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Abstracts*)

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TARGETED GENOMIC CAPTURE AND MASSIVELY PARALLEL SEQUENCING TO IDENTIFY GENES FOR HEREDITARY HEARING LOSS IN PALESTINIAN FAMILIES

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Massively parallel sequencing technologies, in conjunction with homozygosity mapping relevant for consanguineous families, is being used to meet the challenge of defining hereditary hearing loss on a molecular genetic level. Despite progress in identification of genes for deafness, with the discovery of 15 different genes containing mutations in the Palestinian Arab population, for a significant portion of our patients, the causative mutation has not been found. In an effort to discover more mutations, a custom 1.46 MB design of cRNA oligonucleotides was constructed containing 284 genes responsible for either human or mouse deafness. Multiplexed libraries were analyzed with paired-end sequencing using the Illumina HiSeq. We generated single nucleotide polymorphism (SNP), insertion/deletion (indel) and copy number variants (CNV) for all samples. Rare variants were identified by filtering against dbSNP135, the 1000 Genomes Project, the Exome Variant Server and additional filters and classified by predicted effect on the protein. The variants were validated by Sanger sequencing and co-segregation with deafness was evaluated. Novel and known mutations, including a *MYO6* (c.G897T) exonic splicing mutation, were identified in 16 genes in a total of 48 patients. Our results also demonstrate that there are new genes to be found in the Palestinian Arab deaf population, indicating whole exome sequencing should be conducted next.

AIR AND WATER POCKETS IN THE SOFT TISSUE CONDUCTION PATHWAY; EFFECT ON AUDITORY THRESHOLDS IN HUMANS AND ANIMALS

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Vibrations induced by applying a clinical bone vibrator to skin at various soft tissue sites on the head, neck and thorax elicit auditory sensation through a soft tissue conduction (STC) pathway to the cochlea. Air and water pockets were introduced in the STC pathway and effects on auditory thresholds were compared. Bone conduction and STC behavioral thresholds were assessed in humans at several sites at baseline with a cheek filled with air, and with the cheek filled with water. With an air-inflated cheek, thresholds were elevated by 13-18 dB, while a water-filled cheek caused no change in threshold. STC (under chin) click ABR thresholds were recorded in fat sand rats at baseline and with subcutaneous injection of either air or saline under the chin. An air pocket caused a 10-20 dB threshold elevation, while a saline pocket caused no change compared to baseline. Soft tissues and water have similar acoustic impedances, whereas the acoustic impedance of air is very different. These results in humans and animals show that a region with an acoustic impedance very different from soft tissues (air) interferes with transmission of vibrations from an STC site to the cochlea, leading to elevated thresholds.

THE CONTRIBUTION OF SEGMENTAL SIGNAL TO NOISE RATIO IN IDENTIFICATION OF WORDS AND SYLLABLES IN NOISE

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The large degree of variance in identification of words in noise has been noted in several previous studies. In this study we set out to examine if this could be explained by the fact that for a nominal Signal to Noise Ratio (SNR) value as measured over the entire word, the SNR value per segment can vary considerably. As a pilot study, 18 subjects heard word lists with additive white noise at a nominal SNR of 0dB. The word lists, composed of 15 lists of 10 Hebrew Consonant-Vowel-Consonant (CVC) words each, were segmented into syllables, and the SNR per each syllable was then calculated. Typically, SNR for consonants was weaker than the nominal 0dB, whereas SNR for vowels was higher. Identification percentages were then calculated per word, consonant and vowel. For consonants, a strong correlation was found between segmental SNR and correct identification, whereas for vowels there was a clear ceiling effect. However, the SNR on the segmental level served as a poor predictor of word identification. This indicated that additional factors could be at play, such as use of linguistic knowledge. This supports the notion that top-down processes may be significant in word identification in noise.

THE EFFICACY OF A TWO-STAGE PROTOCOL FOR NEWBORN HEARING SCREENING USING TRANSIENT EVOKED OTOACOUSTIC EMISSIONS AND AUTOMATED AUDITORY BRAINSTEM RESPONSES

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Since 1997, a universal newborn hearing screening (UNHS) program is successfully operating at Sheba Medical Center using transient-evoked otoacoustic emissions (TEOAE) one-stage protocol. Starting January 2010, all newborns in Israel are screened with a two-stage protocol using TEOAE and automated auditory brainstem responses (A-ABR) for those who fail TEOAE test and those at-risk for auditory neuropathy (AN). Our goal was to evaluate the efficacy of the two-stage compared to the one-stage protocol. During the period February –July 2010, 5,312 infants were born at Sheba and screened using the two-stage protocol. Their screening results, audiological follow-up and medical records were retrospectively examined. The results were compared to those of all children born between 1997-2009. Results show: (1) A 51% decrease in false positive rates due to the addition of A-ABR; (2) While 27% of the infants were suspected for AN, no such cases were identified at follow-up in this cohort; (3) The prevalence of permanent HI was 1.9/1000 (n=10), similar to that found for the 1997-2009 cohort. Of these, two infants with mild-to-moderate sensory-neural hearing loss were detected following audiological follow-up for high-risk infants. The results confirm the advantage of the two-stage protocol in reducing the false alarm rate and emphasize the importance of audiological follow-up for the detection of mild-to-moderate hearing loss and late onset cases.

RAPID AND SLOW LEARNING: THE CASE OF RAPID (TIME-COMPRESSED) SPEECH

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Fast speech is harder to comprehend and remember than slower speech, especially when listening to speech in a non-native language. Although listeners are known to adapt to rapid speech over the course of as few as 10 trials, whether longer-term practice with rapid speech results in further learning remains unclear. We administered 5 sessions of practice on a sentence verification task presented in a non-native language (Hebrew) in which speech rate increased gradually using a WSOLA compression algorithm. Practice resulted in learning of the trained task and in generalization to untrained materials. Over the course of training, the performance of the majority of trained listeners improved significantly; by the last training session they were able to consistently verify sentences compressed to 25% of their original duration. Learning transferred to conditions in which the trained materials were presented by novel speakers, but not to a condition in which new materials were presented by the speaker used during training. We therefore suggest that consistent with the Reverse Hierarchy Theory of perceptual learning, learning of rapid speech involves two phases – a brief phase in which learning generalizes widely to untrained materials and a prolonged phase in which learning is more specific.

THE EFFECTS OF NOISE ON WORKING MEMORY PERFORMANCE IN ADULTS

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Background noise can impair memory for complex material, especially when the competing noise is hard to ignore. The present study examines the influence of irrelevant babble noise on the rehearsal aspect of working memory, and the relation between performance in noise and individual preference for studying in a quiet or noisy environment. Participants were forty female students with normal hearing, 20 – 30 years old, with no history of speech, language, learning or attention deficits and no prior knowledge relevant to the study. Four lists of 4-7 words adopted from the FRIGVI (Friedman & Gvion, 2003) were recorded by a female speaker in quiet and in babble noise (+8dB SNR), and presented randomly in both conditions. Participants, tested individually in a soundproof room, were asked to repeat the sequence of words in each utterance. Finally, each participant reported her preferred environmental condition for studying. The number of rehearsed words was higher in the silent condition, and overall errors were significantly higher in the noisy condition. Omissions predominated in longer utterances. Positive correlation emerged between preference for studying in noisy environments and rehearsals in noise. The outcomes suggest that background babble noise interferes with the accomplishment of working memory rehearsal tasks.

TARGETED EXOME CAPTURE AND MASSIVELY PARALLEL SEQUENCING REVEALS NEW MUTATIONS FOR HUMAN HEREDITARY DEAFNESS IN THE JEWISH ISRAELI POPULATION

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Classic techniques such as linkage analysis and Sanger sequencing have led to the discovery of nine genes for non-syndromic hearing loss in the Jewish Israeli population in a period of 15 years, solving one third of the genetic deafness of a Jewish cohort of 300 deaf individuals. The responsible genes of the other two thirds remain to be discovered. This challenge can be met by using targeted DNA capture and deep/massively parallel sequencing. In our studies involving 50 deaf Jewish probands, this technique led to the identification of mutations in an additional ten genes. We constructed a custom 1.6 MB design of cRNA oligonucleotides containing 284 genes responsible for human and mouse deafness. Over 7,000 variants for each proband were filtered against dbSNP131 and the 1000 Genomes project to identify private and rare variants. Potentially functional variants were evaluated by bioinformatics tools and experimentally validated. The novel mutations increased the number of genes found to be involved in deafness in our cohort by 100% in less than a year. Discovery of deafness genes and mutations has crucial clinical implications, as well as for the comprehensive understanding of biological mechanisms involved in the pathophysiology of deafness.

UNDER WATER HEARING: BY BONE CONDUCTION OR BY SOFT TISSUE CONDUCTION

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Hearing under water is considered to be performed by bone conduction (BC). A new mode of auditory stimulation has been described: soft tissue conduction (STC), where the standard clinical bone vibrator is applied to soft tissue sites on the head, neck and thorax. Therefore, hearing under water was investigated to determine whether it is by BC, or by STC. The forehead of normal human subjects was immersed in a water bath together with the water-protected bone vibrator. The subjects clearly heard the tones presented. A human skull was studied in a similar way: the bone vibrator was applied directly to the skull forehead in air. A Laser Doppler Vibrometer (LDV) clearly recorded skull vibrations at the skull inion. However, when the forehead of the skull together with the bone vibrator were immersed in the water bath, the LDV was unable to record vibrations on the skull inion in air, even at sound intensities greater than those heard by the subjects. Thus, even though the normal subjects clearly heard the sounds in the water bath, skull bone vibrations could not be detected. This provides evidence suggesting that hearing under water is by STC.

AUDITORY LEARNING OF AN INVENTED NON-LINGUISTIC RULE

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There is data to suggest that the underlying mechanisms subserving learning of a language may not be specific to the language domain. The memory system, including the procedural and declarative memory systems, is an example of such a mechanism. Procedural memory, for example, is used to explain the ability of young children to acquire language and its rules just from mere exposure to it. It is the same system that helps to explain learning of skills. The purpose of the present study was to investigate the role of the memory systems in learning a sequence of *non-linguistic* sounds. Stimuli consisted of the same four sounds that differ in the order of presentation according to an invented rule. Ten young adults were trained to learn the rule in 5 sessions. Each session included listening to correct sequences as well as listening to new items and incorrect sequences. Listeners were asked to judge for correctness and produce a correct sequence. Fifty percent of the subjects were able to judge correctly the sequences. Only one listener, however, showed generalization of the rule to new sequences thus demonstrating explicit learning. The results share characteristics of learning an invented *linguistic* rule, thus supporting a general mechanism that underlies learning of linguistic and nonlinguistic rules.

IDENTIFICATION OF DEAFNESS GENES IN PALESTINIAN ARABS USING HOMOZYGOSITY MAPPING AND DEEP SEQUENCING

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The advent of dense whole-genome mapping platforms using single nucleotide polymorphism (SNP) arrays and deep

sequencing or massively parallel sequencing (MPS), as well as the availability of the human genome sequence, has accelerated identification of single-gene mutations of Mendelian diseases and disorders. These technologies have been applied to gene identification in consanguineous families. The underlying assumption for homozygosity mapping (HM) is that when a recessive condition arises in a consanguineous family, it is due to a mutation that is identical by descent (IBD), and affected children are expected to be homozygous for the disease haplotype, i.e. the causative mutation and closely linked markers. HM is powerful because a locus can be identified even in families too small to obtain the "classical" threshold of a high (>3) LOD score. We utilized the 250K *Nsp*I SNP array on the Affymetrix GeneChip Platform Arrays for families with deafness. Chips were scanned using the Affymetrix Gene Chip Scanner 3000 with the Gene Chip Operating System 1.4 (GCOS), and analyzed using the Genotyping Console 4.1 software (GTC) and KinSNP software. Homozygous segments of 2Mb or longer were studied by candidate gene analysis. We identified linked regions and are utilizing MPS to identify deafness-causing genes in the homozygous regions.

LATERALIZATION BASED ON TEMPORAL CUES IN BILATERAL COCHLEAR IMPLANT USERS

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Introduction: Interaural time difference (ITD) is the difference in arrival time of a sound between the two ears. It is important mainly in lateralization of low frequency sounds and based primarily on temporal cues of the stimulus. The aim of this study was to evaluate the electrical ITD (eITD) discrimination in bilateral cochlear implant (CI) users, applied to binaural pitch matched electrodes at basal, medial, and apical locations.
Methods: Ten bilateral cochlear implant users (5 adults ages: 18:10-42:9 and 5 children ages: 8:10-10:6), where tested following a training session including pitch and loudness matching. eITD thresholds were measured by using a set of biphasic pulse trains-width: 100μs, rate: 100pps – which were delivered through apical electrodes (around 500Hz), medial electrodes (around 1kHz) and basal electrodes (around 2kHz). Acoustical ITD (aITD) was also measured in a control group of three normal hearing subjects. The task of the subjects was to report whether the stimulus is sensed in central, right or left side of the head.
Results: 1. 7/10 bilateral CI users demonstrated JND to eITD between 200μs-600μs compared to normal listeners who showed JND to aITD of 20μs-110μs. 2. JND to eITD is statistically significant depending on stimulus location. 3. Stimulating more apical region of the cochlea improved JND to eITD. 4. First implanted ear, showed statistically significant better eJND to ITD in apical electrodes in comparison to the second ear. 5. Adults showed statistically significant better JND to eITD compared to children.
Conclusion: This study supports the assumption that bilateral CI users make use of temporal cues in order to locate sound source and that apical electrodes provide temporal cues better than medial and basal electrodes.

SUDDEN HEARING LOSS WITH POSTERIOR SEMICIRCULAR CANAL BENIGN PAROXYSMAL POSITIONAL VERTIGO (BPPV)

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Sudden sensorineural hearing loss (SSNHL) commonly presents with dizziness, a symptom that has been associated with worse prognosis for hearings recovery. We present five patients diagnosed with unilateral profound SSNHL and Vertigo. The Neurotologic examination (Dix-Hallpike) revealed an ipsilateral torsional-down -beating nystagmus. The rest of the exam was normal. This was in keeping with the diagnosis of SSNHL with ipsilateral posterior semicircular canal benign paroxysmal positional vertigo (BPPV). All patients were treated with the Epley maneuver and oral steroids were administered for two weeks. In all cases vertigo resolved and the Dix-Hallpike became normal within several weeks. However, the hearing loss remained unchanged in two patients. Magnetic resonance imaging of the head and electronystagmography were normal. We postulate that SSNHL with ispilateral posterior semicircular canal BPPV may actually be quite common, but the diagnosis of the BPPV is missed because a complete neurotolgical physical examination is not performed. In cases of BPPV of the posterior canal with simultaneous hearing loss, the pathogenesis of posterior BPPV may be different and caused by degeneration of the saccular macula and not the utricle, due to a common blood and nerve supply. Accordingly, we strongly suggest that a thorough neurotologic exam is essential; at least in the cases in which the patient with SSNHL volunteers a history of dizziness or vertigo. This is most important since this situation offers the opportunity to diagnose a treatable disease. The opposite may also be true; patients with BPPV may also have hearing loss.

DEFICIT IN TEMPORAL ORDER JUDGMENT AND ITS LINGUISTIC IMPLICATIONS: DATA FROM AGING ADULTS, DYSLEXIC READERS, AND SLEEP-DEPRIVED STUDENTS

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Rationale: Auditory temporal processing (ATP) is reported to be deficient among different populations, such as dyslexic

readers and aging adults. Despite having similar perceptual deficits, these populations exhibit different clinical complains (reading and phonological awareness for dyslexic readers; speech perception for aging adults). In the current study we aimed to test whether each group exhibits other linguistic difficulties, and whether an additional group with ATP deficit, sleep deprived, will also show similar linguistic difficulties.
Methods: The study included 51 dyslexic readers, 29 aging adults, 55 sleep deprived young adults, and 18 young adult students that served as a control group. All participants performed auditory temporal order judgment (TOJ), speech perception and phonological awareness tasks.
Results: Sleep deprived, aging adults, and dyslexic readers had longer TOJ thresholds than controls. Dyslexic readers showed deficit in speech perception, in addition to deficit in phonological awareness. Aging adults showed deficit in phonological awareness, in addition to deficit in speech perception. Sleep deprived had decrease in both phonological awareness and speech perception. Their performance resembled aging adults' and was better than dyslexic readers'.
Conclusions: ATP is related to difficulties in phonological awareness and speech perception in a number of populations. Sleep deprivation needs to be considered when these abilities are tested.

ELECTROPHYSIOLOGICAL AND BEHAVIORAL MANIFESTATIONS OF BINAURAL PROCESSING IN CHILDREN WITH BILATERAL COCHLEAR IMPLANTS

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Cochlear implants (CI) are increasingly being implanted in both ears in order to provide the benefits of binaural hearing. Considering the limitations of CI devices and the deleterious effects of deafness and auditory deprivation on the developing auditory system, it is unclear whether binaural processing takes place while using two CIs. In the current study we explored binaural processing in children with bilateral CIs by means of a cortical binaural interaction component (BIC) and a behavioral spatial acuity task, both reflecting integration of information from each ear. Cortical potentials were obtained from a group of prelingually deafened children that were implanted bilaterally, simultaneously or sequentially. Multiple-site electrodes were used to record cortical potentials while subjects performed a speech discrimination task (/ta/ vs. /ka/) in three listening conditions: monaural right, monaural left, and binaural. A binaural interaction waveform was derived by subtracting the waveform elicited in the binaural condition from the sum of waveforms elicited in the monaural right and left conditions. In addition, children performed an adaptive spatial acuity task (Litovsky et al., 1997) where they were asked to locate a sound source to the right or the left side of midline (0°). Performance was quantified by calculating the minimum audible angle (MAA; smallest angle that can be discriminated on a right versus left discrimination task). The P3 cortical BIC was evident in a small group of simultaneously implanted children that exhibited MAA of 3-10 degrees, a result similar to that found in 5 year old normal hearing children. In contrast, cortical BICs were absent in sequentially implanted children with long delay and MAA were substantially greater (>40 degrees). While data collection is still in progress, an association between electrophysiological and behavioral manifestations of binaural processing is evident.

POSSIBLE ROLE OF HEARING IN MAINTAINING POSTURAL BALANCE

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Background: Hearing input provides acoustic information about close and distant objects surrounding the body and may contribute to the ability to maintain postural balance in addition to the visual, vestibular and somatosensory inputs. Balance function may be disturbed in subjects suffering from conductive and sensorineural hearing loss but the impairment has been attributed to the pathology underlying the hearing loss.
The purpose of the study was to investigate the possible interference of simulated conductive hearing loss with the ability to maintain postural balance.
Methods: Twenty normal hearing subjects, 20-30 years old underwent the computerized dynamic Posturography (CDP) test battery (Equitest system, NeuroCom, Inc., OR) before and after plugging their external ear canals with earplugs (superfit 30) simulating a 40dB conductive hearing loss.
Results: The composite equilibrium score of the six test conditions comprising the sensory organization test (a CDP subtest) was significantly diminished after plugging the ears. The fourth test condition, in which the somatosensory input is disrupted while the eyes are open and the visual surround is fixed, was specifically affected.
Conclusions: Simulated conductive hearing loss affects the ability to maintain balance and especially the ability to make proper use of the visual input.

PROCESSING OF TEMPORAL AND SPECTRAL CUES IN THE HUMAN BRAIN DURING PERCEPTION OF SPEECH AND CORRESPONDING NON-SPEECH SIGNALS

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Elucidating the neural mechanisms underlying functional asymmetries in speech processing remains an unresolved question. Whereas some researchers suggest that lateralization reflects a speech–specific mechanism, others proposed that the two hemispheres differ in their relative sensitivity to temporal and spectral features of sounds in general. To address this question we examined how the brain processes linguistically relevant spectral and temporal information compared with the processing of corresponding non-speech signals. Auditory Evoked Potentials (AEPs) were recorded from 61 scalp electrodes during active discrimination of spectral (/ubu/-/udu/) and temporal (/ubu/-/upu/) stimulus pairs and their analogous non-speech stimuli. Electrophysiological responses to the first stimulus in pairs were analyzed and current density source estimation (sLORETA) and statistical activation maps were derived to compare brain activity distributions. Speech and analogous non-speech stimuli evoked significantly different voltage differences around the main scalp recorded AEPs peaks. Spectral and temporal processing resulted in different AEP waveforms only in response to non-speech stimuli. Speech-evoked AEPs, on the other hand, showed sensitivity to stimulus phonetic category. Source estimation revealed more activity in auditory cortices to non-speech stimuli beginning from early (around N1) stages of processing. Around the time of P2b differences were prominent mainly within the right superior temporal cortex and the right parieto-temporal junction. Later processing of non-speech stimuli evoked more activity in both hemispheres. Analyzing the time course of the right and left hemisphere activation indicated that laterality fluctuates to also include activity in the 'non dominant' hemisphere, as revealed by periods of right hemisphere prominence during speech perception. The time course of activation at different brain areas showed that speech stimuli and analogous non-speech stimuli activate similarly distributed neural networks. These networks show different degrees of sensitivity to the stimulus type (speech/ non-speech) and to the relevant acoustic cue (spectral/temporal). We suggest that brain specialization for speech processing is not hemisphere specific, but results from specific and unique activation patterns of distributed neural networks in both hemispheres.

IS THERE A RIGHT COCHLEAR IMPLANT ADVANTAGE IN CHILDREN USING TWO IMPLANTS?

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Previously we have shown that speech perception performance of unilaterally implanted children with right cochlear implants (CI) was slightly, yet significantly better than that of children with left CIs. With the continuous increase in bilateral implantation in children, we asked whether the 'right CI advantage' is evident in bilaterally implanted children. Two groups of children with bilateral CI performed word identification task. Group 1 consisted of 8 children that were implanted simultaneously between 10-36 months and were using their implants for at least 12 months. Group 2 consisted of 20 children that were implanted sequentially: 10 were first implanted to the right, and 10 to the left. Age at first implantation was 11-52 months; Age at second implantation was 1.8-16 years. Results indicated that in the simultaneously implanted group a significant right CI advantage was evident and manifested in higher performance while using the right versus the left CI. A more pronounced right CI advantage was evident in children that had significant auditory experience prior to implantation. In the sequentially implanted group performance was higher while using the first implanted CI, regardless of side. When the right ear was first implanted, however, difference between performance with the right and left CI was greater and in favor of the right CI. In conclusion, simultaneous stimulation of both ears after short auditory deprivation may restore normal speech lateralization patterns. Nonetheless, sequential stimulation following prolonged unilateral auditory deprivation may lead to reorganization of speech laterality patterns.

TRANSITIONS OF THRESHOLDS ON SKIN OVER THE HEAD, NECK AND THORAX

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During mapping of the skin sites at which a bone vibrator (BV) elicits auditory sensation, the thresholds on the head, neck and thorax were very different from each other. This was further assessed in 10 normal hearing subjects equipped with ear plugs to reduce air-conducted hearing from the BV. Mean thresholds over the thoracic vertebra were uniformly 40-50 dB greater than those at the mastoid; on the head sites, thresholds were uniformly only 4-7 dB greater than at the mastoid. Over the cervical vertebra, there was a transition from 4.5 dB at C1 to 40 dB at C7. Thus, the vibratory energy introduced by the BV in the soft tissue may be dispersed in the volume of soft tissue in the region so that only a small part reaches the inner ear, eliciting auditory sensation. When delivered to the small volume of the head, thresholds are uniformly low; when applied to the much larger thoracic volume, there is greater dispersion of energy so that less energy reaches the inner ear, and thresholds are uniformly elevated. The thresholds on the neck (cervical vertebra) therefore represent a transition zone between the larger volume of the thorax and the smaller volume of the head.

CAN ELDERLY IMPROVE PERFORMANCE FOLLOWING TRAINING IN PSYCHOACOUSTIC AND AUDITORY LINGUISTIC TASKS?

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As part of the aging process, older adults are known to encounter difficulties at different levels of auditory processing. It has also been suggested that the aging brain is less adaptable to changes than the brain of the young adult. The purpose of the following experiments was to determine whether despite the deterioration in auditory and cognitive capabilities, elderly can improve performance following training. The first experiment tested learning-induced gains following multiple-session training of a gap detection task in 10 elderly compared to 10 young adults. In a second experiment, 8 elderly and 8 young adults were trained on learning an artificial language rule during 10 sessions. The results show that in both experiments, the starting performance of the elderly was considerably poorer than that of the young adults. Both groups showed large learning-induced gains, and for some elderly, performance reached that of the younger adults by the end of training, but the elderly improved at a slower rate. Similar transfer of learning and preservation was evident in both groups. Thus, following intensive training, the elderly improved in auditory tasks of varying cognitive complexity which involved the implicit and/or declarative learning systems. Such findings have important implications on auditory rehabilitation protocols of the elderly.

TOP-DOWN AND BOTTOM-UP PROCESSING IN NORMAL HEARING AND HEARING-IMPAIRED INFANTS WITH COCHLEAR IMPLANTS

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The last decade has proven cochlear implants (CI) to be a viable tool for early habilitation of infants with severe-to-profound hearing loss that are in the initial stages of language acquisition. The purpose of the present study was to assess basic discriminative abilities (bottom-up processing BUP) and the influence of lexical knowledge on word discrimination (top-down processing TDP) in normal hearing (NH) and CI infants. A total of 102 NH infants aged 11-14 months and 24 CI infants aged 10-35 months with listening experience of 1-13 months participated in a set of experiments. Using the visual habituation procedure, discrimination was tested using two pairs of meaningful words that differed in their stress pattern and one pair of nonsense. Each word pair was also tested in the reverse order (e.g., a-BA vs A-ba and A-ba vs a-BA). If discrimination was based only on basic psychoacoustic abilities then the order of the stressed syllables in the words should not influence discrimination. If, however, prior knowledge of the words influences discrimination then that would support TDP. Results showed that all infants were able to discriminate the words based on differences in stress-pattern only, regardless of the order of the stressed syllables in the words. However, both groups showed better discrimination when the pair of words was presented from the uncommon representation (e.g., a-BA) to the common one (e.g., A-ba) than vice versa. This influence of top-down processing on discriminative abilities in CI infants with limited listening experience provides valuable insight to their higher level of speech processing.

CLONAZEPAM QUIETS TINNITUS: A RANDOMIZED CROSSOVER STUDY WITH GINKGO BILOBA

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A recent review stated that no drugs provide replicable long-term reduction of tinnitus. However, two well-designed studies using the short-acting benzodiazepine, alprazolam, found a significant quieting of tinnitus using a visual analog scale (VAS). No such studies have assessed long-acting benzodiazepines. Open-label, randomized, crossover study of 38 adults (27 M, 11 F) with tinnitus for more than 2 months randomized to either clonazepam or ginkgo for the first 3 weeks. For the next 2 weeks no medication was taken. For the final 3 weeks, subjects received the other drug. The initial dose was one tablet daily (clonazepam 0.5 mg; ginkgo 40 mg). Subjects increased the dose by one tablet every 3 days to a maximum of 4 tablets at bedtime until a satisfactory decrease in tinnitus loudness or intolerable side effects occurred. Tinnitus was assessed with pitch- and loudness-matching, tinnitus handicap inventory (THI), and VAS of loudness, duration, and annoyance. Clonazepam significantly reduced tinnitus loudness (74% of subjects), duration (63%), annoyance (79%), and THI score (61%), whereas ginkgo showed no significant benefit for any of these measures. Three subjects had no tinnitus with clonazepam, none with ginkgo. This third well-designed study establishes that benzodiazepines can significantly quiet tinnitus. As a long-acting medication, clonazepam is preferable to alprazolam, because long half-life medications have less withdrawal issues and better compliance due to once a day dosing.

PREVENTION OF CISPLATIN-INDUCED HEARING LOSS BY INTRATYMPANIC DEXAMETHASONE

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Objective: To examine the possible role of intratympanic Dexamethasone (ITD) in the prevention of Cisplatin-induced

hearing loss in oncological patients receiving it in a cumulative dose greater than 300 mg.
Patients and Methods: 18 patients were recruited to this prospective controlled cohort study. Immediately prior to each Cisplatin treatment 0.8-1ml of Dexametathasone 10mg/ml was delivered to one ear while the other served as the control. Audiometry and distortion-product otoacoustic emissions (DPOAEs) parameters were compared between and within the study and control groups.
Results: 8 patients have received to date the minimal required cumulative dose of 300 mg Cisplatin ranging from 416 to 888 mg (537±152.6 mg). The average pure tone threshold at 8000 Hz in the last follow-up evaluation was significantly increased in both the study and control ears when compared to the baseline values obtained before the first Cisplatin treatment ($p<0.05$). Significant increase in the average pure tone threshold for 6000 Hz was found in the control but not in the study group ($p<0.05$). Also, significant decrease in the average DPOAEs SNR values for 4000-8000 Hz f2 frequencies were documented in the control but not in the study group ($p<0.05$).
Conclusions: These preliminary results point to a promising potential in the prevention of Cisplatin-induced hearing loss by ITD.
Comment: Interim results for 8 patients receiving the target cumulative dose of Cisplatinum are reported. We expect to include the results of additional 8 patients at the time of ISAR scientific meeting.

MUTATIONS IN NESPRIN 4, A KASH DOMAIN PROTEIN LINKING THE NUCLEUS TO THE CYTOSKELETON, LEAD TO HEARING IMPAIRMENT IN HUMANS AND MICE

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Hereditary hearing loss in humans and mice is shown for the first time to be caused by mutations in the gene encoding Nesprin 4 (Nesp4), a kinesin-binding protein of the outer nuclear membrane. Nesp4 is a member of the KASH-domain protein family, which, together with SUN domain proteins of the inner nuclear membrane, form the nuclear envelope-associated LINC (LInker of Nucleoskeleton and Cytoskeleton) complexes. Linkage analysis deep sequencing/massively parallel sequencing detected a two-nucleotide deletion in exon 2 of Nesp4 in two unrelated families displaying progressive hearing loss. This mutation is predicted to result in a large (75%) truncation with loss of both the Nesp4 KASH domain, required for localization to the outer nuclear membrane, and the kinesin-binding domain. Nesp4 is expressed in the outer hair cells (OHCs) of the mouse cochlea. In the absence of Nesp4, OHCs are formed, but degenerate rapidly as the auditory system matures. Auditory brainstem response (ABR) measurements show that Nesp4-deficient mice display a pattern of progressive hearing loss that mirrors the hearing loss in human patients. OHC degeneration and loss is associated with nuclear displacement from a basal to a more apical location, together with gross morphological changes in cellular architecture. Our findings mark Nesp4 as an essential protein for cochlear OHC viability and hearing, potentially due to their role in maintaining correct nuclear position in the OHCs of the sensory epithelia.

THE ASSOCIATION BETWEEN MedEl AUDITORY NERVE RESPONSE TELEMETRY (ART) AND MAP MOST COMFORTABLE LEVELS

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Electrically evoked compound action potential (ECAP) thresholds are commonly used to ascertain the integrity of the neural/electrode interface as well as to facilitate the programming process. Numerous studies have determined the relations between ECAPs and thresholds (T levels) as well as comfortable levels (C/M levels) obtained from Cochlear and Advanced Bionics recipients. Data concerning ECAP measurements in the MedEl device, and their relationship with programming levels, is scarce. The objective of the present study was, therefore, to explore the association between Auditory Nerve Response Telemetry (ART) measurements and programming levels of the MedEl device. For this purpose we studied post-operative ART thresholds and behaviorally obtained most comfortable levels (M) in a group of adults that were using their implants for at least three months. ART thresholds and M levels were compared at basal, medial, and apical electrodes. While data collection is still in progress, preliminary analysis showed that ART thresholds and behavioral M levels shared a similar profile across the electrode array. These initial results coincide with previous findings obtained from Cochlear and Advanced Bionics recipients.

AIR CONDUCTION (AC), BONE CONDUCTION (BC) AND SOFT TISSUE CONDUCTION (STC) BEFORE AND AFTER FIXATION OF THE MOBILE COMPONENTS OF THE MIDDLE EAR

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A new mode of auditory stimulation, called Soft Tissue Conduction (STC) has been recently described which complements AC and BC. Since STC stimulation uses the same bone vibrator as in BC, it is possible that STC is simply a form of BC. In order to investigate this possibility, AC, BC and STC thresholds were determined in fat sand rats, and then the classical mechanisms of BC were eliminated by fixation of the ossicular chain and the two windows, followed by re-determination of the thresholds. AC thresholds were elevated (a conductive hearing loss), but BC and STC thresholds were unchanged. Thus even though the two windows were no longer mobile and bulk fluid flow is therefore no longer possible, and a pressure difference across the basilar membrane would not be induced, STC threshold was not altered. This provides evidence that STC is not a variant of BC, and that STC and BC activation may not be based on a passive traveling wave which requires two mobile windows.

MANAGEMENT OF HEARING IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 2: NEW PARADIGMS

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The hallmark of Neurofibromatosis type 2 is bilateral vestibular schwannomas and most of the patients become deafened by the tumor growth or due to the treatment of the tumors. Until recently, surgery was the mainstay of treatment and various surgical paradigms have emerged. Useful technology to assist these patients includes hearing aids, bone conducting solutions, cochlear implants and auditory brainstem implants. Our center and others have been involved in the use of a number of medications including avastin, lapatinib and Rad 001 in controlled trials with serial volumetric MRI analysis and audiograms with some success. The presence of and promising results with the drug trials has changed the surgical paradigms in the management of this debilitating disease. This presentation will give an overview of the surgical management with regards to hearing and present new results data with the drug trials. Additionally we will review recent results of tumor analysis in a phase 0 trial with lapatinib. This combined therapy management option has changed the way clinicians think about hearing preservation and rehabilitation in patients with Neurofibromatosis type 2.

UPDATE ON ROBOTICALLY INSERTED STEERABLE COCHLEAR IMPLANT ELECTRODES

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Cochlear implants are the medical/surgical treatment of choice in children and adults with severe to profound sensorineural hearing loss and more recently have been implemented successfully in patients with various degrees of better hearing that obtain limited benefit from traditional amplification. Electro-acoustical hearing in the same ear has also been successful with the use of hybrid type devices. As such, much attention is now given to hearing preservation surgery, limiting intra-cochlear trauma and precise electrode placement within the cochlea. A number of recent publications have documented the ability to save residual hearing, even with long electrode placement, and electrode placement completely within the scala tympani results in improved outcomes. This presentation will give an update on the ongoing robotically inserted electrode project. Intracochlear real time impedance sensing or cochlear fluid chemical sensing are two ways to gain real time feedback for placement. Pre-programmed path planning is also an option under exploration. Cochlear models and cadaveric temporal bones have been used in the experimental set up and more recently the continuous impedance monitoring tool has been use in human CI insertions. It is the hope that implementing this technology will result in better and better outcomes.

DISCOVERY AND REGULATION OF MicroRNAS IN THE MAMMALIAN INNER EAR

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MicroRNAs (miRNA) are small non-coding RNAs that regulate gene expression through the RNA interference (RNAi) pathway. By binding to sequences in the 3″ untranslated region (UTR) of genes, a miRNA can inhibit target mRNAs by translational suppression and mRNA destabilization. miRNAs play an important role in the development and regulation in the inner ear, and mutations in miRNAs lead to deafness in humans and mice. In order to further address the role of miRNAs in the inner ear, we used Illumina deep sequencing technology to identify novel miRNAs found in inner ear sensory epithelia. Using this method, we identified three novel mouse miRNAs. qRT-PCR and *in situ* hybridization validated expression of these miRNAs in the mouse inner ear. Predictions of gene-targets to these miRNAs were then verified by luciferase assays. The interaction between the miRNAs and their targets is being studied. Understanding these interactions may shed some light on known and novel miRNAs, their effect on the development of normal and impaired hearing, and the mechanisms leading towards deafness.

COCHLEAR IMPLANT IN FAR ADVANCED OTOSCLEROSIS

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Background: Involvement of the cochlea in otosclerosis is a well-defined presentation of the disease. Despite this, only a small number of patients present with profound sensorineural hearing loss. For these far advanced patients, cochlear implant has become a potential solution. Specific problems regarding implantation in these patients include coping with cochlear ossification, relatively high prevalence of facial nerve stimulation and unpredictable audiometric results. Recent studies point out the excellent results of cochlear implant in otosclerosis. In most cases complete insertion of the electrode is possible. Facial nerve stimulation can quite easily be addressed, necessitating implant removal in but rare cases. Hearing results are fair.
Methods: We performed a retrospective review of all cochlear implantations performed in the Sheba Medical Center from 1989 to the present.
Results: 700 patients were operated in these years, out of which 9 had far advanced otosclerosis. Hearing results for this group are similar as for implanted adults, otherwise healthy. Only one patient has extracochlear stimulation, and needed shut-down of most of her electrodes.
Conclusions: Cochlear implant is a reasonable solution for far advanced otosclerosis.

NEW HUMAN AND MOUSE MUTATIONS IN THE *POU3F4* TRANSCRIPTION FACTOR LEAD TO PROFOUND HEARING LOSS

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In the study of hereditary disease in general, and specifically in deafness, human families have proven invaluable in the search for mutations in genes causing disease. Furthermore mice are excellent animal models for the validation of novel gene defects, and for further analysis of underlying mechanisms. Here we report two new mutations in the transcription factor *POU3F4*, which result in profound hearing loss (HL): a human Q79>X mutation in an Israeli family, revealed by massive parallel sequencing; and a mouse C300>X mutation in an ENU-induced mutant mouse, schwindel (*sdl*). POU3F4 is a transcription factor, essential for the differentiation of mesenchymal cells in the spiral ligament, and the causative gene for DFNX2 deafness. In addition to HL, the mutant mice present vestibular disorders and elevated serum potassium levels. Inner ear abnormalities underlie this form of deafness, yet the primary defect is unknown. This is the first Pou3f4 mouse mutant in which a mutant protein that accumulates in the cytoplasm instead of entering the nucleus has been demonstrated. In this regard, this mouse model is likely to improve our understanding of the role of POU3F4 in hearing, and help to resolve the underlying mechanism leading from *POU3F4* mutations to deafness.

DEVELOPMENTAL TRENDS IN SPEECH-IN-NOISE DISCRIMINATION

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There is evidence that central auditory processing abilities continue to develop beyond early childhood. One issue needing further exploration is age-related changes in speech-in-noise discrimination. Three groups of children (15 third-fourth graders, 12 fifth-sixth graders and 10 seventh-eighth graders) and one group of 11 young adults performed a computerized Speech Discrimination in Noise test (SDN). The test included a list of 50 monosyllabic Hebrew words with background white noise. Subjects were asked to repeat the word they heard while the Speech in Noise Ratio (SNR) was adapted by the computerized interface. The initial SNR was 6 dB and shifted 1 dB up after one incorrect response and 1 dB down after two consecutive correct responses. The final SDN score was calculated as the mean of the last six SDN extrema of each subject's response curve. Results showed that the youngest children scored significantly poorer than those of both the adults and the oldest group of children. Although there were no other significant differences between the groups, a trend of improvement of SDN scores with age was found. We conclude that SDN abilities continue to develop beyond ten years of age and become more adult-like only after 11 years of age.

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