2.0)	.02
PTA Standard right ear	11.8 (2.2)	12.2 (2.2)	5.7 (2.1)	n.s.
PTA VH left ear	26.0 (5.0)	25.0 (5.0)	4.2 (4.7)	.002
PTA VH right ear	30.3 (5.3)	32.0 (5.3)	5.0 (5.0)	<.001

Pure-tone average for standard frequencies (PTA Standard, from 0.25 kHz to 8 kHz) and for very-high frequencies (PTA VH, from 9 kHz to 16 kHz) are in dB HL

Table II: Tinnitus likeness ratings and loudness matching differences (standard deviation) between test and retest for the three groups.

Frequency in kHz	Mean likeness rating difference in numerical rating value			Mean loudness matching difference in dB SL		
	Musicians	**Non-musicians**	**S.malingerers**	**Musicians**	**Non-musicians**	**S.malingerers**
0.25	0 (0)	0 (1)	1 (1)	0 (1)	1 (2)	0 (13)
0.5	0 (0)	1 (1)	1 (2)	0 (1)	2 (3)	6 (18)
0.75	0 (1)	1 (2)	1 (3)	1 (5)	1 (4)	4 (21)
1	0 (1)	1 (2)	1 (2)	1 (8)	3 (6)	5 (28)
1.5	0 (0)	1 (3)	2 (2)*	4 (8)	5 (8)	3 (29)
2	0 (2)	1 (2)	0 (4)	1 (13)	5 (7)	7 (34)
3	0 (2)	0 (3)	1 (3)	1 (7)	1 (4)	6 (29)
4	1 (3)	0 (2)	2 (3)	2 (2)*	2 (4)	11 (20)
6	1 (3)	1 (2)	0 (3)	1 (5)	3 (4)	18 (12)**
8	1 (3)	2 (3)	2 (3)	0 (9)	2 (8)	16 (18)*
9	3 (5)	0 (3)	0 (2)	1 (14)	2 (7)	14 (14)*

10	2 (4)	0 (3)	0 (2)	2 (6)	1 (7)	21 (16)**
11.2	2 (3)*	1 (2)*	1 (2)	3 (12)	1 (5)	18 (16)**
12.5	1 (4)	1 (1)	0 (2)	2 (6)	1 (9)	19 (14)**
14	1 (3)	1 (2)	1 (2)	5 (11)	2 (8)	22 (15)**
16	4 (6)	0 (4)	1 (3)	3 (8)	1 (7)	32 (13)***

The asterisks represent *p*-values of *$p<.05$, **$p<.01$, ***$p<.001$, for paired-sample t-tests between test and retest for each group. Paired sample t-tests were used as post-hoc tests following up a 3-way interaction between Groups X Session X Frequency. The interaction was driven mainly by the simulated malingerers group at high-frequencies who were inconsistent between test and retest (>6 kHz) The dotted line represents the limit between the standard audiometric measurements (<8 kHz) and the very high frequencies (>8 kHz).

Table III: Psychoacoustic characteristics of tinnitus pitch and loudness (standard deviation) for musicians with tinnitus, non-musicians with tinnitus and simulated malingerers, at test (A) and retest (B) assessed by the likeness rating method.

A	**Musicians** (n=16)	**Non-musicians** (n=16)	**S.malingerers** (n=18)	***p*-Value**
Mean predominant tinnitus pitch in kHz	10.3 (4.6)	14.2 (1.7)	8.9 (5.0)	.002
Mean loudness at the predominant pitch in dB SL	11.3 (12.6)	1.2 (5.9)	38.8 (18.9)	<.001
B	**Musicians** (n=9)	**Non-musicians** (n=9)	**S.malingerers** (n=10)	***p*-Value**
Mean predominant tinnitus pitch in kHz	12.9 (3.9)	13.9 (1.7)	9.1 (3.8)	n.s.
Mean loudness at the predominant pitch in dB SL	-1.1 (7.5)	2.0 (6.7)	22.5 (17.8)	<.001

Table IV: Pitch matching values in kHz (standard deviation) for the three groups, at test (A) and retest (B) for both methods.

Tinnitus Pitch Matching	**Musicians**		**Non-musicians**		**S.malingerers**	
A	**Mean in kHz**	***p*-Value**	**Mean in kHz**	***p*-Value**	**Mean in kHz**	***p*-Value**
Likeness rating method	10.3 (4.6)		14.2 (1.7)		8.9 (5.0)	
Slider method	9.6 (5.2)		13.5 (3.0)		8.0 (5.2)	
Difference between methods	0.8 (3.6)	.40	0.7 (3.2)	.40	1.0 (3.9)	.31
B	**Mean in kHz**	***p*-Value**	**Mean in kHz**	***p*-Value**	**Mean in kHz**	***p*-Value**
Likeness rating method	12.8 (3.9)		13.9 (1.7)		10.1 (3.8)	
Slider method	11.9 (3.9)		13.9 (1.5)		10.0 (4.6)	
Difference between methods	1.0 (4.8)	.56	.02 (1.3)	.96	.11 (4.4)	.94

Table V: Pearson product-to-moment correlations of the inter-trials reliability of the tinnitus pitch matching using the slider for the three groups, at test (A) and retest (B).

	Musicians			**Non-musicians**			**S.malingerers**		
A	**Mean diff. in kHz (SD)**	***r***	***p***	**Mean diff. in kHz (SD)**	***r***	***p***	**Mean diff. in kHz (SD)**	***r***	***p***
Trial 1 – Trial 2	0.5 (1.4)	.96	<.001	0.4 (1.6)	.89	<.001	0.4 (2.1)	.92	<.001
Trial 2 – Trial 3	0.2 (1.1)	.98	<.001	0.5 (1.7)	.92	<.001	0.4 (1.3)	.97	<.001
Trial 1 – Trial 3	0.3 (1.4)	.97	<.001	0.1 (0.9)	.97	<.001	0.04 (2.0)	.92	<.001
B	**Mean diff. in kHz (SD)**	***r***	***p***	**Mean diff. in kHz (SD)**	***r***	***p***	**Mean diff. in kHz (SD)**	***r***	***p***
Trial 1 – Trial 2	0.4 (2.0)	.90	.001	0.2 (0.6)	.94	<.001	0.8 (1.4)	.98	<.001
Trial 2 – Trial 3	0.3 (2.4)	.81	.008	0.08 (0.8)	.89	.001	0.2 (1.1)	.97	<.001
Trial 1 – Trial 3	0.7 (2.6)	.80	.009	0.3 (0.8)	.91	.001	0.6 (1.1)	.99	<.001

Table VI. Psychoacoustic characteristics of tinnitus (pitch, loudness) and psychological distress (VAS, THQ) (standard deviation) between reported tonal tinnitus and noise tinnitus.

Reported type of tinnitus	**« Tonal »**	**« Noise »**	***p*-Value**
N	24	8	
Number of predominant frequencies	1.4 (0.6)	2.9 (1.9)	.07
Predominant Pitch in kHz (likeness)	12.8 (3.9)	10.7 (3.8)	n.s.
Predominant Pitch in kHz (slider)	11.8 (4.6)	10.3 (4.6)	n.s.
Loudness at the predominant pitch in dB SL	6.6 (12.4)	5.4 (4.9)	n.s.
VAS Score	37.7 (5.5)	31.1 (9.0)	n.s.
THQ Score	26.6 (16.5)	23.8 (20.1)	n.s.

Table VII: Correlations among visual analog scales scores, Tinnitus Handicap Questionnaire scores, and psychoacoustic pitch and loudness.

Visual Analog Scales	**THQ total score**		**Predominant pitch**		**Loudness at the predominant pitch**	
	R	*p*-Value	*r*	*p*-Value	*r*	*p*-Value
Question 1	.75**	<.001	.25	.22	-.09	.68
How annoying is your tinnitus **usually**?						
Question 2	.70**	<.001	.31	.13	-.08	.70
How annoying is your tinnitus **now**?						
Question 3	.67**	<.001	.30	.13	-.17	.40
How loud is your tinnitus **usually**?						
Question 4	.60*	=.001	.29	.16	-.10	.62
How loud is your tinnitus **now**?						
Question 5	.72**	<.001	.32	.11	-.24	.23
How much **attention** do you **spend on** your **tinnitus** usually?						

The asterisks represent *p*-values of **$p<.01$, ***$p<.001$.

Figure legends

Figure 1: Instructions displayed on the touchscreen for performing tinnitus matching using the likeness rating method. Participants initiated a trial by pressing the green button. They had to rate how the tone contributed to their tinnitus on the 10-point scale. Then, they had to match its loudness by moving the gauge on the left side. When this was done, they could press the red button to initiate the next trial.

Figure 2: A schematic view of the tinnitus matching procedure using the slider. Each trial included three rounds. In the first round, the slider was set between 500 Hz and 20 kHz for all participants. In the second round, the range was limited to two octaves around the final tone chosen by the participant in round one (here, two octaves around 8 kHz). Once the final tone was chosen in round two, the third round was further limited to one octave around this tone (here, one octave around 8 kHz).

Figure 3: The tinnitus spectrum (gray dotted line) mirrors hearing loss for both musicians (A) and non-musicians (B). Pure-tone thresholds (black line) are reported for the right ear. All groups rated the predominant tinnitus pitch in the high frequencies (>8 kHz). For simulated malingerers (C), tinnitus loudness matching (clear line) is well above the one of tinnitus participants. Error bars represent the standard error of the mean.

Figure 4: Likeness ratings for the three groups. Simulated malingerers differed from tinnitus participants in the low frequency range (*p<.05; **p<.01). Error bars represent the standard error of the mean.

Figure 5: Differences in cents between target and matched frequencies using the slider for musicians, non-musicians, and simulated malingerers (test session). Error bars represent the standard error of the mean.

Figure 1, Expérience 2.

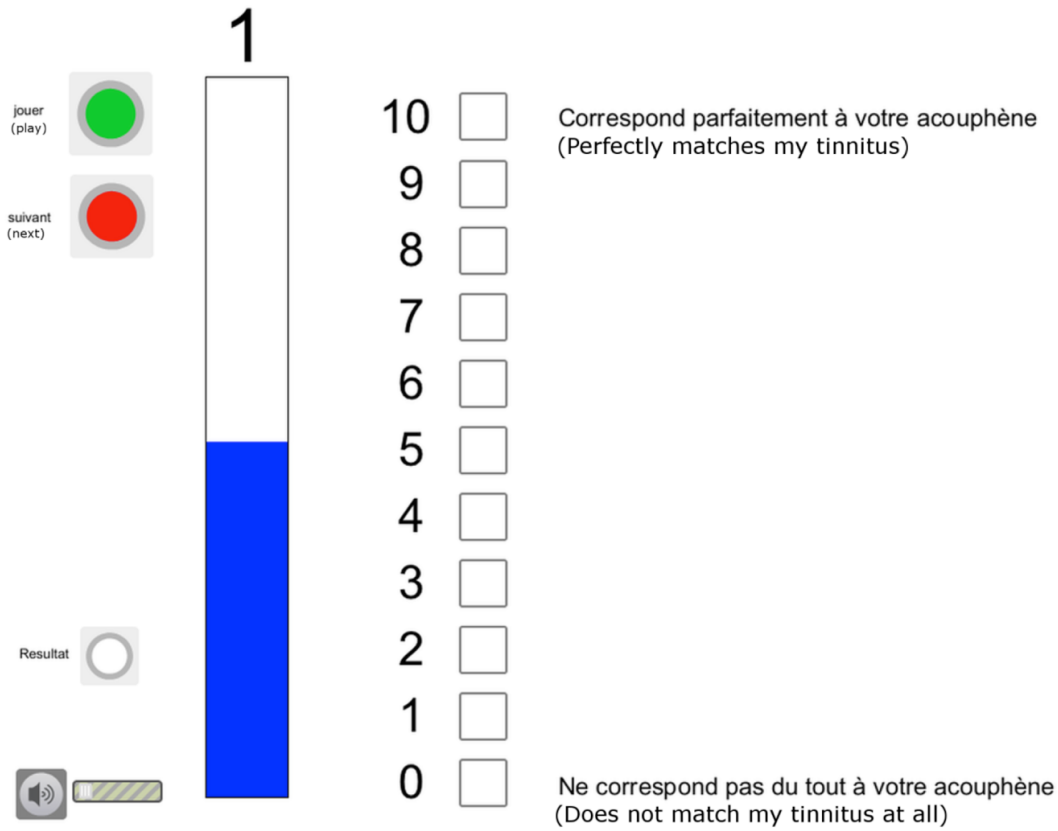


Figure 2, Expérience 2.

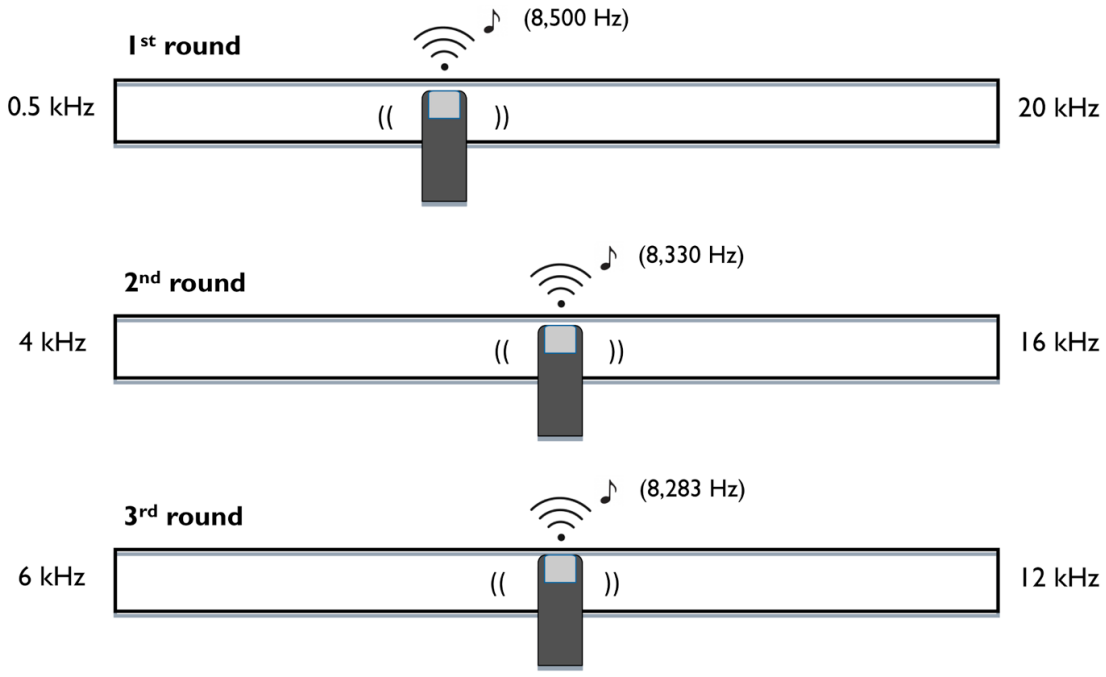
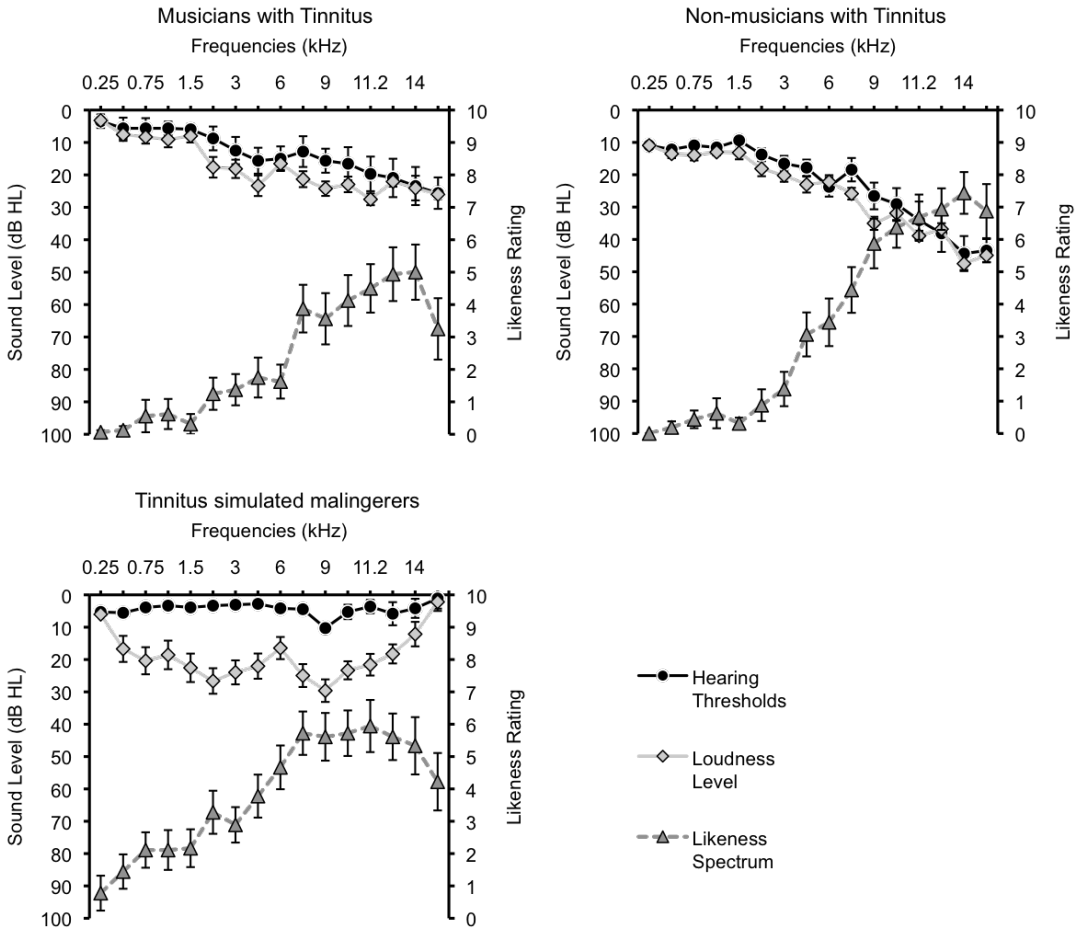


Figure 3, Expérience 2.



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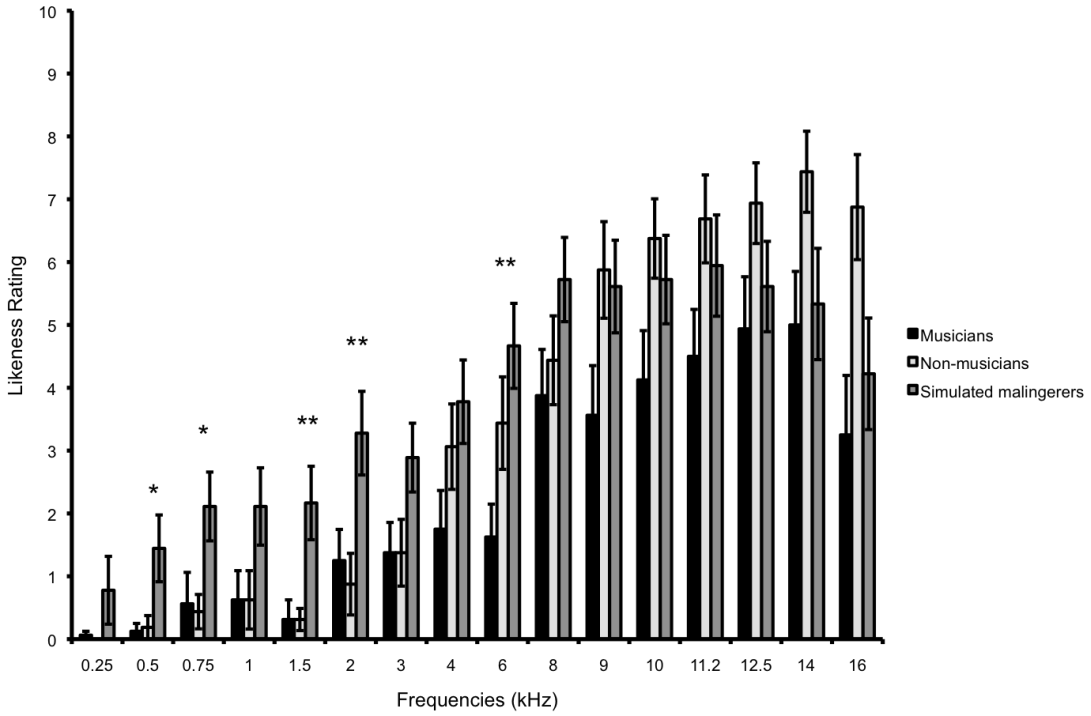
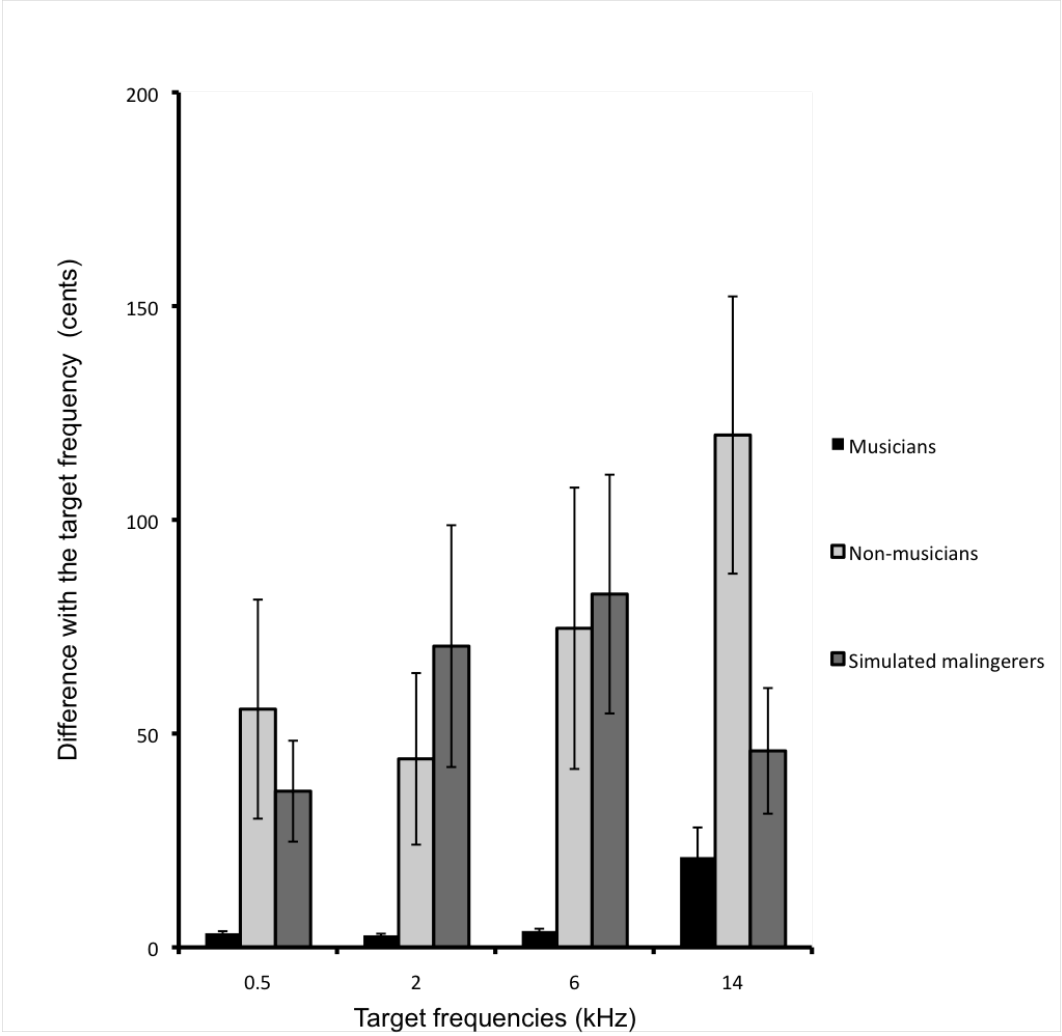


Figure 5, Expérience 2.



EXPÉRIENCE 3

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.

Key words: Acoustic Startle Reflex, Gap, Tinnitus, Human, Auditory cortex

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, Li 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, Gendelman et al. 1982; Lee, Lopez 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).

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 *sensorimotor gating*. The basic PPI circuitry has been localized to the brainstem, as PPI can be observed in animals with surgically (Bowen, Lin et al. 2003) or chemically suppressed cortical function (Ison, O'Connor et al. 1991; Threlkeld, Penley et al. 2008) as well as in humans during sleep (Silverstein, Graham 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, Du 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, Stone et al. 1978), Huntingdon's disease (Swerdlow, Paulsen et al. 1995), post-traumatic stress disorder (Grillon, Morgan et al. 1996), and

primary insomnia (Frau, Orrù et al. 2008; Hairston, Talbot 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, Brozoski et al. 2006). In contrast, in rats with salicylate- (Turner and Parrish 2008) or noise- (Turner, Brozoski 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 the tinnitus (i.e., high frequency). The gap paradigm has therefore been proposed to provide an objective measure of tinnitus (Turner, Brozoski et al. 2006) and has been used in both rats and mice (Turner, Brozoski et al. 2006; Yang, Lobarinas et al. 2007; Turner and Parrish 2008; Wang, Brozoski et al. 2009; Holt, Bissig et al. 2010; Kraus, Mitra et al. 2010; Ralli, Lobarinas et al. 2010; Zhang, Zhang et al. 2010; Engineer, Riley et al. 2011; Longenecker and Galazyuk 2011; Mao, Pace et al. 2011; Middleton, Kiritani 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, Micheyl et al. 2002; Roberts, Moffat 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.

Methods

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 bilateral, continuous, high-pitch tinnitus for at least 6 months (mean duration = 9.3 years, range = 0.5-37) and reported a ringing tinnitus. Four participants also reported some other sounds. Sociodemographic characteristics of both groups are presented in Table I (A). It is worth noting that these young participants were similar to older tinnitus participants included in several previous studies from our lab (Hébert, Paiement et al. 2004; Hébert and Carrier 2007; Hébert and Lupien 2007; Hébert and Lupien 2009), as reflected by their higher hyperacusis (Khalfa, Dubal et al. 2002) and BDI-II scores (Beck, Steer 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, Checkley et al. 1996). Participants who were nonresponsive 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 sociodemographic characteristics are presented in Table I (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.

Table I

Materials and procedure

Hearing tests

Hearing detection thresholds were assessed monaurally from 250 Hz to 16 kHz in both ears in ½-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 counterbalanced orders between participants. TDH-39p headphones were used for frequencies of 250 Hz to 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).

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 one-second pure tones ranging from 250 Hz to 16 kHz by ½ 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 1dB 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, Vinay 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.

Startle stimuli and task

A schematic view of Startle, Gap, and Prepulse trials is shown in Figure 1. Startle noises were 50 ms broadband noise bursts (20 Hz−20 kHz) set at 105 dB(A) 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). The low-frequency background noise was centered at 500 Hz (200-1,200 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) 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, Stone 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 to 23s 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).

Figure 1

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, Cuthbert 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 1,000 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) 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 a SE SoundPro DL 1/3 Octave level meter (Quest Technologies, USA) using a 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.

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 nonresponses 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) x 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, Cuthbert 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).

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 ≥ 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 2X(2X3) 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 2X(2X2) 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 2X(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 2X(3X2) 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.

Results

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, $t(24) = -4.3$, $p < .001$ (Figure 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, 1,000 , 3,000 and 6,000 Hz for the right ear respectively, $p < .05$.

Figure 2

Tinnitus-matching

Mean likeness ratings and sound levels for each frequency in the tinnitus-matching task are shown in Figure 2 (A). The frequency with 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: 2,671) and was not statistically significant ($p = .59$) (Table II). 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

Figure 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 Figure 2 (B), representing the number of participants who gave each of those frequencies a rating ≥ 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 ≤ 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.

Table II about here

Startle Magnitude

As shown in Figure 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 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 II). There were no significant differences in magnitude scores between test and retest.

Figure 3

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 Figure 4). To follow-up on this interaction, and to more specifically address the effects of high and low frequency in the gap condition, a 2X2 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 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 η^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 η^2 = .35 (i.e., a very large effect). There was also a main effect of 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 II). 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.

Figure 4

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 II). There were no significant differences in magnitude scores between test and retest.

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, $t(63)= -1.3$, $p = .20$.

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.

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 and collaborators' (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 and collaborators (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, Lobarinas et al. 2007; Ralli, Lobarinas 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.

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 (Hébert and Carrier 2007; Hébert, Fullum et al. 2011), complex patterns of abnormal stress responses (Hébert and Lupien 2007; Simoens and Hébert 2012), emotional exhaustion and depressive symptomatology (Hébert, Canlon et al. 2012; Hébert, Canlon et al. 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, Penley et al. 2008), whereas PPI does not (Ison, O'Connor et al. 1991; Bowen, Lin 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, Elbert et al. 1998; Weisz 2005; Bakker, Tijssen 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, Brozoski et al. 2006; Wang, Brozoski et al. 2009; Zhang, Zhang et al. 2010; Engineer, Riley et al. 2011; Longenecker and Galazyuk 2011; Middleton, Kiritani et al. 2011) or salicylate to induce tinnitus (Yang, Lobarinas et al. 2007; Turner and Parrish 2008; Ralli, Lobarinas 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, Riley et al. 2011).

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, Curhan et al. 2010), known to be associated greater magnitude startle response

(Grillon, Rezvan et al. 1994; Bakker, Tijssen 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, Allen et al. 2007; Sun, Lu et al. 2009).

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, Micheyl et al. 2002; Roberts, Moffat et al. 2008). Indeed, despite overall standard "normal'' hearing thresholds (250 to 8,000 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.

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, Barrenas 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.

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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Table I. 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)	$^{**}p<0.005$
Education in years	17.5 (1.9)	17.4 (2.5)	n.s.
BDI-II	9.4 (8.4)	3.7 (4.7)	$^{*}p<0.05$
Hyperacusis questionnaire	23.5 (9.9)	10.9 (6.5)	$^{**}p<0.005$

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)	$p=0.05$
Education in years	17.4 (1.9)	17.9 (3.0)	n.s.
BDI-II	9.2 (8.8)	2.2 (2.2)	$^{*}p<0.05$
Hyperacusis questionnaire	25 (9.9)	9.22 (5.2)	$^{**}p<0.005$
Delay in weeks between test and retest sessions	23(13)	16 (14)	n.s.

Table II. Paired-sample T-test and Pearson correlations between the test and retest sessions

Measure			Paired T-Test	Significance	Pearson's correlation coefficient	P value
Magnitude						
	Pulse-alone Trials					
		High frequency background	t(18)= -0.1	0.92	0.912	<0.001
		Low frequency background	t(18)= 0.0	1.00	0.846	<0.001
		No background (silence)	t(18)= 1.2	0.23	0.925	<0.001
	Pulse+discrete prepulse trials					
		High frequency discrete prepulse	t(18)= -1.2	0.25	0.829	<0.001
		Low frequency discrete prepulse	t(18)= -1.5	0.16	0.720	=0.001
	Pulse+gap prepulse trials					
		High frequency background	t(18)= -0.2	0.85	0.857	<0.001
		Low frequency background	t(18)= -0.2	0.84	0.701	=0.001
Latency	Overall		t(62)=-1.3	0.20	0.393	=0.001
%inhibition						
	Pulse+discrete prepulse trials					
		High frequency discrete prepulse	t(15)=1.1	0.31	0.733	=0.001
		Low frequency discrete prepulse	t(15)=0.2	0.85	0.795	<0.001
	Pulse+gap prepulse trials					
		High frequency background	t(15)= -0.72	0.49	0.394	n.s.
		Low frequency background	t(15)= -1.6	0.12	0.505	=0.046

Tinnitus frequency	t(11)= -0.56	0.59	0.754	=0.005
Tinnitus loudness	t(11)=0.3	0.77	0.910	<0.001

Figure legends

Figure 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.

Figure 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.

Figure 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.

Figure 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.

Figure 1, Expérience 3.

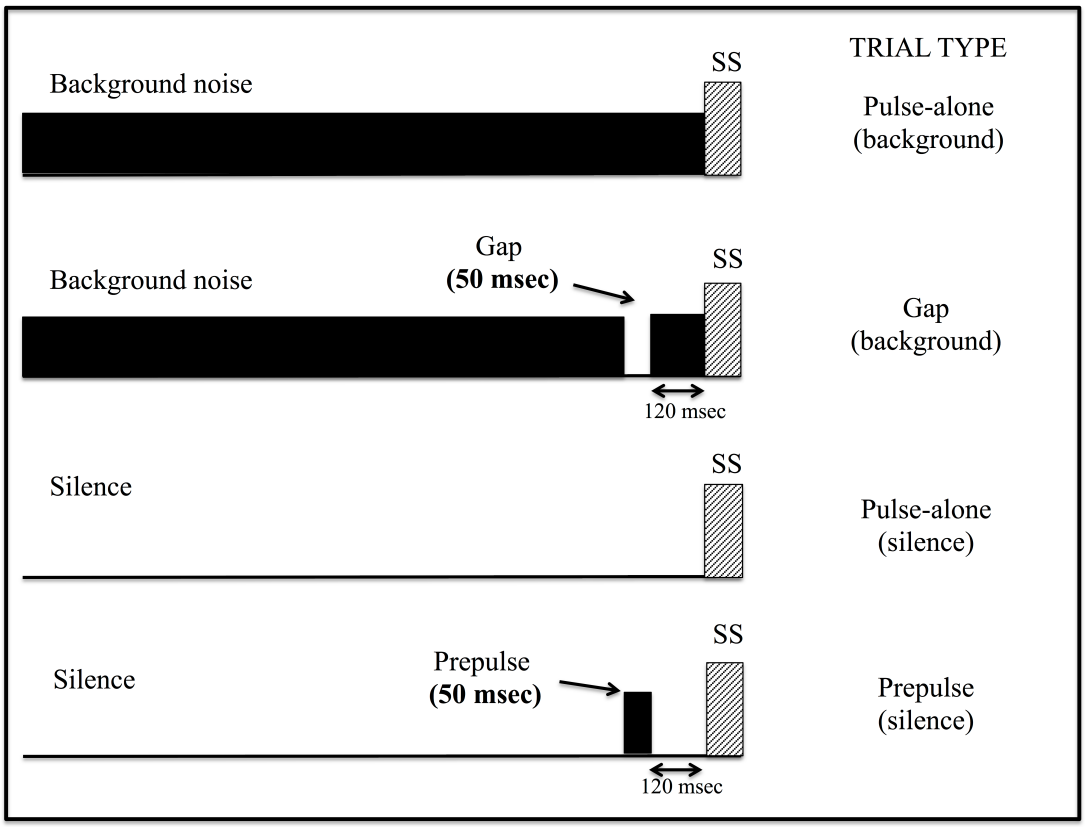


Figure 2, Expérience 3.

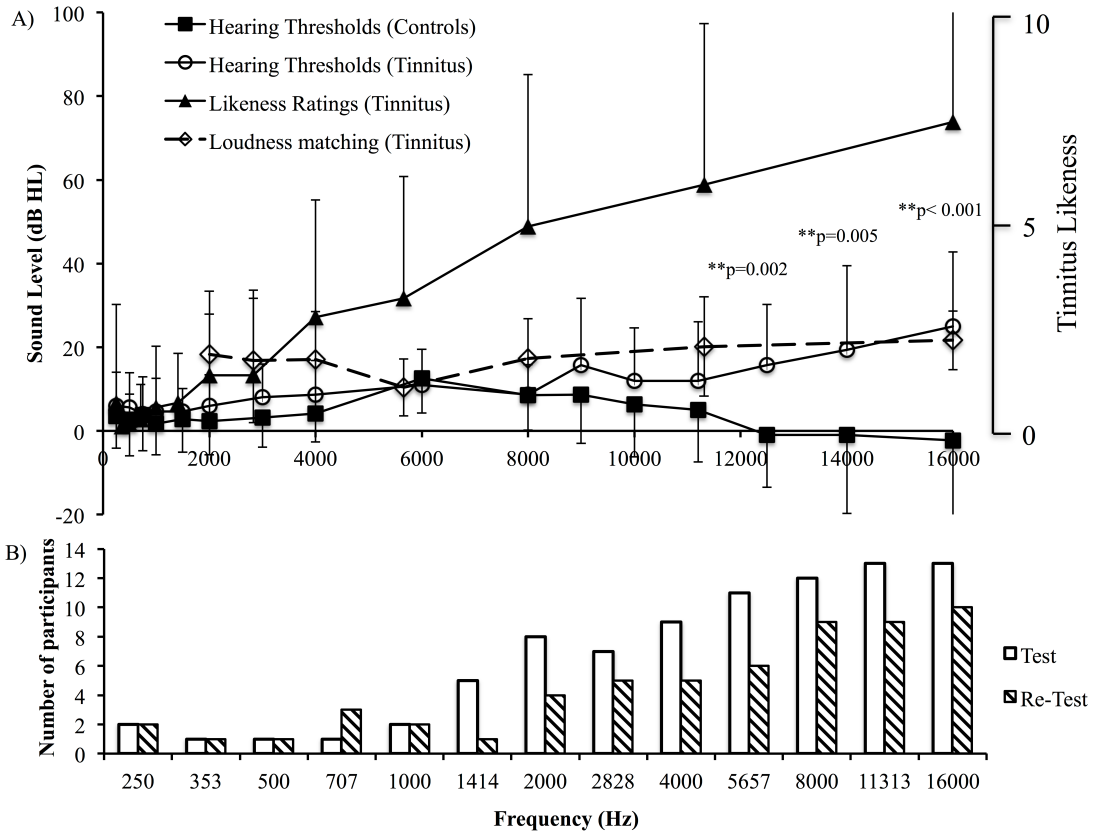


Figure 3, Expérience 3.

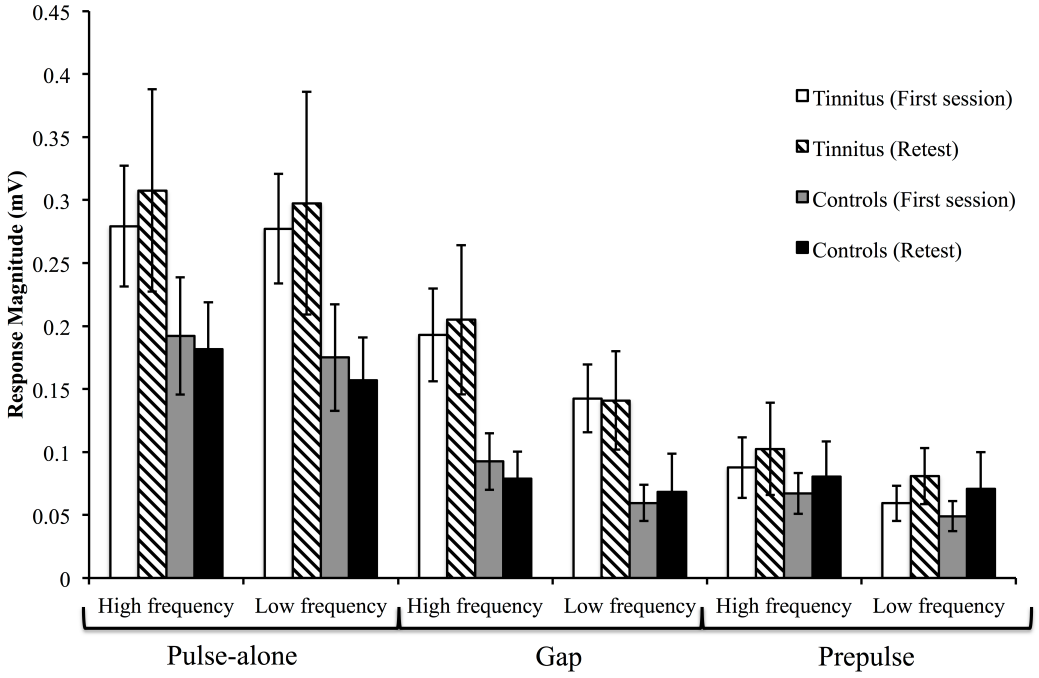
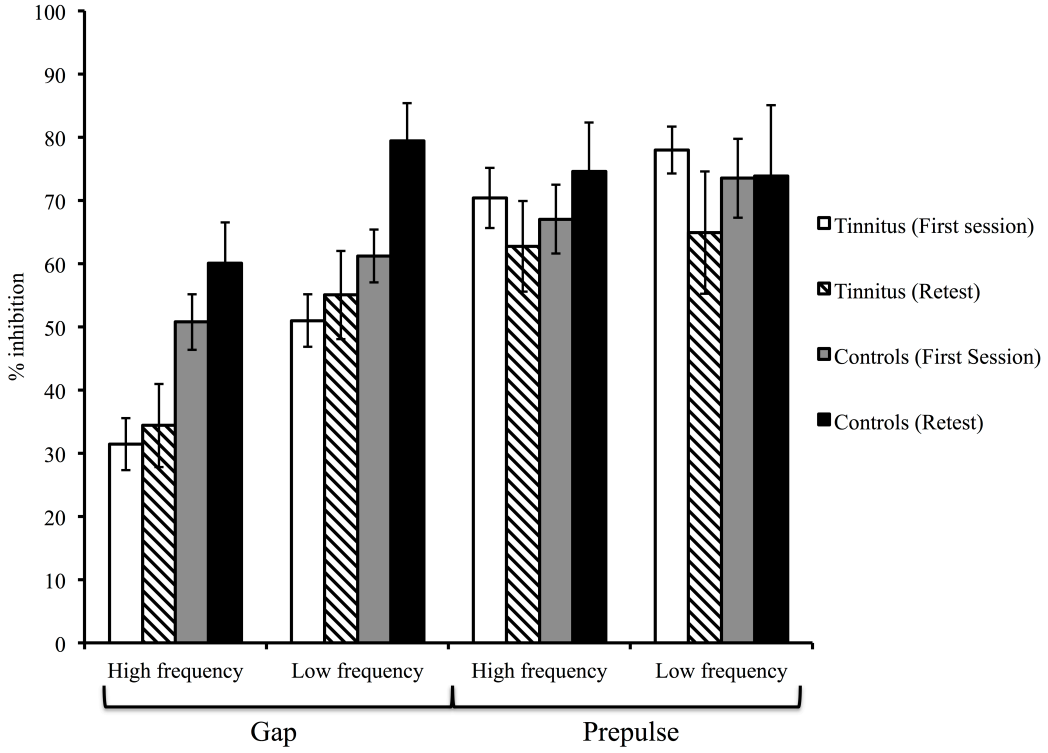


Figure 4, Expérience 3.



5. DISCUSSION

5.1 RÉSULTATS PRINCIPAUX

Les résultats principaux relatifs aux objectifs de la thèse sont les suivants : 1) le paradigme d'inhibition du réflexe acoustique de sursaut par un court silence est applicable chez l'humain normo-entendant; 2) les mesures psychoacoustiques informatisées de l'acouphène incluant l'appariement en fréquence et en intensité sont des mesures précises et fidèles du percept de l'acouphène 3) il est possible d'appliquer le paradigme d'inhibition du réflexe acoustique de sursaut par un court silence à des participants humains atteints d'acouphène tel qu'utilisé en recherche animale pour « objectiver » la présence d'acouphène. Toutefois, le déficit d'inhibition mesuré ne semble pas être spécifique à la présence de l'acouphène puisqu'il n'est pas spécifique à sa fréquence lorsque validé à partir des données d'appariement psychoacoustiques.

5.1.1 Expérience 1 : Résultats principaux

Les résultats obtenus à l'expérience 1 ont tout d'abord permis de déterminer que l'inhibition du réflexe acoustique de sursaut par un court silence (GPIAS) est applicable chez l'humain. En effet, l'ensemble des durées de court silence utilisées à l'intérieur d'un bruit afin d'inhiber le réflexe acoustique de sursaut, soit 5, 25, 50, 100 et 200 ms, a démontré une inhibition significative du réflexe selon un intervalle de confiance à 99%. De plus, la relation « durée du court silence - inhibition » a démontré une augmentation rapide de l'inhibition pour les durées de 5 à 50 ms, puis une augmentation beaucoup

moins prononcée de 50 à 200 ms. Ces résultats suggèrent qu'un court silence d'une durée de 50 ms est approprié dans l'utilisation du paradigme de GPIAS sur des sujets humains atteints d'acouphène : l'inhibition d'environ 56% à cette durée n'est ni maximale ni minimale, laissant place à des changements pouvant être à la hausse ou à la baisse. De plus, les résultats ont démontré un effet fréquentiel (bruit de fond) sur l'inhibition obtenue à partir du GPIAS. En effet, l'utilisation d'un bruit de fond en basses fréquences augmente significativement l'inhibition comparativement à celui de hautes fréquences. En somme, les résultats principaux de l'expérience 1 ont permis de déterminer que l'application du GPIAS à l'humain normo-entendant est réalisable en appliquant les mêmes caractéristiques de durée de court silence de 50 ms utilisée dans la technique pour objectiver la présence d'acouphène chez les rats (Turner, et coll., 2006). La différence d'inhibition retrouvée entre le bruit de fond de basses fréquences et celui de hautes fréquences restreint l'utilisation d'une mesure intra-sujet pour démontrer la présence de l'acouphène. Ces résultats sont en contradiction avec une étude réalisée chez l'humain qui a utilisé deux sons purs de fréquences différentes (1000 et 2500 Hz) comme bruit de fond constant et a employé un court silence de 24 ms afin d'inhiber le réflexe de sursaut déclenché par une tape sur la glabelle (région entre les deux sourcils) (Cranney, et coll., 1985). Ils n'ont trouvé aucune différence d'inhibition entre les deux bruits de fond. Les bandes passantes physiologiques pourraient expliquer les différences retrouvées entre notre étude et celle de Cranney et collaborateurs (1985). En effet, un son pur possède une bande passante physiologique plus restreinte qu'un bruit à bande étroite. Dans la présente étude, en utilisant la même bande passante physique de 1 kHz pour le bruit centré à 500 et 4000 Hz, nous utilisons des bandes passantes différentes en termes physiologiques: la

largeur du bruit à 4 kHz est d'environ un quart d'octave alors que celui du bruit à 500 Hz est d'environ deux octaves. La différence de bande passante en terme de filtre physiologique pourrait donc être une variable confondante dans les présentes données et expliquer l'augmentation de l'inhibition du bruit en basses fréquences retrouvée dans notre étude. Toutefois, une récente étude utilisant un paradigme similaire au GPIAS appliqué à des potentiels évoqués auditifs a également démontré une plus grande inhibition des composantes N1, N2, P2 (particulièrement P2) lors de l'utilisation d'un son pur de 8 kHz comparativement à celui de 600 Hz tous deux utilisés comme bruit de fond (Ku et coll., 2015). Ces résultats ne peuvent être expliqués en terme de bande passante physiologique puisqu'ils utilisaient des sons purs présentés au même niveau de dB SL. Il est également possible que la différence fréquentielle entre les deux sons purs utilisés par Cranney et collaborateurs (1000 et 2500 Hz) ait été insuffisante pour générer une différence d'inhibition. En effet, notre étude (500 et 4000 Hz) et celle de Ku et collaborateurs (600 et 8000 Hz) ont utilisés une différence de plus de 3500 Hz entre les deux stimuli. L'origine de cet effet fréquentiel sur l'inhibition demeure toutefois inconnue.

De plus, les résultats obtenus à l'expérience 1 ont également démontré qu'un paradigme d'inhibition du réflexe acoustique de sursaut utilisant un court silence, mais placé entre le bruit de fond et le son de sursaut présentait un patron d'inhibition différent de celui du GPIAS, et ce, en utilisant les mêmes durées de court silence. En effet, ce paradigme ne démontrait une inhibition significative que pour les durées de 50, 100 et 200 ms selon un intervalle de confiance à 99%. Cette différence de patron d'inhibition suggère que l'inhibition présente dans chacun des deux paradigmes est soutenue par des

mécanismes neurophysiologiques différents. En effet, des études animales ont démontré que l'inhibition obtenue par le GPIAS pouvait être supprimée suite à la désactivation du cortex auditif (désactivation chirurgicale ou chimique) pour les valeurs de courts silences de 50 ms et moins (Ison, O'Connor, Bowen, & Bocinea, 1991; Threlkeld, Penley, Rosen, & Fitch, 2008). Ces résultats suggèrent une implication du cortex auditif dans l'inhibition du réflexe acoustique de sursaut utilisant le GPIAS pour des silences de durée de 50 ms et moins. À l'opposé, cette même désactivation corticale n'a aucun effet sur l'inhibition du réflexe de sursaut par un court silence, mais placé entre le bruit de fond et le son de sursaut, suggérant une origine sous-corticale à l'inhibition pour ce paradigme (Bowen, Lin, Merrit, & Ison, 2003; Ison, et coll., 1991). Notre étude est la première à comparer et démontrer une différence d'effet de la durée du court silence sur l'inhibition du réflexe acoustique de sursaut à l'aide de ces deux paradigmes (court silence à l'intérieur d'un bruit vs suivant le bruit) chez l'humain.

5.1.2 Expérience 2 : Résultats principaux

Les résultats obtenus à l'expérience 2 ont permis de déterminer que les mesures d'appariement psychoacoustiques informatisées en fréquence et en intensité de l'acouphène sont précises et fidèles. En effet, pour l'appariement en fréquence, la technique « cotation d'appréciation » s'est avérée aussi précise à déterminer la fréquence prédominante de l'acouphène qu'une technique d'ajustement qui permettait une précision à un hertz près. De plus, les deux techniques ont démontré une fidélité test-retest très élevée pour l'ensemble des groupes testés. Toutefois, l'appariement en fréquence ne permettait pas de départager les participants atteints d'acouphène des simulateurs. Seul l'appariement en intensité a permis de départager les personnes atteintes d'acouphène des

simulateurs avec un degré de sensibilité et de spécificité dépassant les 90%. De plus, l'appariement en intensité a également démontré une fidélité test-retest très élevée, mais seulement pour les groupes de personnes atteintes d'acouphène. En effet, en plus d'apparier l'intensité de l'acouphène présumé à des niveaux de 4 à 20 fois supérieurs à ceux des personnes atteintes, les simulateurs ne sont pas constants dans leurs appariements de l'intensité, et ce, particulièrement pour les fréquences supérieures à 6 kHz. L'ensemble de ces résultats permet de conclure que les techniques informatisées d'appariement en intensité et en fréquence de l'acouphène développées dans notre laboratoire sont des mesures précises et fidèles de l'acouphène.

5.1.3 Expérience 3 : Résultats principaux

L'expérience 3 a permis de démontrer la mise en oeuvre et la validation du paradigme de modulation du réflexe acoustique de sursaut par un court silence (GPIAS) déjà utilisé chez les rats à des participants humains contrôles et avec acouphène. Toutefois, le déficit d'inhibition mesuré par le GPIAS chez les personnes atteintes d'acouphène n'était pas spécifique à la fréquence de celui-ci (déficit retrouvé en hautes fréquences et en basses fréquences) tel que contre-vérifié par une mesure psychoacoustique d'appariement en fréquence. En effet, la fréquence prédominante appariée de l'acouphène chez le groupe de sujets expérimentaux était de 16 kHz alors que le déficit d'inhibition se retrouvait dans la condition de court silence à l'intérieur de bruits de fond centrés à 0.5 et 4 kHz au test et au retest. De plus, la fréquence de 500 Hz n'a été mesurée dans le spectre de l'acouphène que pour un seul participant et le 4000 Hz pour seulement la moitié des participants. La fidélité test-retest de l'appariement de la fréquence prédominante et de l'intensité associée était excellente (fréquence: r = .75,

intensité: r = .91) comparativement à l'inhibition obtenue au paradigme du GPIAS qui s'est avérée faible pour l'inhibition du court silence pour le bruit de fond en hautes fréquences (r = .39) et moyenne pour celui de basses fréquences (r = .5).

5.2 DISCUSSION GÉNÉRALE DE LA THÈSE

5.2.1 Est-il possible d'objectiver l'acouphène par le GPIAS ?

Cette thèse a permis de démontrer la faisabilité de l'application à l'humain de la technique du GPIAS utilisée pour « objectiver » la présence de l'acouphène chez le rat. En effet, l'utilisation de courts silences insérés à l'intérieur d'un bruit de fond inhibe le réflexe acoustique de sursaut, et ce, sur une grande variété de durées, de très petites (5 ms) à très grandes (200 ms). Lorsqu'appliquée à des participants atteints d'acouphène bilatéral de type cillement, l'inhibition est réduite pour les bruits de fond centrés en hautes (4 kHz) et en basses fréquences (500 Hz). L'utilisation d'une technique informatisée d'appariement en fréquence de l'acouphène a permis une validation croisée des résultats obtenus par la méthode du GPIAS. En effet, la fréquence prédominante de l'acouphène des participants était d'environ 16 kHz alors que la technique du GPIAS mesurait un déficit d'inhibition à 0.5 et 4 kHz. De plus, cette technique d'appariement informatisée a permis de déterminer que la fréquence de 500 Hz n'était comprise dans le spectre de l'acouphène que d'un seul participant et que le 4000 Hz par seulement la moitié des participants. Ces résultats remettent donc en doute l'interprétation initiale des inventeurs de la technique. Selon eux, l'acouphène remplirait le court silence (voir figure

3, Section Introduction) lorsque celui-ci est inséré dans un bruit de fond dont la fréquence centrale est similaire à celle de l'acouphène présumé. La détection du court silence serait compromise par la présence de l'acouphène, ce qui empêcherait l'inhibition du réflexe de sursaut. Or, les résultats de la présente thèse ont démontré que l'inhibition n'est pas spécifique à la fréquence de l'acouphène puisque le déficit d'inhibition était présent lors de l'utilisation d'un bruit de fond de hautes et de basses fréquences, alors que les participants avaient un acouphène de très hautes fréquences.

Depuis la parution de l'article de l'expérience 3 (Fournier & Hébert, 2013), plusieurs études ont également remis en doute l'interprétation initiale de Turner et collaborateurs (2006), soit que l'acouphène « remplirait » le court silence et empêcherait ainsi l'inhibition du réflexe de sursaut. En effet, deux études sur des sujets humains avec acouphène ont démontré qu'ils sont en mesure de détecter des courts silences à l'intérieur d'un bruit de fond de manière similaire aux contrôles en utilisant une technique de détection comportementale (Boyen, Baskent, & van Dijk, 2015; Campolo, Lobarinas, & Salvi, 2013). Hickox et Liberman (2014) ont également testé cette hypothèse chez les souris, mais en utilisant deux paradigmes d'inhibition du réflexe acoustique de sursaut : le GPIAS et le paradigme de court silence suivant le bruit de fond similaire à celui utilisé dans notre expérience 1. L'inhibition produite par ces deux paradigmes était comparée avant et après que les souris aient subi un traumatisme sonore connu pour induire de l'acouphène. Si l'acouphène « remplissait » le silence, celui-ci devrait être indépendant de la position du court silence à l'intérieur du bruit de fond et devrait donc engendrer un déficit d'inhibition dans les deux paradigmes. Or, les résultats obtenus ont démontré un déficit d'inhibition seulement dans la condition dans laquelle le court silence suivait le

bruit de fond et non dans la condition GPIAS. Ces résultats sont en opposition avec l'interprétation initiale de Turner et collaborateurs (2006) puisqu'il est improbable que l'acouphène puisse « remplir » le silence dans un paradigme et non dans l'autre. De plus, les auteurs ont rapporté une augmentation de l'inhibition causée par un paradigme de « Pré-pulse », similaire à celui de l'étude 2 et 3, seulement chez un groupe de souris; ce groupe démontrait des signes physiologiques et histologiques de dégénérescence nerveuse du nerf 8, comparativement aux groupes exposés au bruit sans ces mêmes signes et aux groupes contrôles non-exposés. Ces résultats suggèrent que les trois paradigmes les plus utilisés dans le domaine, soit le « Pré-pulse », le « GPIAS », ainsi que le court silence placé tout juste avant le son de sursaut (aussi connu sous le nom de « Near-gap », ou « Gap following ») reflètent différents mécanismes neurophysiologiques d'inhibition du réflexe de sursaut et ne sont pas affectés de la même façon par les mêmes conditions pathophysiologiques. Une meilleure compréhension des mécanismes neurophysiologiques sous-jacents à chacun de ces paradigmes pourrait permettre une meilleure interprétation des déficits retrouvés chez les sujets atteints d'acouphène. Il est également possible que différents types de neurones soient impliqués dans chacun des mécanismes. En effet, il a été proposé que l'*inhibition* du réflexe de sursaut serait liée à des neurones réagissant à des stimuli de type transitoire («transient stimulation») alors que la facilitation du réflexe acoustique de sursaut, qui est définie comme une augmentation de l'amplitude de la réponse de sursaut en présence de bruit constant, serait liée à des neurones qui répondraient à des stimuli soutenus et constants («sustained stimulation») (Graham, 1975). Une meilleure compréhension de la relation entre le type de neurone impliqué (fusiforme, chopper, etc) et l'inhibition dans chacun des paradigmes

semble donc nécessaire afin de mieux lier les résultats aux enregistrements neurophysiologiques généralement associés à l'acouphène avec les différents résultats obtenus à l'aide des paradigmes d'inhibition de réflexe de sursaut.

Depuis la publication de l'étude initiale de Turner et collaborateurs en 2006, la technique du GPIAS a connu un intérêt marqué de la part des chercheurs en animaux et est encore aujourd'hui préférée aux techniques de conditionnement classique (Engineer et coll., 2011; Hickox & Liberman, 2014; Holt, Bissig, Mirza, Rajah, & Berkowitz, 2010; Kraus et coll., 2010; Lobarinas, Hayes, & Allman, 2013; Longenecker & Galazyuk, 2011; Mao et coll., 2012; Middleton et coll., 2011; Ralli et coll., 2010; Turner, et coll., 2006; Turner & Parrish, 2008; Yang et coll., 2007; Zhang, Zhang, & Zhang, 2011). La technique du GPIAS est généralement jointe à des techniques invasives d'électrophysiologie afin d'établir les possibles corrélats neurophysiologiques de l'acouphène. Par exemple, la technique de GPIAS démontrant un acouphène « présumé » à 16 kHz suite à l'injection de salicylate joint à des techniques d'enregistrement de plaques multi électrodes, a permis de déterminer une augmentation de l'activité évoquée associée à 16 kHz et 20 kHz dans le cortex auditif (Yang, et coll., 2007). La combinaison de ces deux techniques permet de mieux cerner les changements neurophysiologiques autour de la fréquence « présumée » de l'acouphène, laquelle est estimée à partir de la technique du GPIAS. Pour déterminer cette fréquence, les chercheurs utilisent une grande variété de fréquences centrales de bruit de fond en combinaison avec le GPIAS. Les fréquences composant l'acouphène sont déduites à partir du déficit d'inhibition spécifique aux rats ayant subi l'induction d'acouphène comparativement au groupe contrôle. Généralement, seules les fréquences démontrant un déficit significatif

d'inhibition sont interprétées comme les fréquences composant l'acouphène. Toutefois, le critère utilisé pour définir la présence de l'acouphène peut varier considérablement d'un laboratoire à un autre (pour une revue des études: Galazyuk & Hébert, 2015). Des mesures physiologiques spécifiques à ces fréquences sont par la suite enregistrées (décharges spontanées, synchronie neurale, etc.) pour en déduire des corrélats neurophysiologiques de l'acouphène. Les résultats de la présente thèse permettent d'émettre des réserves quant à cette utilisation du GPIAS, mais surtout à l'interprétation du déficit d'inhibition qu'en font les auteurs. En effet, nos résultats permettent d'affirmer qu'un déficit d'inhibition au GPIAS à une fréquence de bruit de fond donnée ne signifie pas nécessairement que cette fréquence fait partie du spectre de l'acouphène. L'expérience 3 de la thèse contient cependant une limite importante : le bruit de fond utilisé n'était pas apparié à la fréquence prédominante de l'acouphène de manière individuelle pour chaque participant. Un appariement de la fréquence centrale du bruit de fond à celle de la fréquence estimée par une technique psychoacoustique pour chacun des participants pourrait peut-être permettre de mesurer un déficit d'inhibition plus grand que ceux obtenus à 0.5 et 4 kHz. Toutefois, cela ne pourrait expliquer l'apparition d'un déficit à 0.5 et 4 kHz. Par ailleurs, deux études utilisant des mesures comportementales de détection de court silence n'ont trouvé aucune difficulté particulière lorsque le bruit de fond était apparié à la fréquence de l'acouphène chez un groupe de participants atteints comparativement au groupe contrôle (Boyen, et coll., 2015; Campolo, et coll., 2013). De plus, la fréquence prédominante de l'acouphène étant située dans la région de la perte auditive, séparer la contribution de cette perte de celle de l'acouphène dans le déficit d'inhibition pourrait s'avérer un défi. La réplication de l'étude initiale de Turner et

collaborateurs (2006) par un groupe de chercheurs indépendants devrait également être poursuivie.

5.2.2 Le GPIAS : Que mesure-t-on ?

La thèse soulève également une question fondamentale sur la technique du GPIAS : que mesure-t-on réellement à l'aide de ce paradigme ? En effet, l'expérience 1 a démontré une courbe « durée de courts silences – inhibition » qui ne suit pas le patron de réponse « durée de court silence – détection comportementale » généralement rapportée dans une population similaire de normo-entendants. En effet, deux études ont démontré que les courbes de détection comportementale de court silence saturent pour des valeurs égales ou supérieures à 5 ms, signifiant que tous les jeunes normo-entendants perçoivent facilement des courts silences d'une durée de 5 ms et que la performance n'est pas améliorée au-delà de cette valeur (Giannela Samelli & Schochat, 2008; Hoover, Pasquesi, & Souza, 2015). Or, la courbe « durée de courts silences – inhibition » du GPIAS produit une rapide augmentation de l'inhibition pour des valeurs de durées allant jusqu'à 50 ms. Cette augmentation a toujours été interprétée par les chercheurs comme une augmentation de la détection ou du traitement temporel. Une seule étude a rapporté une certaine concordance entre l'inhibition obtenue au GPIAS et celle obtenue à l'aide d'une technique comportementale de détection de court silence chez le même groupe de participants humains (Ison & Pinckney, 1983). Toutefois, les durées de courts silences utilisées étaient limitées aux valeurs de 1 à 10 ms et le critère utilisé pour déterminer la concordance entre les deux approches semble a priori inapproprié, utilisant les moyennes de groupes plutôt que les données individuelles. Le lien entre la détection comportementale de courts silences et l'inhibition du réflexe acoustique de sursaut par

des courts silences (GPIAS) demeure inconnu. Considérant qu'une détection comportementale requiert des habiletés cognitives telles que l'attention que le GPIAS ne requiert pas nécessairement, il est envisageable que le GPIAS reflète une mesure pré-attentionnelle de détection. Le GPIAS est présentement la mesure de référence pour évaluer le traitement temporel ainsi que ses pathologies chez l'animal (Allen, Schmuck, Ison, & Walton, 2008; Barsz, Ison, Snell, & Walton, 2002; Ison, Agrawal, Pak, & Vaughn, 1998; Ison & Allen, 2012; Ison & Pinckney, 1983; Swetter, Fitch, & Markus, 2010). Puisque ces recherches animales infèrent un déficit de détection des habiletés auditives temporelles chez l'humain à partir des résultats du GPIAS, il apparaît important de clarifier le lien entre ces deux techniques.

Malgré tout, des études ont tout de même permis de déterminer quelles zones du cerveau contribuent à l'inhibition dans le paradigme du GPIAS. En effet, tel que précédemment mentionné, la désactivation du cortex auditif empêche l'inhibition du GPIAS pour des valeurs de courts silences de 50 ms et moins, suggérant un rôle essentiel du cortex auditif dans l'inhibition de ce paradigme pour de très courtes durées de silence (Ison, et coll., 1991; Threlkeld, et coll., 2008). Une récente étude sur l'acouphène a également permis de déduire le rôle important joué par le cortex auditif dans l'inhibition et l'absence d'inhibition du GPIAS. En effet, Engineer et collaborateurs (2011) ont traumatisé acoustiquement des rats afin de leur induire un acouphène et ont validé sa présence à l'aide du GPIAS. Ils ont trouvé un déficit d'inhibition à 8 et 10 kHz chez les rats traumatisés comparativement aux contrôles. Ils ont également trouvé des changements neurophysiologiques associés au traumatisme sonore qui inclut : une réorganisation de la carte tonotopique du cortex auditif, une augmentation de la

synchronie neurale, une augmentation de l'excitabilité corticale et une augmentation de l'activité neurale spontanée. Les auteurs ont par la suite utilisé une technique de stimulation acoustique combinée à une stimulation du nerf vague afin de remodeler la carte tonotopique abîmée des rats, afin de rétablir l'organisation à celle d'origine, celle d'avant le traumatisme. Cette technique a non seulement permis de rétablir l'organisation tonotopique du cortex auditif à son état d'origine, mais a également rétabli l'inhibition du GPIAS à 8 et 10 kHz à des valeurs similaires aux contrôles. Ce résultat permet de lier directement le changement d'inhibition du GPIAS à un changement s'opérant au niveau du cortex auditif. Toutefois, il n'est pas possible de lier directement l'inhibition du GPIAS à un changement neurophysiologique spécifique s'étant opéré après le traitement puisque le changement d'inhibition (GPIAS) corrèle avec le degré de réorganisation et le niveau d'excitabilité corticale. De plus, les effets indésirables connus de la technique de stimulation du nerf vague qui incluent des problèmes respiratoires, cardiaques ainsi qu'une dégradation de l'humeur (Tecoma & Iragui, 2006) pourraient également avoir un effet sur le réflexe acoustique de sursaut et/ou sur l'inhibition produit par le GPIAS.

5.2.3 Hyper-réponse au réflexe de sursaut : une mesure de l'hyperacousie ?

Un résultat inattendu est l'augmentation de la réponse du réflexe de sursaut du groupe de personnes avec acouphène comparativement au groupe contrôle apparié. En effet, les personnes avec acouphène ont démontré une réponse électromyographique beaucoup plus grande au son de sursaut (bruit blanc de 105 dBA SPL). Ce résultat a par ailleurs été reproduit un an après la parution de l'article de l'expérience 3 (Shadwick & Sun, 2014). Cette augmentation du réflexe acoustique de sursaut a également été mesurée

chez l'animal suite à l'injection de salicylate et suite à un traumatisme sonore (pour une revue des études: Fournier, Schönwiesner, & Hébert, 2014). Cette augmentation a été proposée par certains auteurs comme reflétant de l'hyperacousie (hypersensibilité auditive) (Sun et coll., 2009). Toutefois, un niveau d'anxiété élevé a également été associé à une augmentation du réflexe de sursaut acoustique chez des patients ayant subi un choc post-traumatique (Morgan, Grillon, Southwick, Davis, & Charney, 1996) ou souffrant de trouble de panique (Grillon, Ameli, Goddard, Woods, & Davis, 1994). L'acouphène étant souvent associé à un niveau d'anxiété plus élevé (Shargorodsky, et coll., 2010), il est également possible que cette hyper-réponse soit le résultat d'un niveau d'anxiété élevé chez les participants atteints d'acouphène.

5.3 IMPLICATIONS CLINIQUES

5.3.1 Appariement en fréquence et en intensité: mesures cliniques aux propriétés insoupçonnées

La technique d'appariement informatisée de fréquence et d'intensité de l'acouphène s'est avérée posséder des propriétés encore insoupçonnées. En effet, l'intensité mesurée aux fréquences prédominantes de l'acouphène a permis de détecter les personnes avec une sensibilité au-dessus de 90% et de rejeter les personnes qui simulaient avec une spécificité également au-dessus de 90%. L'appariement en fréquence ne permettait pas, à elle seule, de départager les simulateurs des « vraies » personnes atteintes d'acouphène avec un niveau suffisant de sensibilité et de spécificité. Ce résultat pourrait être expliqué par le fait que les simulateurs ont été choisis sur la base d'avoir

déjà expérimenté un acouphène transitoire. Ils pouvaient donc utiliser cette information en mémoire pour effectuer leur appariement. Toutefois, le souvenir de l'intensité pourrait être beaucoup plus difficile à apparier puisque le souvenir d'un bruit ou d'un son très dérangeant pourrait être associé à une forte intensité. La fidélité test-retest était également très élevée pour l'appariement en fréquence et en intensité pour les deux groupes atteints d'acouphène. Pour le groupe simulateur toutefois, la fidélité test-retest n'était élevée que pour l'appariement en fréquence. L'appariement en intensité démontrait une grande variabilité entre les mesures test et retest pour les fréquences au-dessus de 6 kHz. Il faut toutefois noter que les mesures de sensibilité et de spécificité ont été déterminées à partir d'un échantillon très restreint (personnes avec acouphène n = 32, simulateurs n = 18). De plus, les critères d'exclusions étaient très contraignants excluant les participants ayant une perte auditive au-delà de degrés léger, ceux ayant une condition médicale non contrôlée ou une pathologie de l'oreille moyenne ou externe, ainsi que les gros fumeurs. La validation diagnostique clinique de cette méthode devra donc être effectuée auprès d'un échantillon beaucoup plus grand et comprenant une clientèle typique non contrôlée, avant de pouvoir conclure sur son application clinique. Il est aussi important de noter que les valeurs de sensibilité et de spécificité n'ont été mesurées qu'à partir de l'intensité des deux fréquences prédominantes de l'acouphène et non de l'entièreté du spectre. Il est donc concevable que le potentiel de prédiction puisse être encore augmenté avec l'ajout de l'intensité de l'ensemble du spectre au lieu des deux seules fréquences prédominantes. En utilisant cette technique, le clinicien possède donc trois indices pouvant lui indiquer si un patient simule ou non un acouphène : l'intensité au test, au retest, ainsi que la variabilité test-retest.

5.3.2 Le spectre de l'acouphène : miroir de la perte auditive

L'expérience 2 et l'expérience 3 ont toutes deux permis de démontrer que les fréquences qui composent le spectre de l'acouphène sont en miroir de la perte auditive tel que démontré par des études ultérieures (Noreña, et coll., 2002; Roberts, et coll., 2008). Elles ont également démontré l'extrême importance de mesurer les très hautes fréquences lors de l'évaluation de l'acouphène. En effet, dans les deux études, les fréquences prédominantes de l'acouphène étaient situées bien au-delà des fréquences mesurées en audiométrie clinique standard (250 à 8000 Hz). De plus, les sujets ayant une audition dite « normale » en audiologie clinique (seuil auditif de 15 dB HL et moins de 250 à 8000 Hz) démontraient une élévation de leurs seuils auditifs en très hautes fréquences comparativement au groupe contrôle, soulignant l'importance de les mesurer lors de l'évaluation d'un patient atteint d'acouphène. Cette concordance entre les fréquences atteintes par la perte auditive et celles constituant le spectre de l'acouphène pourrait également être utilisée à titre d'indice supplémentaire pour détecter un simulateur d'acouphène.

5.3.3 Rapport du patient : bruit vs cillement

Le rapport du patient a également fait l'objet d'une étude approfondie dans l'expérience 2. En effet, le spectre de l'acouphène ainsi que la perception subjective, incluant la détresse liée à l'acouphène, ont été comparés entre un sous-groupe de patients rapportant un acouphène de type cillement à celui rapportant un acouphène de type bruit. Aucune différence significative entre les deux sous-groupes n'a été notée sur l'ensemble des mesures comparées, remettant ainsi en doute l'utilité de séparer un groupe de patients

atteints d'acouphène basé sur cette seule information (De Ridder et coll., 2010). Bien que le nombre de participants qui rapportaient un acouphène de type cillement était plus important que le sous-groupe de type bruit, cette comparaison met bien en évidence les difficultés des participants à décrire leur acouphène. Il est donc recommandé aux cliniciens de ne pas dépendre exclusivement du rapport du patient et d'utiliser d'autres mesures afin de bien caractériser l'acouphène du patient.

5.3.4 Aucune influence de l'expertise musicale sur les capacités d'appariement de l'acouphène

Aucune étude à ce jour n'avait évalué l'influence de l'expertise musicale sur les capacités d'appariement de l'acouphène. Il est connu que les musiciens professionnels possèdent des capacités de discrimination auditive supérieures à celles des contrôles appariés non-musiciens (Estis, Dean-Claytor, Moore, & Rowell, 2011; Micheyl, Delhommeau, Perrot, & Oxenham, 2006; Zarate, Ritson, & Poeppel, 2012). Il a donc été postulé que ces capacités supérieures devraient logiquement se traduire par une plus grande facilité et une plus grande précision à apparier l'acouphène par les musiciens comparativement à un groupe contrôle ne possédant pas cet entraînement (Evered & Lawrenson, 1981; Henry, et coll., 2001; Henry & Meikle, 2000; Henry, et coll., 2004). La formation musicale pourrait donc constituer une source de variabilité importante dans l'appariement en fréquence et en intensité entre les patients et pourrait expliquer les divergences rapportées quant à la fiabilité test-retest entre différentes études. L'expérience 2 a testé cette hypothèse en utilisant deux groupes de personnes atteintes d'acouphène, l'un comprenant des musiciens professionnels et l'autre sans aucune formation musicale. Les résultats ont démontré qu'il n'existait sensiblement aucune

différence entre les deux groupes sur l'ensemble des mesures d'appariement d'acouphène (fréquence, intensité au test et au retest). Afin de valider que notre groupe de musiciens possédait bien des habiletés de discrimination auditive supérieures à nos autres groupes, une tâche d'appariement de sons externes en fréquence a été utilisée. Nos musiciens étaient en mesure d'apparier des sons externes avec une précision dépassant largement les deux autres groupes. Ces résultats suggèrent que les capacités d'appariement de l'acouphène et celles de sons externes sont bien différentes. Il est également possible que les deux groupes ne diffèrent pas sur leur capacité d'appariement de l'acouphène puisqu'ils possèdent tous deux le percept de l'acouphène en continu : l'expérience constante de cette perception pourrait faciliter l'appariement. Malgré tout, les capacités supérieures d'appariement de sons externes ne semblent avoir aucune influence sur les capacités à apparier un son interne.

5.3.5 Un appel à mesurer le percept et la détresse

L'expérience 2 a démontré que, bien que les paramètres psychoacoustiques d'intensité et de fréquence sont précis et stables, ils ne corrèlent que très faiblement avec l'intensité subjective de l'acouphène ainsi qu'avec le dérangement tel que mesuré à partir d'un questionnaire validé (TRQ). Une autre étude a rapporté des résultats similaires : l'intensité subjective mesurée à l'aide d'une échelle visuelle analogue corrèle avec la détresse et l'humeur et non avec le niveau d'intensité en dB SL (Andersson, 2003). Les mesures subjectives (détresse, handicap...) et psychoacoustiques (intensité, fréquences) devraient donc toujours être utilisées en complémentarité lorsque l'acouphène doit être évalué. Actuellement, le domaine de la recherche en acouphène abonde d'études qui tentent de démontrer l'efficacité de différents traitements et approches, mais qui

n'utilisent que les échelles visuelles analogues ou les questionnaires afin de déterminer leur efficacité (Aazevedo, Langguth, Oliviera, & Figueiredo, 2009; De Ridder, et coll., 2010; Minami et coll., 2011; Schaette, König, Hornig, Gross, & Kempter, 2010; van de Heyning et coll., 2008). Cette façon de faire nuit considérablement à l'avancement des connaissances sur l'acouphène et ses mécanismes neurophysiologiques sous-jacents puisqu'aucune mesure du percept n'est évaluée. Encore pire, certains auteurs se permettent de conclure sur l'implication de certains centres auditifs dans la génération de l'acouphène à partir de résultats obtenus aux échelles visuelles analogues. Par exemple, une absence d'effet mesuré sur une échelle visuelle analogue après un traitement de stimulation transcrânienne du cortex auditif est parfois interprétée comme une preuve que le rôle du cortex auditif est secondaire à l'acouphène. Dans ce cas bien précis, l'intensité appariée de l'acouphène aurait pu être diminuée de moitié sans que cette diminution soit perçue par les patients comme une diminution significative, expliquant ainsi les mêmes résultats avant et après le traitement au VAS. Le domaine de la recherche en acouphène bénéficierait grandement d'une plus grande rigueur en incluant des mesures du percept (mesures d'appariements) et des mesures subjectives (questionnaires, VAS) lors d'essais cliniques.

5.3.6 Mesurer pour mieux intervenir

Le potentiel des mesures psychoacoustiques de l'acouphène dans le choix des interventions est de plus en plus étudié et pourrait permettre une intervention beaucoup plus ciblée et similaire à ce qui est déjà utilisé en surdité. En effet, deux études ont démontré que la stimulation acoustique utilisant des appareils auditifs ou des générateurs de bruits sont efficaces pour réduire l'acouphène seulement lorsque la fréquence

prédominante de celui-ci se retrouve dans la plage de stimulation de l'appareil utilisé (McNeill, Távora-Vieira, Alnafjan, Searchfield, & Welch, 2012; Schaette, et coll., 2010). Dans ce cas-ci, l'utilisation routinière des mesures d'appariements en fréquence de l'acouphène pourrait permettre au clinicien de prédire les chances de succès de l'appareillage auditif ou du générateur de bruits chez un patient, basé sur la fréquence prédominante mesurée.

Il est également important de rappeler qu'avant même l'apparition des appareils auditifs à haute technologie tels que nous les connaissons aujourd'hui, il y a eu tout d'abord la création de l'audiogramme et de la mesure du seuil auditif. Ainsi, cette mesure a permis l'évolution des appareils auditifs qui ne comprenaient historiquement qu'un seul canal, à ceux de multiples canaux, tenant ainsi compte des différences d'audibilité aux différentes fréquences. Ces mesures de seuils auditifs sont également les précurseurs des formules prescriptives qui sont fréquemment utilisées en audiologie clinique (NAL, DSL, etc.) lors d'un appareillage. Il est plausible que ces mêmes avancées technologiques puissent voir le jour grâce aux mesures psychoacoustiques d'appariement d'acouphène décrites dans la présente thèse.

6. Conclusions

La présente thèse répond à l'objectif principal en démontrant l'application du paradigme de modulation du réflexe acoustique de sursaut par un court silence (GPIAS), déjà utilisé chez les animaux pour objectiver la présence de l'acouphène, à des participants humains contrôles et avec acouphène. Sa mise en oeuvre a toutefois permis de déterminer que cette mesure n'objective pas la présence de l'acouphène puisqu'elle n'est pas spécifique à sa fréquence. Cette conclusion est notamment supportée par la validation croisée obtenue par l'appariement psychoacoustique en fréquence. Somme toute, les mesures psychoacoustiques d'appariement en fréquence, mais surtout en intensité, ont démontré un potentiel clinique important, notamment une fidélité test-retest remarquable, ainsi qu'une sensibilité et une spécificité accrues pour l'intensité seulement. D'autres études, utilisant un échantillon clinique beaucoup plus grand, pourront permettre de valider leur utilisation clinique.

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