Universidad de Las Palmas de Gran Canaria
Doctorado en Investigación Aplicada a las Ciencias Sanitarias

Efectos de la estimulación eléctrica del órgano otolítico en pacientes con disfunción vestibular bilateral.

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Índice general

Capítulo 1

Motivación y Justificación de unidad temática

La motivación de esta tesis doctoral se fundamenta en la posibilidad de incorporar, por un lado investigación básica , asi como investigación aplicada en el area de Medicina , y añadir elementos de innovación tecnológica dentro de dicha área.

A través de una misma línea de investigación "Sistema de estimulación vestibular" se ha podido a través de estos años pasar por estas fases que se representa en esta tesis:

- Investigación básica
- Investigación clínica aplicada
- Desarrollo tecnológico (patente)

El proyecto de investigación que ha supuesto la línea continua de la investigación se denomina: "Investigación Clínica de sistema Neuro-estimulador vestibular en pacientes con disfución vestibular" (European development of bionics vestibular implant for bilateal vestibular dysfiction – BIONICVEST). Esta línea de investigación ha sido financiada por la Union Europea (FET-OPEN) , en el plan Horizon 2020 Research and Innovation Programme bajo el Grant Agreement Nº 801127 .

Capítulo 2

Introducción

Más de 100 millones de personas en todo el mundo padecen trastornos vestibulares graves, por lo que corren un alto riesgo de caídas y lesiones. Esto perjudica gravemente la calidad de vida de estos pacientes, impidiéndoles realizar las actividades cotidianas, como conducir e incluso caminar. Los canales semicirculares, el sáculo y el utrículo proporcionan información sensorial a los circuitos neuronales que facilitan la percepción precisa de la orientación espacial y el rumbo, apoyan una postura estable y mantienen una visión estable. Esto contribuye en un 60 % a la función vestibular y al equilibrio postural. La función del sáculo y del utrículo son esenciales para el equilibrio postural en posición erguida y al caminar.

A pesar de la alta prevalencia de trastornos del equilibrio, no existe ningún tratamiento o dispositivo que pueda recuperar o reemplazar la función del utrículo y del sáculo. La estimulación vestibular eléctrica (EVS) es un abordaje no fisiológico, que se ha estudiado en el pasado, principalmente para investigar las estructuras y vías anatómicas y neuro-fisiológicas del sistema vestibular. Cohen y Suzuki indicaron en la década de 1960 que los movimientos oculares se podían provocar mediante la estimulación eléctrica de los nervios ampular y otolítico en animales [Cohen y Suzuki, 1963; Suzuki y col., 1964; Suzuki y col., 1968; Suzuki y col., 1969a, b]. A pesar de ello aun no existe un dispositivo de uso clínico que permita la recuperación de la función vestibular mediante el uso de prótesis activas como el implante vestibular.

El objetivo de esta tesis es analizar la función del órgano otolítico y su estimulación eléctrica para ofrecer tratamiento a pacientes con disfunción vestibular bilateral.

El primer objetivo de la tesis es analizar la función del órgano otolítico, su función, evolución e importancia en la función vestibular. Este objetivo es clave para definir el órgano objetivo a estimular. El segundo objetivo es estudiar si es posible estimular los otolitos, o sus terminaciones nerviosas, de manera eléctrica. Y por último, el tercer objetivo, es evaluar el rendimiento y beneficio de un implante vestibular otolítico.

En la primera sección, se hará una breve introducción sobre la anatomía y fisiología del

sistema vestibular humano, la via de abordaje quirúrgico y los modos de estimulación eléctrica otolítica En el segundo capítulo se explican los objetivos y el procedimiento. El tercer capítulo está relacionado con la recopilación de las cuatro publicaciones de la tesis y una patente. En el cuarto capítulo se presentará la conclusión principal. Finalmente, los trabajos futuros que surjan del presente trabajo darán por finalizado la investigación completa.

Esta tesis se enmarca dentro del proyecto Europeo BionicVEST donde se busca desarrollar y evaluar el primer implante otolítico para el tratamiento en pacientes con disfunción vestibular bilateral.

2.1. Sistema vestibular

2.1.1. Anatomia

El sistema vestibular se localiza en el oído interno, está formado por el vestíbulo y los conductos semicirculares. En el interior del vestíbulo se distinguen dos estructuras membranosas, el utrículo y el sáculo, en donde se encuentran unos órganos receptores periféricos denominados máculas, que están integrados por células receptoras sensoriales ciliadas, las cuales están recubiertas por una membrana sobre la que hay una serie de cristales de carbonato Cálcico que reciben el nombre de otolitos, los cuales son muy susceptibles a los cambios de gravedad.

En cuanto a los conductos semicirculares, son tres, horizontal, anterior y posterior. Estos se encuentran orientados en los tres planos del espacio. Presentan una dilatación en su parte inferior denominada ampolla, en el interior de la cual se encuentra un órgano del equilibrio, que recibe el nombre de cresta ampular, la cual está integrada por células sensoriales receptoras ciliadas, que a su vez están recubiertas por una membrana gelatinosa en forma de cúpula. Estas células descansan sobre otras de tipo conjuntivo y, conectadas con las neuronas que inician el nervio que conducirá la información hasta el interior del cerebro. Las vías vestibulares comprenden las fibras que, partiendo de los conductos semicirculares y del vestíbulo, llegan hasta el tronco del cerebro y de aquí se dirigen a la corteza cerebral. Estas vías se inician en las crestas ampulares de los canales semicirculares y de las máculas del utrículo y el sáculo.

El objetivo del sistema vestibular es mantener la bipedestación del individuo. El sistema vestibular es uno de los centros de información sobre el estado de equilibrio del cuerpo. Existe un equilibrio estático donde actúa solo la fuerza de la gravedad, un equilibrio cinético generado por fuerzas pasivas y un equilibrio dinámico generado por el desplazamiento de parte o de todo nuestro cuerpo.

Sistema vestibular central: Contribuye a la adaptación postural y ocular para mantener el equilibrio del cuerpo y enfoque visual. El sistema trabaja permanentemente y de forma inconsciente, dando información sobre la posición en el espacio de la cabeza y su desplazamiento.

Tiene el receptor en los canales semicirculares que dan información de aceleraciones angulares y en el utrículo y sáculo que dan información de aceleraciones en sentido lineal y posición de la cabeza en el espacio. Cada fibra de la raíz vestibular una vez en el troncoencéfalo, se divide en una rama ascendente y otra descendente, constituyendo el llamado tracto vestibular, que termina en los núcleos vestibulares superior, inferior, medial y lateral localizados en el bulbo y en la parte inferior de la protuberancia. Otras ramas forman la vía vestíbulocerebelosa directa, ya que avanzan directamente a través del pedúnculo cerebeloso inferior homolateral hasta el núcleo del techo. Nucleos vestibulares y las conexiones de los nucles vestibulares desde donde se establecen conexiones con otros núcleos de pares craneales, cerebelo, córtex cerebral, médula espinal, sustancia reticular y cuerpo estriado; integrando toda la información aportada por el sistema vestibular con la visual y propioceptiva, y logrando una coordinación postural y control motor.

Sistema vestibular periférico: Los canales semicirculares contienen endolinfa, la cual está compuesta de potasio a altas concentraciones y sodio a bajas concentraciones, y circula libremente por el interior de cada canal en respuesta a la dirección de la rotación angular de la cabeza. El neuroepitelio sensorial que tapiza el laberinto posterior, está en contacto con las ramas terminales del nervio vestibular que penetran por los agujeros cribosos del laberinto óseo. La formación del nervio vestibular se hace por la unión de la rama superior, rama posterior y rama inferior. En el fondo del conducto auditivo interno, las 3 ramas terminales se unen y engrosan para formar el ganglio vestibular y la parte vestibular del nervio VIII par. Esta parte vestibular y la coclear se reúnen formando el nervio cócleovestibular, el cual discurre junto con el nervio facial. Salen del conducto y atraviesan el espacio pontocerebeloso penetrando en el troncoencéfalo donde vuelven a separarse la raíz coclear de la vestibular.

2.1.2. Fisiología del equilibrio

La conservación del equilibrio en situación de bipedestación erguida y locomoción, es el resultado de un funcionamiento integrado en el cual participan numerosos datos sensoriales como lo son la visión, la propiocepción musculoarticular y vestibular, la cutánea plantar y estructuras nerviosas centrales como son los sistemas extrapiramidal y piramidal. El equilibrio se rige por arcos reflejos rápidos y se nutre de informaciones sensoriales de asistencia a los programas motores, que tienen un papel primordial durante el desarrollo ontogenético y, en el adulto, en situaciones inesperadas.

Fisiología de las máculas otolíticas

Las máculas otoli?ticas están situadas en 2 órganos sensoriales perpendiculares entre si, utrículo y sáculo, y dispuestas para detectar las aceleraciones o desaceleraciones lineales en

los tres planos del espacio. El estímulo percibido por estos receptores es la aceleración lineal producida en el plano paralelo a la mácula, el principal estímulo percibido es la gravedad. Considerando al ser humano en bipedestación, las máculas del sáculo se encuentran situadas en un plano vertical y captan de forma eficaz las aceleraciones de los movimientos cefálicos de ascenso y descenso, y por lo tanto de las fuerzas gravitatorias. Al sáculo, además de su función como captor de aceleraciones verticales, se le atribuye una función inmunoprotectora del laberinto, observándose en él abundantes linfocitos. Por otro lado, las máculas del utrñiculo, al estar situadas en un plano horizontal, capta las aceleraciones lineales laterales y ventro-dorsales así como las inclinaciones de la cabeza. Por lo tanto, las aceleraciones o desaceleraciones lineales en los 3 planos del espacio son el estímulo más eficaz detectado por las máculas otolíticas. Son las células ciliadas de las máculas las encargadas de transformar la energía mecánica, producida por el movimiento, en señales nerviosas. La actividad de las estas cñelulas esta determinada por su polarización morfofuncional u organización ciliar, que es distinta en el utrículo y en el sáculo. Mientras en el utrículo el quinocilio se encuentra en la zona celular más cercana a la estriola, en el sáculo se encuentra en la porción mas alejada a la misma. Durante la aceleración de la cabeza, la membrana otolítica se mueve con respecto a las cñelulas ciliadas maculares, produciendo una deflexión de los cilios, acercando estos al quinocilio y provocando una excitación de las mismas. Así, el acercamiento de los estereocilios produce la apertura de los canales de K+, en presencia de Ca2+, produciendo la despolarización hacia su polo basal y la liberación del contenido neuromediador de las vesículas que rodean la barrera sináptica. De este modo, la flexión de los estereocilios hacia el quinocilio, provoca un aumento de la tasa de estimulación neural. Este aumento de la tasa de estimulación es proporcional a la magnitud del estimulo. Al alcanzar el movimiento una velocidad constante, no existe ya un desfase entre el movimiento de cilios ni excitación de las células. Cuando el movimiento de la cabeza se desacelera, de nuevo existe un desfase entre el movimiento de las células maculares y de la membrana otolítica, sufriendo los cilios una deflexión en sentido contrario al quinocilio y por tanto una reducción en la liberación de aminas neurotransmisoras y una reducción en la tasa de estimulación neural hasta que la desaceleración cesa. Las células ciliadas de los receptores otolñiticos, no sólo están activas en movimiento sino que mantienen una actividad eléctrica espontánea en reposo, constante e intensa, existiendo una descarga continua de potenciales de acción en las fibras de los nervios vestibulares. Esta actividad continua está producida por el efecto excitador permanente de la fuerza de la gravedad sobre las máculas, sufriéndose una desaferenciación en la ingravidez. Esta actividad de base contribuye al mantenimiento del tono muscular en reposo y al mantenimiento de la postura además de ser un eficaz sistema para detectar la polaridad de las respuestas (positiva-aceleración y negativa-desaceleración) y excelente para mantener menores umbrales de excitación del receptor. [3]

2.1.3. Maniobras de exploración vestibular

Prueba calórica

Se estimula con agua caliente (44ºC) y fría (30ºC) cada oído, individualmente y de manera alternativa. Se dirige un chorro de unos 200 cc de agua por el conducto auditivo externo. El objetivo es provocar una diferencia de temperatura a lo largo del hueso temporal (donde se encuentra alojado el oído interno). Esto determina un desplazamiento de los líquidos del oído interno por los canales semicirculares lo cual desencadena una reacción de vértigo transitorio y un nistagmo o movimiento ocular involuntario en sacudidas. La estimulación con agua caliente de un oído produce un nistagmo en una dirección diferente a la que se produce con la estimulación con agua fría. Por este motivo al estimular con las dos temperaturas los dos oídos podemos obtener una idea precisa de la función relativa entre ambos.

Prueba rotatoria

En este caso el movimiento reflejo ocular se estudia igual que en las pruebas antes descritas. El paciente se sienta en una silla cuyo movimiento es programado desde un ordenador que genera un movimiento preciso. Los movimientos son similares a los que el paciente hace a lo largo de sus actividades cotidianas y el posicionamiento del paciente es preciso y seguro para evitar movimientos de la cabeza durante las rotaciones que puedan invalidar los resultados. Los movimientos que realiza la silla son sinusoidales, de vaivén a derecha e izquierda, a diferentes velocidades y frecuencias, no superando los 50º por segundo de velocidad máxima.

2.1.4. Pruebas diagnósticas

Electro y video nistagmografia

Se basa en un reflejo entre el oído interno y el ojo (reflejo vestíbulo-oculomotor) que hace referencia al movimiento ocular provocado por el estímulo del sistema vestibular. En esta prueba el movimiento ocular se va a registrar de dos maneras, a través de electronistagmografía (ENG), en el que se colocan pequeños electrodos en la piel alrededor de los ojos y a través de videonistagmogravía (VNG), donde se utilizan cámaras especiales que filman el movimiento ocular. Primero se explorará la funcionalidad del ojo en cuanto a su capacidad para seguir un objeto en movimiento (seguimiento) o de dirigirse a un objeto de interés que aparece de manera súbita en la periferia de nuestro campo visual (sacadas). Posteriormente se medirá el movimiento ocular al situar al paciente en determinadas posiciones, como son el decúbito supino, lateral derecho e izquierdo, y con la cabeza hiperextendida (nistagmus de posición) así como al adoptar ciertas posturas que en algunos casos producen mareo y vértigo (maniobra de Dix-Hallpike) pudiendo identificar de manera precisa la causa de su problema.

Posturografía dinámica

Método de gran utilidad para cuantificar el estado funcional del paciente que ya ha sido diagnosticado por otros métodos y aumenta las posibililidades de identificación de las alteraciones del equilibrio. La capacidad de mantener el equilibrio depende no sólo de la vista y del sistema vestibular sino también de la información que el cerebro recibe de los músculos y articulaciones. La posturografía dinámica permite analizar la interrelación entre las tres partes del sistema de equilibrio (ojos, sistema vestibular, músculos y articulaciones). Permite determinar si uno de ellos es anormal en su funcionamiento o si es incapaz de analizar y considerar los estímulos antifisiológicos o que alteran el equilibrio. De las técnicas que permiten la valoración objetiva del control postural, la posturografía es aquella que lo estudia a través de los movimientos del centro de presión, proyección del centro de gravedad del cuerpo, sobre una plataforma dinamométrica. Actualmente la Posturografía Dinámica Computerizada (PDC) se considera como el "Gold Standard" para el estudio del control postural. La American Academy of Otolaryngology-Head and Neck Surgery y American Academy of Neurology han descrito la PDC como un método clínicamente útil para el estudio del equilibrio humano, que aísla y cuantifica los componentes sensoriales y motores que contribuyen al mantenimiento del control postural y permite valorar la integración sensorimotora tanto en sujetos normales como en aquellos con déficits de equilibrio. Recientemente ha sido incluida por la American Medical Association entre los métodos que permiten la documentación de los déficits y discapacidades. Además, es importante destacar que son las vías visuales y las cerebelosas las que se trabajan con la posturografia; siendo las vías visuales una red que transmite los impulsos nerviosos desde la retina al cerebro, y las vías cerebelosas donde se integran las vías sensitivas y motoras, transmitiendo información y control desde la corteza a distintos lugares del cuerpo y viceversa.

Potenciales vestibulares miogenicos evocados

Los Potenciales Vestibulares Miogénicos Evocados (PVME), más conocidos por sus siglas en inglés VEMP (Vestibular Evoked Myogenic Potential), son una de las más recientes incorporaciones a las técnicas de diagnóstico vestibular con que contamos en nuestra clínica. Se basa en el estudio del reflejo vestibulocervical (RVC) o reflejo de la musculatura cervical anterior (esternocleidomastoideo) que se activa con estimulación acústica. El RVC presenta dos componentes, de los cuales, el primero, es el potencial vestibular miogénico evocado (PVME), potencial inhibitorio relacionado con la vía vestibular (sáculo y vías saculoespinales), por lo que su estudio nos proporciona información sobre el estado de ésta. El segundo componente es más tardío, no siempre aparece en sujetos normales, está relacionado con la vía cocleoespinal, y no tiene aplicación clínica. Para la aplicación del estímulo utilizamos auriculares de inserción con tips desechables, adaptados a la edad del paciente y al tamaño de su conducto auditivo. Son

cómodos y son los que más reducen los artefactos y el ruido ambiente. Se emplean estímulos acústicos breves (tipo click o short tone burst) por encima del umbral auditivo y de forma repetitiva, primero en un oído y después en otro. En algunos casos (pacientes con hipoacusia de transmisión) es necesario aplicar el estímulo acústico por vía ósea. Para el registro de los potenciales que se producen en respuesta a dicho estímulo empleamos electrodos autoadhesivos desechables, de tamaño adecuado a la edad del paciente, que se colocan en el tercio superior del músculo esternocleidomastoideo de ambos lados. El registro puede realizarse con el paciente sentado o tumbado, pero el músculo esternocleidomastoideo debe estar contraído, por lo que habitualmente se coloca la cabeza en flexión cervical anterior o girada hacia el lado contrario al explorado.Esta prueba es totalmente indolora y no conlleva ningún riesgo para el paciente. La respuesta al estímulo es un potencial de acción inhibitorio en el músculo esternocleidomastoideo del mismo lado del oído estimulado. Dicha respuesta es recogida, analizada informáticamente y representada en una gráfica de manera automática. Para su valoración, se comparan los resultados obtenidos con los valores de referencia, aunque éstos varían en función de la contracción muscular, de la edad y de la intensidad del estímulo.

2.1.5. Prevalencia de la disfunción vestibular bilateral

Según los datos encontrados en National Health Interview Survey, indica que la prevalencia de hipofunción bilateral vestibular en el 2008 fue de 28 de cada 100,000 adultos estadounidenses; en nuestra población general (Las Palmas de Gran Canaria) tenemos una prevalencia estimada del 5 % de personas con trastornos del canal vestibular. Del 2 al 4 % de las personas con trastornos del equilibrio y perdida auditiva profunda podrían ser candidatos a implantes vestibulares.

2.2. Implante cocleo-vestibular multi-canal

Hace solo 50 años, no existian tratamientos efectivos para la sordera y pérdidas severas en la audición. El desarrollo del implante coclear (IC) cambió por completo el tratamiento de la patólogía [**?**].

En 1961, William House, de Los Ángeles, y John Doyle, desarrollaron un electrodo monocanal que colocaron en la ventana redonda en dos pacientes. Estos pacientes refirieron sensacion auditiva, cambios de volumen cuando el nivel de estimulación variaba y, el cambio del tono con la variación en la velocidad de la estimulación [**?**].

En 1967, Graeme Clark, un profesor de otorrinolaringología de Melbourne, estudió la fisiopatología de la sordera profunda en animales y la tolerabilidad de los materiales implantados. Esto permitió el desarrollo del primer sistema de implante coclear multicanal en 1984, dando

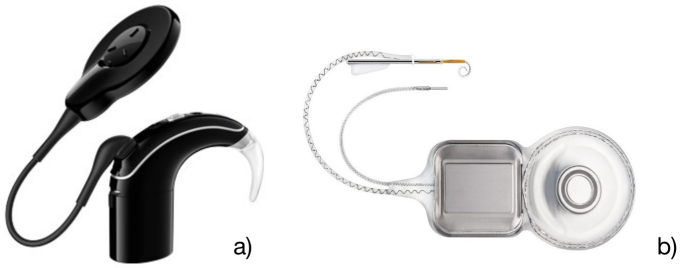

Figura 2.1: Sistema de implante coclear. a) Parte externa del sistema compuesto por la batería, los micrófonos, el procesador y la antena; b) parte interna compuesta por la antena / decodificador y el conjunto de electrodos. Images adapted from Cochlear.

lugar a la compañia Cochlear [**?**].

Al mismo tiempo, en Europa, Kurt Burian, desarrollo en 1975 un dispositivo multicanal. Su trabajo fue continuado por su alumna, Ingeborg Hochmair y su marido Erwin Hochmair, en Innsbruck. Su trabajo culminó en 1982 con el lanzamiento de los implantes MedEl [**?**].

Estos trabajos previos demostraron la eficacia del sistema de implante coclear para tratar la sordera profunda, y también, que las prótesis multicanal son mejores que los dispositivos monocanales [**?**].

Los IC modernos están compuestos por dos partes: un procesador de sonido externo portátil y un receptor/estimulador implantado con un conjunto de electrodos intracocleares y extracocleares. Figura 2.1. El procesador de sonido consiste en un micrófono que recoge el sonido; un procesador electrónico digital, que codifica el sonido en impulsos eléctricos y un transmisor de radiofrecuencia, que envía los parámetros de estimulación al receptor/estimulador a través de una bobina transmisora. Esta transmisión se realiza a través de la inductancia (variaciones de campo magnético), que induce pulsos de corriente alterna en la bobina receptora. El receptor/estimulador es un dispositivo electrónico implantado quirúrgicamente. Recibe y decodifica señales del procesador de sonido y genera señales eléctricas para activar selectivamente los electrodos intracocleares. Los pequeños pulsos de corriente eléctrica se envían a estos electrodos para estimular las fibras nerviosas auditivas en el sistema auditivo periférico, causando sensaciones auditivas.

En este proyecto se ha trabajado en un nuevo dispositivo implantable el cual se compone de una variante de implante coclear a la cual se le añade una guía de electrodos vestibular extra, tal como se muestra en la Figure 2.2. Este dispositivo funciona de manera identica a un implante coclear aunque tres de los electrodos cocleares pasan a ser de estimulación otolítica.

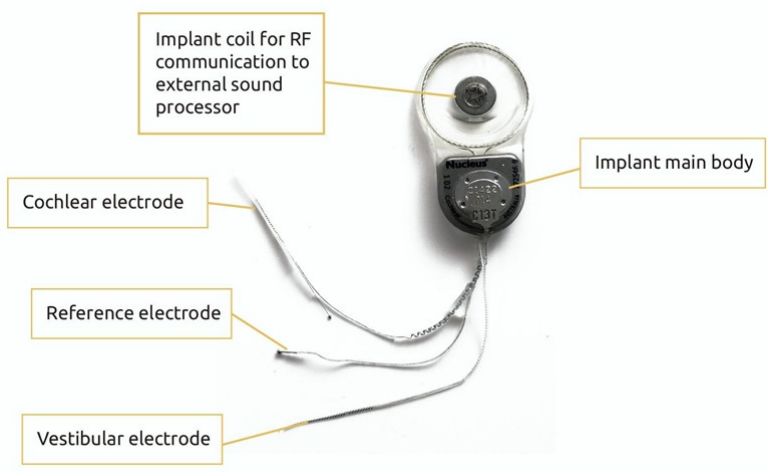

Figura 2.2: Sistema de implante cocleo-otolítico. Está compuesto de 3 guias: la primera es el electrodo de referencia; la segunda es la guía coclear standard; la tercera es la guía vestibular.

2.2.1. Procedimiento quirúrgico de un implante otolítico vestibular

Siguiendo los mismos principios que en la cirugía estándar de implante coclear, se realiza mastoidectomía cortical extendida al ático. Como puntos de referencia anatómicos se identifica seno sigmoideo, yunque y canal semicircular lateral (LSC). Como el implante coclear se realiza simultáneamente, la timpanotomía posterior se realiza en este momento con una exposición clara del proceso largo del yunque, estribo y ventana oval. Después de la inserción regular a través de la ventana redonda del componente del implante coclear, la apertura del vestíbulo se realiza mediante una estapedotomía de 0,5 mm con láser de CO2 medial e inferior a la crura anterior del estribo. Para alcanzar el área más cercana al nervio vestibular inferior aferente cerca de la mácula del sáculo. La mácula del sáculo se encuentra en la región antero inferior, presentando una distancia media desde la ventana oval de 1.4 mm (mínimo de 0.8 mm). El utrículo se encuentra en la región postero-superior a 1.4 mm desde la ventana oval (distancia mínima de 0.2 mm). Se realiza una profundidad máxima de inserción de 2.2 mm a 2.3 mm en cada caso, insertando los tres primeros contactos del componente vestibular.

Incisión

Incisión reroauricular, aproximadamente 1 cm. posterior al oído externo. Es necesario hacer una extensión superior y hacia atrás en un ángulo de 45 grados.

Hueso Cortical

Realizar un colgajo utilizando un solo corte a través de las capas musculares hasta el hueso cortical (piel, tejido subcutáneo, músculo y periostio), y realizar un bolsillo para su colocación. Realización del lecho para el implante VI / CI. En este paso es importante fresar un lugar en el hueso cortical para ubicar la intersección del dispositivo del electrodo (triángulo), o ubíquelo dentro del área de la mastoidectomía.

Abordaje conservador a través del receso facial

Abordaje estándar de timpanotomía posterior transmastoidea a través de un receso facial con exposición de la ventana redonda extendida anteroinferior y un abordaje de la ventana oval extendida superior. Necesitamos visualizar la supraestructura completa del estribo, la segunda porción del nervio facial y el canal semicircular lateral. Se debe minimizar el trauma de inserción completando la apertura de la paltina del estribo abriéndola (perforación precisa o usando láser de CO2). Justo detrás de la crura anterior del estribo (Estapedotomía : 0,5-0,6mm). Si es necesario, retirar la supraestructura del estribo.

Estapedotomía de la ventana oval

El área más accesible y segura, para un electrodo penetrante, es el área sacular, localizada en la parte más anterior y cercana a la cóclea, donde el ganglio Scarpa del nervio vestibular inferior es más accesible.

- El área del utrículo es más posterior y está relacionada con la ampolla del canal posterior e inferior al SSC
- La relación entre ventana oval y redonda es aceptable para la inserción a través de una estapedotomía cercana a la crura anterior.

Inserción de electrodos

El haz de electrodos cocleares se inserta primero de acuerdo con la técnica de inserción regular (sistema AOS), y la apertura de la ventana redonda se cerrará suavemente de la manera habitual utilizando tejido autólogo. (El procedimiento quirúrgico en todos los casos debe realizarse utilizando una inserción de ventana redonda (RW) para evitar variaciones debido al procedimiento quirúrgico).

Posteriormente, los electrodos vestibulares deben insertarse, insertando los 3 primeros contactos (los únicos activos) justo inferiormente a la apertura anterior de la platina del estribo, y colocando el cuarto contacto en el mismo nivel que la estructura de la platina 2.3. La fijación de la matriz vestibular debe hacerse:

- en Fossa incudis (anteriormente) usando un surco de 0.8-1 mm
- en el ángulo entre la pared del canal posterior y el tegmen (usando una gota de pegamento de fibrina).

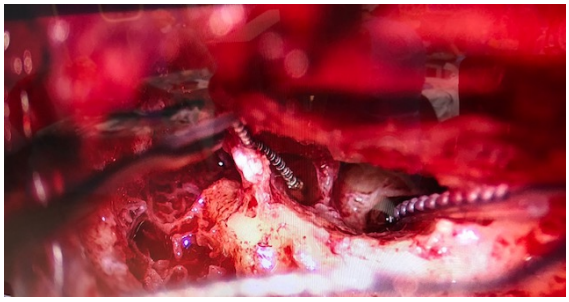

Figura 2.3: Izq. Electrodo vestibular. Der. electrodo coclear. [?]

Test Intraoperatorios y confirmación de la situación

La selectividad está determinada por la colocación del electrodo y la forma de estimulación. Los electrodos más selectivos son los electrodos bipolares [Curthoys, 1987; Uchino y Kushiro, 2011], aunque muchos estudios han utilizado electrodos monopolares.

- Test intraoperatorios:
  - Implante Vestibular y Coclear
    - CT or ConeBeam CT para confirmar la situación del electrodo
    - Análisis de impedancias de los electrodos
  - Implante Coclear
    - Neural Response Telemetry
  - Implante Vestibular
    - Vestibular Response Telemetry

2.2.2. Modos de estimulación

Los IC pueden definir las conexiones internas para proporcionar diferentes modos de estimulación. Esta opción de aumentar la focalización del estímulo para obtener una mejor discriminación de electrodos, lo que ha producido diferentes modos de estimulación.

La estimulación monopolar (MP) es la más utilizada porque es relativamente simple y tiene un rendimiento aceptable en el consumo de energía. En el modo monopolar, la corriente fluye

desde un electrodo intracoclear a un electrodo de referencia que es un electrodo extracoclear. El resto de los electrodos no están activos y actúan como un potencial flotante (electrodos aislados). La mejor característica de este modo de estimulación es que alcanza el mismo nivel de activación neuronal con menor intensidad que con otros modos de estimulación [**?**, **?**]. Por otro lado, el costo de esta reducción de potencia conduce a una amplia dispersión de corriente que produce una peor discriminación de electrodos [**?**], Figura 2.4.

El modo de estimulación bipolar (BP) está diseñado para focalizar la estimulación en un área estrecha del tejido neural. En este caso el electrodo de referencia no es extracoclear, sino que es un electrodo intracoclear. La elección de ese electrodo de referencia depende de cuán lejos queramos tener el electrodo de referencia, por tanto BP + 1 significa que el electrodo de referencia es el electrodo más cercano al activo y BP + n significa que el electrodo de referencia está n electrodos del electrodo intracoclear activo. En la evaluación de la estimulación bipolar se ha observado un alto consumo y poco beneficio en la focalización del estímulo eléctrico, Figura 2.4. El modo de estimulación multipolar es una generalización de la estimulación bipolar donde tenemos un electrodo intracoclear activo y m electrodos intracocleares como referencia.

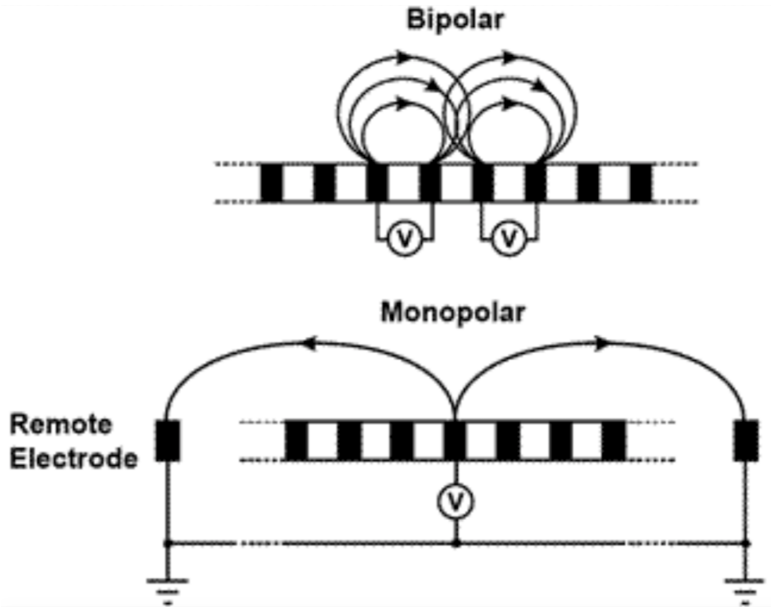

Figura 2.4: Tipos de estimulación. Arriba, estimulación bipolar. Abajo estimulación monopolar. [**?**]

Capítulo 3

Objetivos de la tesis

Como objetivos específicos se han considerado:

- Demostrar la utilidad y seguridad de un sistema de estimulación vestibular para uso humano mediante verificación de acuerdo con los últimos requisitos esenciales de las directivas europeas de un dispositivo médico implantable activo utilizado como un dispositivo en investigación.
- Determinar su eficacia clínica en la restauración de la función vestibular midiendo la mejora en pruebas objetivas y objetivar la mejora de la Calidad de Vida de los pacientes, estudiando sus beneficios a largo plazo.

Para ello, y expresados en las aportaciones que son el eje de esta tesis se divide la tesis en tres partes:

3.0.1. Investigación básica

El objetivo en esta fase es analizar la función del órgano otolítico, su función, evolución e importancia en la función vestibular. El segundo objetivo es estudiar la posibilidad de estimular los otolitos, o sus terminaciones nerviosas, eléctricamente y conseguir una estimulación neural eficaz. Esta parte se aborda con las publicaciones :

- Angel Ramos de Miguel, Juan Carlos Falcon Gonzalez, Angel Ramos Macias. Vestibular Response to Electrical Stimulation of the Otolith Organs. Implications in the Development of A Vestibular Implant for the Improvement of the Sensation of Gravitoinertial Accelerations. J Int Adv Otol 2017; 13(2): 154-61 • DOI: 10.5152/iao.2017.4216
- Angel Ramos de Miguel , Andrezj Zarowski , Morgana Sluydts, Angel Ramos Macias, Floris L Wuyts The superiority of the otolith organ. Audiol Neurotol 2020;25:35—41doi: 10.1159/000504595

3.0.2. Investigación clínica aplicada

El objetivo en esta fase es evaluar el rendimiento y beneficio de un implante vestibular, diseñado por nuestro grupo en la ULPGC, para estimulación del órgano otolítico. Esta parte se aborda con las publicaciones :

- Ángel Ramos, Ángel Ramos-Miguel, Isaura Rodríguez Montesdeoca, Silvia Borkoski Barreiro, Juan Carlos Falcón González. Chronic electrical stimulation of the otolith organ. Preliminary results in humans with bilateral vestibulopathy and sensorineural hearing loss. Audiol Neurootol. 2020;25(1-2):79-90. doi: 10.1159/000503600.

- Raymond van de Berg , Angel Ramos , Vincent van Rompaey , Alexandre Bisdorff , Angelica Perez-Fornos , Jay T Rubinstein , James O Phillips , Michael Strupp , Charles C Della Santina , Nils Guinand. The vestibular implant: Opinion statement on implantation criteria for research. J Vestib Res 2020;30(3):213-223. doi: 10.3233/VES-200701.

3.0.3. Innovación tecnológica.

De acuerdo con la normativa del Reglamento de estudios de doctorado de la ULPGC en la que, se valorarán los artículos publicados en revistas de reconocida valía, aceptándose como tales las que ocupen posiciones relevantes en el listado correspondiente a su categoría científica en el «Journal Citation Reports (JCR), Science Edition», también se consideran como aportaciones de relevancia, las patentes, si la concesión se ha llevado a cabo con examen previo . Se tendrá en cuenta la extensión de la protección de la patente (nacional, europea, internacional), valorándose más la de protección más extensa. En este punto se aporta también la patente de carácter INTERNACIONAL :

- “Vestibular stimulation prothesis”(Pub . No .: US 2021/0023366 A1) (patente de titularidad de la ULPGC , desarrollada por el doctorando y transferida a la industria)

Capítulo 4

Publicaciones

4.1. Primera publicación

4.1.1. Información de la publicación

Título: The Superiority of the Otolith System.

Autores: Angel Ramos de Miguel, Andrzej Zarowski, Morgana Sluydts, Angel Ramos Macias and Floris L. Wuyts

Revista: Audiology & Neurotology

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Review

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The Superiority of the Otolith System

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Keywords
Otolith function · Vestibular implant · Balance · Utricle · Saccule · Vestibulo-ocular reflex · Ocular counter roll

Abstract
Background: The peripheral vestibular end organ is considered to consist of semi-circular canals (SCC) for detection of angular accelerations and the otoliths for detection of linear accelerations. However, otoliths being phylogenetically the oldest part of the vestibular sensory organs are involved in detection of all motions. ***Summary:*** This study elaborates on this property of the otolith organ, as this concept can be of importance for the currently designed vestibular implant devices. ***Key Message:*** The analysis of the evolution of the inner ear and examination of clinical examples shows the robustness of the otolith system and inhibition capacity of the SCC. The otolith system must be considered superior to the SCC system as illustrated by evolution, clinical evidence, and physical principles.

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Introduction

The peripheral vestibular system consists of the semicircular canals (SCC) and the otoliths. In general, it is conceived that SCC and otoliths are complementary, since the SCC detect angular accelerations [Fernandez and Goldberg, 1971], whereas the otoliths detect linear accelerations [Fernandez and Goldberg, 1976] including gravity. In this study, we will build up a rationale for extending this standard view. In essence, the otoliths detect all accelerations, i.e., angular and linear accelerations, and thus can be considered as the core motion detectors.

Evolution

Throughout evolution of life on Earth, gravity and more specifically 1 g, gravitational acceleration on Earth of about 9.8 m/s^2, has been the sole constant factor, in contrast to environmental conditions such as temperature, humidity, pressure, oxygen level, etc.

Detection of gravity appears to be essential for complex life. Even plants have evolved multiple mechanisms

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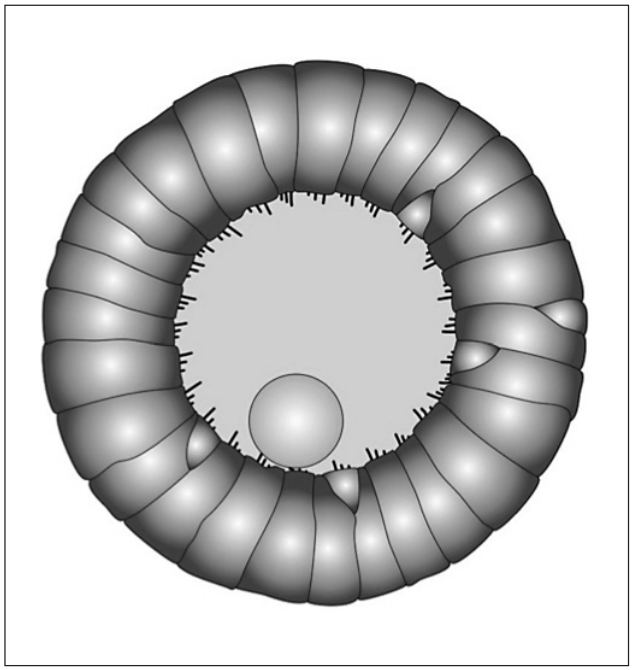

Fig. 1. Statocyst consists of a sac-like structure containing a statolith, a mineralised mass.

to sense gravity. Gravitropism directs plants growth relative to gravity. It determines the orientation and the final architecture of the plant.

Flowering plants, for example, sense gravity via specialized cells termed statocytes [Fukaki et al., 1998; Kiss, 2000]. Within these statocytes, dense starch-filled organelles (statoliths) settle relative to the gravity vector, providing directional information to the plant [MacCleery et al., 1999; Saito, 2005]. In case of a reorientation of the plant, the settling of the statoliths starts a biochemical cascade to promote differential growth in the elongation zone of the plant root or shoot.

Moving to the animal kingdom, it seems that the simplest animals, like jellyfish, also have statoliths to perceive gravity as well as water current. Jellyfish appeared in the Ediacaran Period 635 million years ago. Approximately 100 million years later in the Cambrian Period, deuterostome (like sea cucumber) appeared and they have a statolith located in the statocyst as balance system (Fig. 1).

With the arrival of the chordate animals, of which vertebrates is a subgroup, jawless fish with a single SCC and a macula appeared around 419 million years ago. This is the seed for the development of the inner ear as it is known today (Fig. 2). Still there are living animals, like the hagfish, with only one SCC and a common macule [Higuchi et al., 2019].

Lungfish, or dipnoans, appeared 400 million years ago, with 3 SCC and 3 otoliths (utricle, saccule, and lagena). However, there was no cochlea.

From vertebrates, tetrapod appears and then amniote 320 million years ago. At this point, the synapsida (future mammals) and sauropsida (reptiles like dinosaur and birds) appeared. Figure 3 represents the inner ear of a *Tyrannosaurus rex*, dating 68 million years ago [Witmer et al., 2009]. Mammals appeared around 200 million years ago with the currently known cochleo-vestibular system.

The third otolith system, i.e., the lagena, is still present in many animals (all descendants of the sauropsida). Crocodiles do not have a real cochlea but their saccule and lagena serve for both hearing and balance, and their utricle only serves for balance [Walsh et al., 2009].

The lagena of some birds and fish has a high concentration of metals that allows to use the lagena as a magnetometer (compass) to feel the Earth's geomagnetic field [Harada et al., 2001].

Summarizing the evolution of the inner ear, the otolith organ emerged in jellyfish 635 million years ago, the SCC 400 million years ago, whereas the coiled cochlea appeared "only" 200 million years ago (Fig. 4). So actually, the vestibular system is not part of the inner ear, but it is the other way around.

The Vestibular System

The aim of the vestibular system as it has evolved up to date is to provide information of balance, self-motion, and position in space. Hereto, the vestibular information about motion and position is integrated with vision and proprioception.

Semi-Circular Canals

The geometrical configuration of the SCC is basically a torus with an embedded deflector (cupula). The sensorial epithelium in the SCC are the hair cells at the base of the cupula, which is a membrane that deflects driven by the inertial mass of the endolymph upon angular acceleration, i.e., rotation. The dynamics of the system can be deduced from hydrodynamic principles [Van Egmond et al., 1949; Jones and Spells, 1963; Mayne, 1965; Steer Jr, 1967]. Essentially, when the head starts to rotate, the inertia of the endolymph causes a

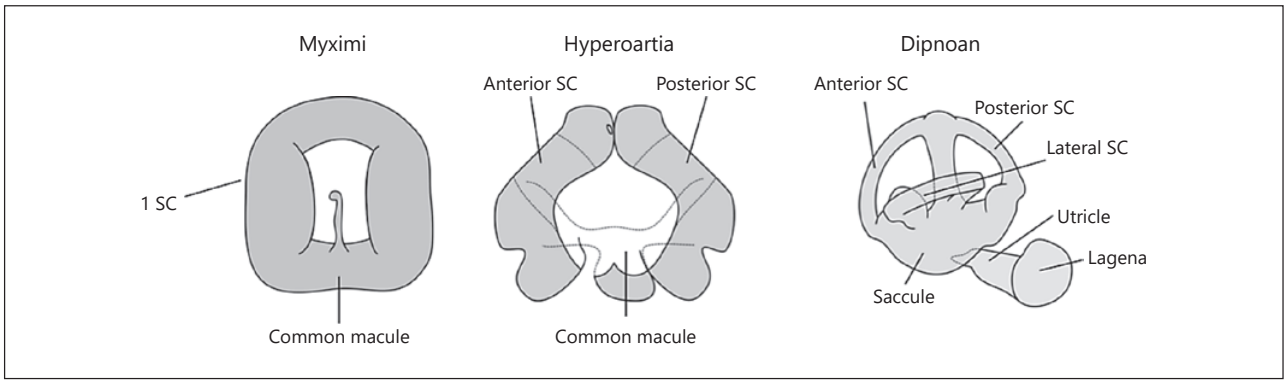

Fig. 2. Evolution of SCC. 1 SCC appears in Myximi, then 2 SCC with Hyperoartia, and finally 3 SCC with Dipnoan. Image adapted from Higuchi et al. [2019].

Fig. 3. Inner ear of a *Tyrannosaurus rex*. Similarities can be observed with crocodile and pigeon that also evolve from Sauropsida [Witmer et al., 2009; Walsh et al., 2009].

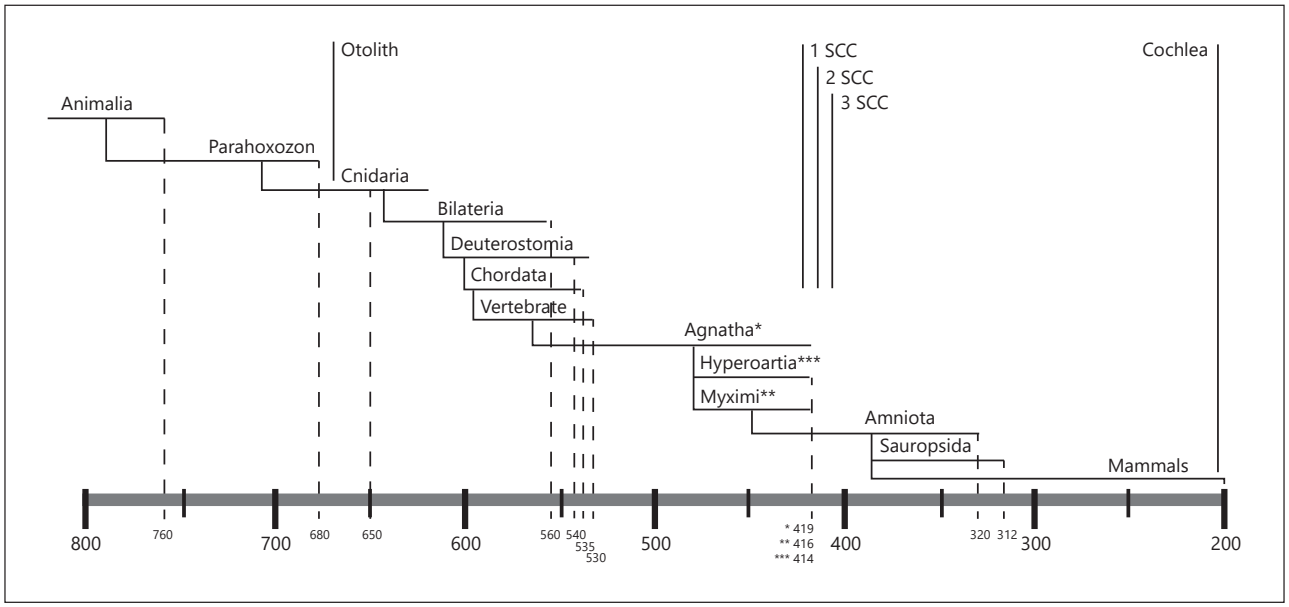

Fig. 4. Summary of the chronological timeline of the inner ear evolution.

deflection of the cupula. This deflection depends on the direction and amplitude of the angular acceleration, and eventually it is proportional to the velocity of the head movement. The derived formulas on the movement of the cupula and the concomitant deflection of the hair cell cilia start from the principle that the centre of rotation is located in the centre of the SCC. However, the canals are located eccentrically. In case of Caucasian adults, the distance between both lateral SCC is 8.87 ± 0.06 cm [Nowé et al., 2003]. Hence, upon rotation of the head around the craniocaudal axis, the SCC perceive additional tangential acceleration of the endolymph and the cupula. This tangential acceleration equals to the angular acceleration multiplied by the distance to the centre of rotation. But this is merely a scaling factor. Sustained rotation will be sensed only for approximately 20 s after cessation of the angular acceleration by means of the velocity storage mechanism (VSM). The VSM is activated by both visual and vestibular rotation cues and is modified by gravity. The network of neurons in the superior vestibular nucleus and medial vestibular nucleus as well as their commissural interconnections are critical for producing velocity storage [Yakushin et al., 2017]. One of the proposed function is to prolong the vestibulo-ocular reflex (VOR) longer than the mechanically governed 10 s, which is the time constant of this damped oscillator. During the rotation (i.e., the acceleration phase and the sustained constant rotation), the otoliths are sensing this movement. This is a consequence of the highly specialized design of the otolith system that is driven by million years of evolution to detect gravity.

Otoliths

The saccule and utricle are complex curved maculae that can detect movement in virtually all directions. Highly simplified, one can represent the otolith organ as 3 layers on top of each other (Fig. 5). The base layer contains the sensorial epithelium with the hair cells. The cilia of the hair cells protrude in the second layer, being a membrane on top of which lie the otoconial calcium carbonate crystals forming the third layer. These so called statoliths, have a density of 2.71 g/cm^3 [Carlström, 1953] that is much heavier than the surrounding endolymph (density ~1 g/cm^3) and membrane. Any linear acceleration will exert a shear force on the otoconial layer and cause a displacement relative to the base layer and consequently causing a change in the membrane potential of the hair cells, which then results in a complex pattern of simultaneous excitation and inhibition.

Although the triggering stimulus for the otoliths is a shear force on the otoconial layer, this force can emerge both by angular as well as linear accelerations. The following rationale will clarify this concept.

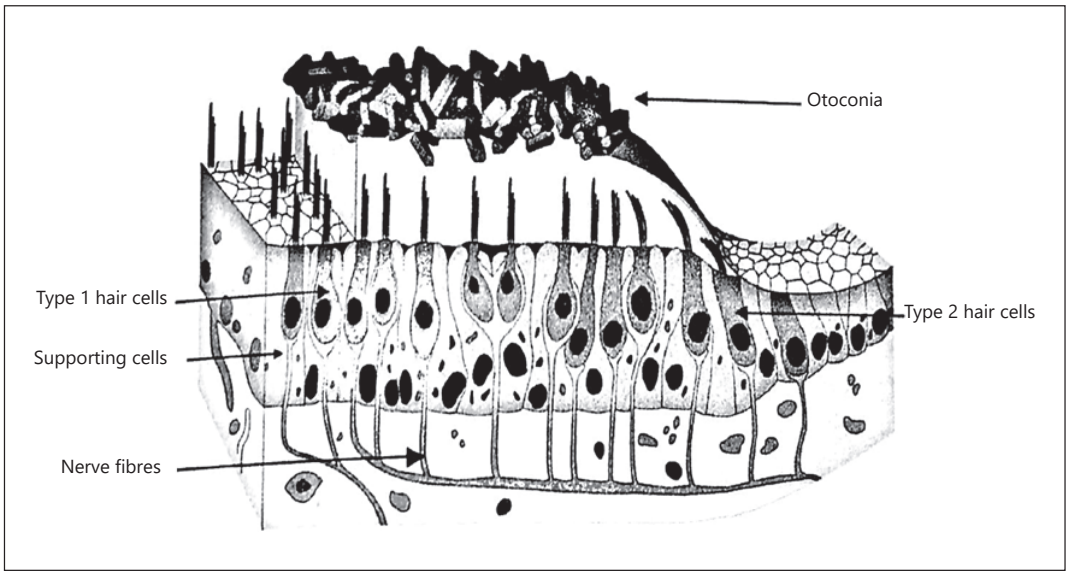

Fig. 5. Macula of the utricle with the calcite crystal or otoconia.

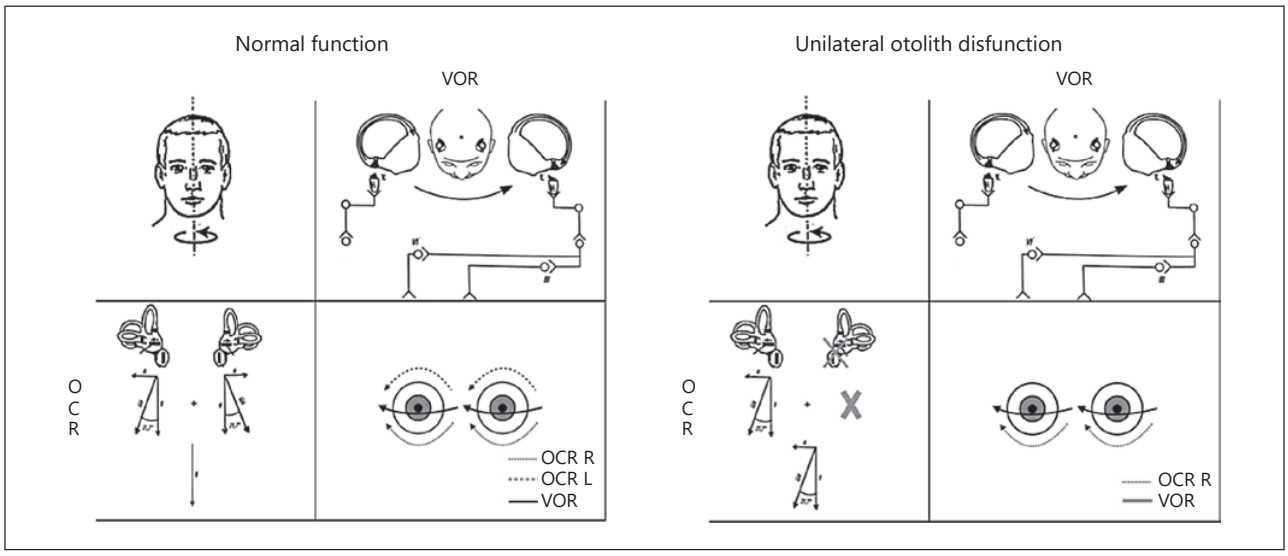

Fig. 6. Complete HIT reflexes during left rotation. Left: healthy labyrinths produce only VOR due to the cancelation of OCR on both sides. Right: unilateral otolith disfunction produce VOR and also OCR to the damaged side.

Indeed, as proven by the evolutionary pathway, both in plants as well as in animals, gravity detection is the core function of the otolith system. Gravity detection ensures optimal growth, upright posture, balanced locomotion, and detects deviations from the vertical, including falls, for example.

Clinical Example of Multidimensionality

During a short head rotation to the left, both SCC left and right are stimulated giving rise to the VOR (Fig. 6, left). The output of the left and right SCC is antagonistic, however, with the left SCC giving rise to an increase in

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spike rate of the hair cells, and the right SCC generating a decrease in spike rate. The left and right vestibular nuclei in the brainstem decode these antagonistic signals from the left and right SCC to drive the respective left oculomotor nucleus and right abducens nucleus that generate compensatory eye movements with eyes going to the right mediated by the respective medial and lateral eye muscles. At the same time, both utricles are stimulated with identical shear forces pulling the otoconial layers outward, because of the centrifugal force that is pointing out from the centre of rotation. The left utricle will then generate a clockwise (from the point of view of the subject) ocular counter roll (OCR) and the right utricle will give rise to a counter clockwise OCR. However, both cancel each other out, generating no net eye movement. But, in case of one deficient labyrinth, this would cause a slight net OCR (Fig. 6, right). For a typical head rotation of 200 degrees per second, as produced during the Head Impulse Test (HIT), this would generate an OCR of 0.4 degrees, given an OCR gain of 15%, which is negligible and hardly detectible with the current methods. Based on this, HIT is the combination of VOR and OCR. In the case of healthy peripheral vestibular system, response during a HIT test is purely VOR. But in the case of one deficient otolith, a small OCR will appear.

This does not imply that the utricles do not contribute to the whole of the reflex. They even send their signal to the respective cortical areas like the operculum parietale 2 (OP2) in the brain, where the SCC signals converge with the otolith signals to appropriately interpret the whole movement stimulus [zu Eulenburg et al., 2012]. For example, in case of tilt-translation ambiguity, otoliths respond identically to translational (inertial) accelerations and changes in head orientation relative to gravity. This sensory ambiguity can be resolved using SCC signals. This procedure is done in the vestibular nuclei, rostral fastigial nuclei, cerebellar nodulus/uvula, and thalamus [Angelaki and Yakusheva, 2009].

Additionally, the otolith system is multidimensional, and there is no left right agonist/antagonist mechanism as in the canal system. This is a very important property because even with one otolith system, normal OCR reflexes are generated upon lateroflexion, showing the robustness of the otolith system [Wuyts et al., 2001]. The otoliths also preserve autonomic function as recently demonstrated in cosmonauts [Hallgren et al., 2016]. The otolith system mediates the VSM through the so-called otolith dump, which is the abolishment of the postrotatory nystagmus by inclination of the head. This is commonly adopted by figure skaters after high-speed pirouettes [Hain et al., 1988]. Otolith input in general inhibits the SCC signals [Hain et al., 1988]. The otoconial membrane neither has a damped spring configuration like the SCC, and hence the otoliths permanently sense the gravity vector. Therefore, based on evolution, robustness and inhibition capacity, the otolith is superior to the canal system.

Clinical observations show that, except for Tumarkin syndrome, almost no other vestibular disorders can be attributed solely to unilateral otolith disfunction. Even during a vestibular neuritis, which affects the superior vestibular nerve (and thus the signals coming from the horizontal and anterior SCC and the utricle), the complaint of the patient is spinning vertigo with a dominant horizontal nystagmus with a slight torsional component, however, without sensations of the Tumarkin type. Neither can other complaints of dizziness or vertigo be attributed to an otolith disorder, despite the absence of vestibular evoked myogenic potentials in some cases. Thus, it can be concluded that isolated otolith deficits are difficult to identify, perhaps because there are few to none. Even if one otolith system fails, the other otoliths are sufficient to ensure gravity detection. So only in case of bilateral total vestibulopathy, there will be a lack of gravity detection. Hence, the necessity to restore, in the first place, the otolith function and this by means of a vestibular implant, for example. Moreover, based on the abovementioned evidence, unilateral restoration should be sufficient.

Conclusion

The otolith system must be considered superior to the SCC system as illustrated by evolution, clinical evidence, and physical principles. Hence, when replacing the vestibular system by means of a vestibular implant in a patient with bilateral vestibular areflexia, we hypothesize to target at first the otolith system.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

All authors declare that they have no conflicts of interest.

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Author Contributions

Angel Ramos de Miguel: hypothesis proposal, design of the work, drafting of the manuscript. Andrzej Zarowski: drafting and reviewing of the manuscript. Morgana Sluydts: clinical examples, as well as drafting and reviewing of the manuscript. Angel Ramos Macias: drafting and reviewing of the manuscript. Floris L. Wuyts: clinical support of the hypothesis, design of the work, drafting of the manuscript.

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4.2. Segunda publicación

4.2.1. Información de la publicación

Título: Vestibular Response to Electrical Stimulation of the Otolith Organs. Implications in the Development of a Vestibular Implant for the Improvement of the Sensation of Gravitoinertial Accelerations.

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Original Article

Vestibular Response to Electrical Stimulation of the Otolith Organs. Implications in the Development of a Vestibular Implant for the Improvement of the Sensation of Gravitoinertial Accelerations

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OBJECTIVE: Electrical stimulation of the utricular and saccular portions of the vestibular nerve improves stability in patients suffering from vestibular dysfunction. The main objective of this study was to evaluate a new technique, vestibular response telemetry (VRT), for measuring the electrically evoked vestibular compound action potential (saccular and utricular) after stimulating the otolith organ (saccular and utricular) in adults. This study used evidence that the otolith organ can be electrically stimulated in order to develop a new vestibular implant design to improve the sensation of gravitoinertial acceleration.

MATERIALS and METHODS: Four adult patients were evaluated by using a variety of measurement procedures with novel VRT software. VRT values were obtained by stimulating with three full-band Nucleus CI24RE (ST) electrodes. Specific stimuli were used. Simultaneously, electrical ocular vestibular evoked myogenic potentials (eoVEMPs) were recorded in the contralateral side.

RESULTS: Electrically evoked compound action potentials were obtained in 10 of the 12 electrodes tested, and eoVEMPs were recorded when VRT was present. In addition to the validation of this technique, a set of default clinical test parameters was established. The VRT response morphology consisted of a biphasic waveform with an initial negative peak (N1) followed by a positive peak (P1), and latencies were typically 400 μs for N1 and 800 μs for P1. The consequences for the development of a vestibular implant for the improvement of gravitoinertial acceleration sensation are also presented.

CONCLUSION: The VRT measurement technique has been shown to be a useful tool to record neural response on the otolith organ, and thus it is a convenient tool to evaluate whether the implanted electrodes provide a neural response or not. This can be used for the early development of vestibular implants to improve gravitoinertial acceleration sensation.

KEYWORDS: Vestibular response telemetry, electrical vestibular myogenic response, vestibular implant

INTRODUCTION

The loss of vestibular function cannot be restored in all cases, but a vestibular prosthesis can improve balance in many of these patients. Vestibular implant (VI) research has mostly focused on the detection of angular velocity of the cephalic movements through gyroscopes and stimulation of the three-ampulla crests of the semicircular canals in order to improve the vestibular ocular reflex [1, 2]. However, there are movements corresponding to vertical and horizontal acceleration that still need to be implemented in a VI and that are related to the sensation of gravitoinertial accelerations. These movements are detected by the macules of the saccule and the utricle.

Cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs, respectively) are reflexes mediated by the saccule and utricle, respectively. These measurements can be elicited by air-conducted sound, bone-conducted vibration, galvanic stimulation, and vestibular cross-stimulation from the intracochlear electrodes. Though the functional significance of these reflexes is not well understood, VEMPs can be used to assess otolith integrity as well as vestibulo-collic and vestibulo-ocular pathways [3]. Vestibular cross-stimulation can be imperceptible and, as such, it likely occurs in a much higher proportion of cochlear implanted patients than previously thought. Although the exact site of vestibular activation with cochlear implants use remains unknown,

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there is evidence to suggest that electric current can bypass the vestibular end organs to more directly stimulate vestibular afferents [4].

In younger populations, the function of the otolith organ is well preserved, but this function decreases with age [5]. It has been observed that there is a reduction of hair cells in the maculae and, additionally, the size and number of neurons and fibers are reduced [6]. It has also been found that there is an age-related decrease in VEMP amplitude and an age-related increase in VEMP latency [7]. Therefore, it is expected that a VI acting on the otolith organs would be helpful, mainly by reducing the risk of secondary-to-imbalance falls in the elderly [8].

There are only a few articles in the literature related to direct stimulation of the otolith organ, and most of them are related to galvanic stimulations and not to electrical stimulations [9]. Other researchers have focused on the concept that if electric current can spread to the facial nerve and stimulate it, the possibility of a vestibular cross-stimulation might be also considered [10-12]. According to this, Gnanasegaram et al. [13] found that electrical pulses from the cochlear implant help to correct asymmetric perceptual tilt in children, especially when the stimulus is provided ipsilateral to the tilt. This effect suggests the existence of a therapeutic benefit of the implant in addition to its main auditory target and related to a possible vestibular cross-stimulation [13]. In this line, Parker et al. described VEMPs responses after cochlear implant stimulation [4].

Most of these studies focused on the oculomotor responses as objective measurement to assess the success of vestibular stimulation. Electrically evoked eye movements have been successfully reported in guinea pigs [14, 15], monkeys [16], and humans [17, 18]. These findings suggest that the electrical stimulation of the vestibule nerve can provide functional inputs.

Results of computational models and electrophysiological experiments have also shown that the distance of the electrode to the neural fibers has an impact on the threshold and the amount of cross talk due to current spread [19, 20]. An intraoperative tool to measure vestibular response telemetry (VRT) is necessary to assure the efficacy of electrode stimulation in order to verify the placement of VIs [21].

In 1992, a bidirectional telemetry feature was implemented in the design of the Nucleus CI24M cochlear implant system that can be used to record auditory electrically evoked compound action potentials (ECAPs) [22]. The action potentials that result from a stimulus are recorded from a neighboring electrode, amplified, and then encoded to be transmitted via the radio frequency link back to the speech processor. Based on this research, we created a custom VRT software in our psychoacoustics and balance laboratory in the hearing loss unit of our department. This software will be presented in advance [23].

The aim of this study was to evaluate the possibility of developing a system capable of recording the ECAPs of the vestibular nerve and of electrically producing an acute stimulation of the otolith organ by using a method in patients with absence of VEMPs and profound deafness before receiving a cochlear implant. This will provide us with information for future development of VIs in order to improve the gravitoinertial accelerations in patients suffering from vestibular dysfunction and not responding to conventional treatment.

MATERIALS and METHODS

Subjects

Four patients (3 women and 1 man; ranging from 26 to 54 years old; mean age, 43 years) were considered in this study. The ethics committee for human research of our institution approved the procedure, and the patients gave their informed consent.

Definite unilateral Meniere's disease according to the guidelines of the Barany Society was previously diagnosed in all cases. The duration of the disease ranged from 3 to 7 years [24].

Preoperative videonystagmography showed vestibular hypofunction in the affected ear and normal function on the unaffected side. Magnetic resonance imaging (MRI) presented normal results in all cases. All patients were previously treated with intratympanic gentamicin with no positive response to treatment. Audiologically, all patients had a sensory neural hearing loss of 90 dB HL or greater, with a speech discrimination score of 10% or less and hearing deprivation for 1–6 years. The preoperative vestibular testing results were the following: VEMPs had no response in the ear to be implanted, video head impulse test showed hyporeflexia on the affected side, and the caloric test showed an asymmetry greater than 50% in all cases. All of the preoperative tests results are presented in Table 1.

Stimulation Technique and Surgical Approach

We used a full-band straight electrode, CI24RE (ST), from Cochlear Ltd (Lane Cove, Australia). This electrode array has a diameter of 0.4 mm on the apical part. Each electrode, on the tip, has a cylindrical band of 0.3 mm width and 0.4 mm diameter. The inter-electrode spacing is 0.2 mm on each lead. Full-band electrodes were selected to assure that the electrodes were facing the neural tissue.

A high-resolution computed tomography (HRCT) scan of all patients was performed to measure the vestibule size. OsiriX software was used to collect all the images, in DICOM file format, of the vestibule. A MatLab script was developed to extract and reconstruct the volume of the vestibule (Figure 1). The vestibule depths varied from 2.79 to 2.53 mm: 2.79 mm, 2.71 mm, 2.53 mm, 2.61 mm.

Table 1. Summary of subjects and preoperative testing

			Audiological		Vestibular		
Subject	Sex	Age	PTA	Speech Discrimination	VEMPs	vHIT (gain)	Caloric Test (asymmetry %)
S1	F	56	101	8%	NR	0.45	60
S2	F	26	117	0%	NR	0.56	58
S3	M	50	98	10%	NR	0.54	68
S4	F	40	112	5%	NR	0.62	54

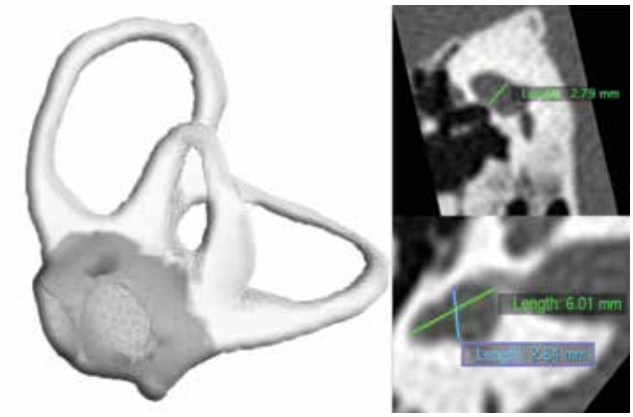

Figure 1. Example of HRCT vestibular reconstruction and analysis of its size.

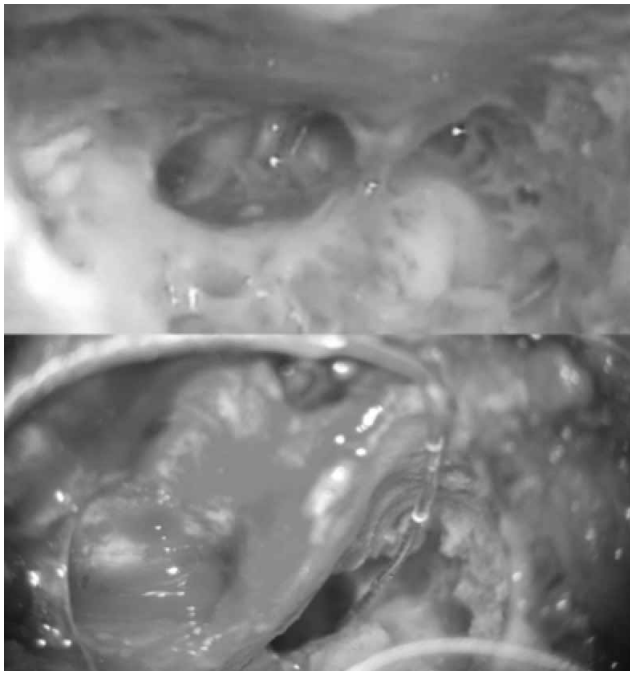

Figure 2. Electrode insertion.

The same surgeon performed all procedures (A.R.). Before a complete transmastoid labyrinthectomy was performed, a transmastoid approach through a posterior tympanotomy was performed. This was enlarged in order to visualize the perfect situation of the oval window superstructures. A 0.6 mm hole in the posterior area of the stapes footplate was made a with a CO_2 laser prior to insertion. A maximum of three electrodes that correspond with 2.5 mm, were inserted in the vestibule, and the VRT measurements were performed (Figure 2). Once the measurements were completed, a regular cochlear implantation was done after labyrinthectomy. During the surgical intervention, the facial nerve was monitored by a NIM 2 system.

Vestibular Response Telemetry Test

The Vestibular Response Telemetry software was designed by using the Nucleus Implant Communicator (NIC) library (Cochlear LTD) for Python (Python Software Foundation, v2.4) in order to obtain

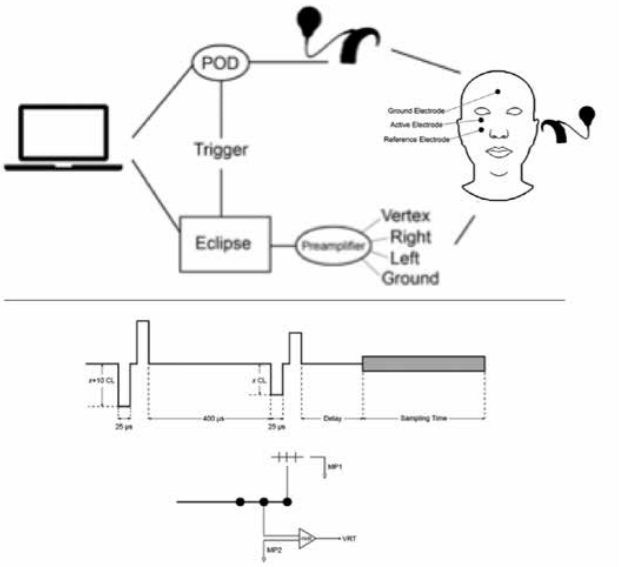

Figure 3. Vestibular response telemetry test (VRT) and eoVEMPs surgical diagram and electrode montage. VRT parameters with the artifact-reduction paradigm shows the masker advance, masker amplitude, masker pulse width, probe amplitude, probe pulse width, measurement delay, and sampling period. During VRT recordings, one electrode served as the stimulation electrode, while the neighboring electrode was set as the recording electrode.

ECAPs from the vestibular nerve. The software automatically evaluates all of the configurations available on the cochlear implant to find the best VRT response for each patient. On average, total acquisition takes 10 minutes. The software communicates with the speech processor to capture, process, and store the measurement data on a computer (Figure 3). The VRT software controls the parameters of the stimulus used to evoke and record the response to be measured.

The Vestibular Response Telemetry measurements were done after insertion of the three electrodes into the vestibule, and the two reference electrodes were correctly placed and covered by tissue. An extracochlear ball electrode on a flying lead was placed under the temporalis muscle (MP1), and a plate electrode was placed on the receiver-stimulator (MP2). Monopolar stimulation (MP) was used in all trials to activate the maculae. We used the three most apical electrodes to perform the VRT measurements. The active recording electrode was selected iteratively to evaluate all of the combinations. We then studied the effect of different test parameters, including stimulation rate, number of repetitions, measurement delay, masker level, and masker advance (Figure 3).

The specific test (stimulation and recording) parameters studied included 1) measurement delay (80 to 120 μs); 2) stimulation rate (90 or 70 Hz); 3) number of samples; and 4) number of averages (50, 100, or 150).

The setup consists of a personal computer, cochlear POD interface, Nucleus Freedom processor (Cochlear Corp., Sydney, Australia), and CI24RE (ST). Additionally, a VEMPs recording system (Eclipse Interacoustic, EP25) was included in order to confirm the stimulation of the vestibular pathway by recording eoVEMPs.

To minimize the stimulation artifacts, the developed VRT software implements the forward-masking paradigm described by Brown et al. [25] and involves a sequence of conditions: probe-only (A), masker-followed-by-probe (B), masker-only stimuli (C), and no stimulation (D). The probe-only condition yields the desired neural response plus an artifact from the probe. The masker-and-probe condition with an appropriate masker advance yields stimulus artifacts for both masker and probe, and the neural responses to the probe are absent or decreased because of the forward masking. The masker-only condition yields only the masker artifact. After the recordings of each of these four stimulation conditions were performed, extraction of the ECAP from the stimulus artifact was accomplished by using the subtraction method (A – (B – (C – D))) to cancel the large masker stimulus artifacts found in each condition, and this allows one to extract the relatively small neural response (Figure 4). The amplitude of the probe pulse was progressively increased by a step size of 10 clinical levels (CL) from a masker level up to the maximal safe current level.

Electrically Stimulated eoVEMPs

In order to record eoVEMPs (responses attributed to the utricular-ocular reflex pathway) simultaneously with the vestibular ECAP, they were obtained while the VRT measurement was performed intraoperatively. A trigger synchronized both systems. Responses were collected and analyzed using a two-channel surface electrode montage and Eclipse Interacoustic EP25 4.4 VEMP 4.3 recording platform.

In order to determine the accuracy of the calibration method, the active electromyogram (EMG) electrode was placed over the medial inferior oblique muscle edge contralateral to the stimulated ear, and the reference electrode was placed on the cheek 1 cm below. The montage ground electrode was placed on the mid-forehead. Impedance was kept below 5 kOhms (Figure 3).

Electromyogram signals were band pass filtered (1 to 3,000 Hz) and recorded in a 25 ms to 50 ms window relative to stimulus onset. No online artifact rejection was used. For all eoVEMP tests, two or more trials (100 sweeps each) were obtained. If such responses were not identified after two trials, testing was ended. The maximum intensity levels were set from 120 to 220 current level (CL), with a 20 CL step size, for both single 57 µs biphasic electric pulses (25 µs/phase with a 10 µs interphase gap). The eoVEMPs tests were first conducted by using electrode 22 and then were repeated by using the other inserted electrodes 21 and 20.

The facial nerve was monitored in all the subjects, and no cross stimulation of the facial nerve was observed in any of these cases.

Statistical Analysis

A descriptive statistical analysis of the data was carried out. The different neural responses of electrodes 22, 21, and 20 were observed in all subjects. A comparison between 70 Hz and 90 Hz stimulus rates remained constant. Measurements of the numerical variables of VRT and eoVEMPs were classified in absolute values with the different latency values N1 and P1 and the N1-P1 amplitudes of the different subjects as well as with the means of these measures. Student's t-test was used to determine the statistical significance (Level of significance $p < 0.05$).

RESULTS

Reliable responses with VRT across the patients under different measurement conditions were obtained. The vestibular ECAP response morphology was similar to that obtained in the auditory nerve– a biphasic waveform with an initial negative peak (N1) followed by a positive peak (P1). The impedance values of the three electrodes were within normal limits, indicating good tissue contact throughout.

Vestibular responses could be obtained from four patients (100%), and on 10 of the 12 electrodes tested (83.3%) (Table 2). The insertion into the vestibule of all the electrodes was evaluated by visual observation. No statistical variability was found in ECAP responses (Table 3). A short vestibule was found in subject 4 and only two electrodes were inserted. In the other cases, all the electrodes were placed inside the vestibule. In subject 2, no response was obtained in electrode 20.

The electrically evoked compound action potentials obtained were reliable measurements to qualify the neural survival and the localized spatial resolution. By varying the stimulus amplitude, the amplitude growth function (AGF) in all cases followed the same behavior as in the auditory nerve. This effect is considered as an indication of neural viability. In each case, the masker was kept at a constant +10 CL compared to the probe. The probe varied across 120–220CL (Figure 5).

Table 2. Summary of measurement results

	Neural Response		
Subject	**Electrode 22**	**Electrode 21**	**Electrode 20**
S1	Yes	Yes	Yes
S2	Yes	Yes	DNR
S3	Yes	Yes	Yes
S4	Yes	Yes	DNI

DNR – Did Not Response
DNI-- Did Not Inserted

Table 3. Record VRT measurements

		Latencias		Amplitud
Subject	**Electrode**	**N1**	**P1**	**P1-N1**
S1	22	334 µs	813 µs	70.3 µV
S1	21	420 µs	808 µs	56.6 µV
S1	20	358 µs	812 µs	81.2 µV
S2	22	340 µs	821 µs	73.5 µV
S2	21	355 µs	820 µs	67.0 µV
S2	20	-	-	-
S3	22	359 µs	821 µs	78.3 µV
S3	21	348 µs	819 µs	66.6 µV
S3	20	410 µs	822 µs	80.4 µV
S4	22	327 µs	822 µs	70.2 µV
S4	21	313 µs	819 µs	67.4 µV
S4	20	-	-	-
Average		356.4 µs	817.7 µs	71.15 µV

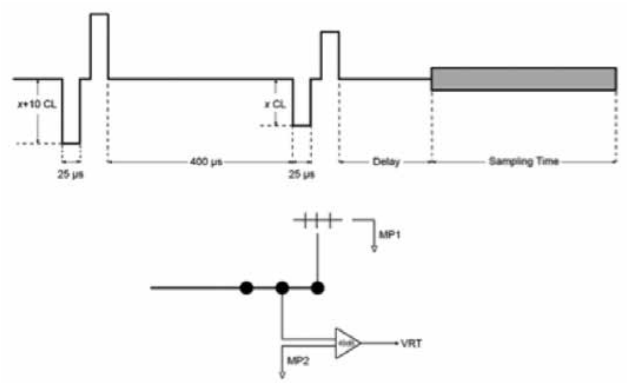

Figure 4. Subtraction method for reducing masker stimulus artifact. Stimulation signals from buffers A, B, C, and D are shown on the left. The subtraction paradigm was (A–(B–(C-D))).

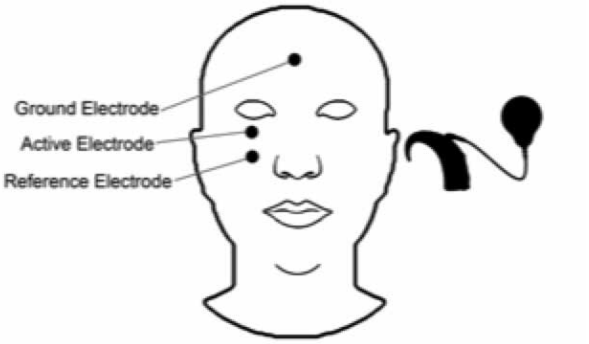

Figure 5. Examples of the ECAP waveforms that were recorded. A typical amplitude growth series indicating how the neural response changes with the stimulation level. The first negative peak (N1) of the vestibular response occurs between 370 µs and 420 µs after the stimulus onset, and this is followed by the first positive peak (P1) occurring at approximately 820 µs after the stimulus onset. The response amplitude is defined as the peak-to-peak amplitude from N1 to P1. Plotting the change in response amplitude as a function of the stimulation level yields the amplitude growth function (AGF).

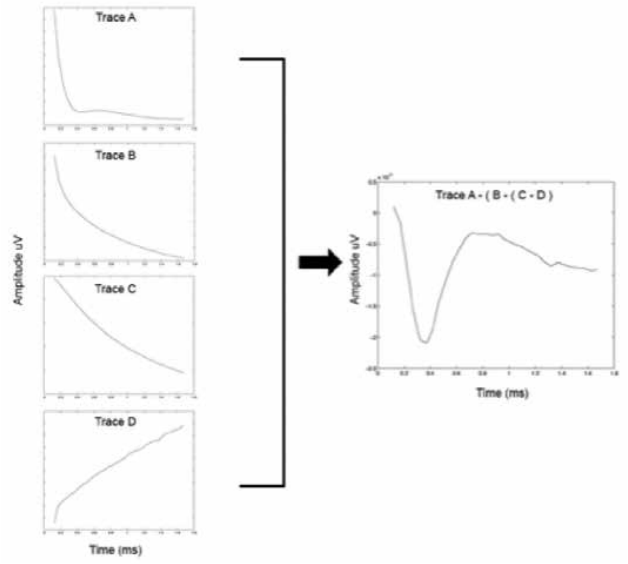

Figure 6. Amplifier saturation due to high amplification.

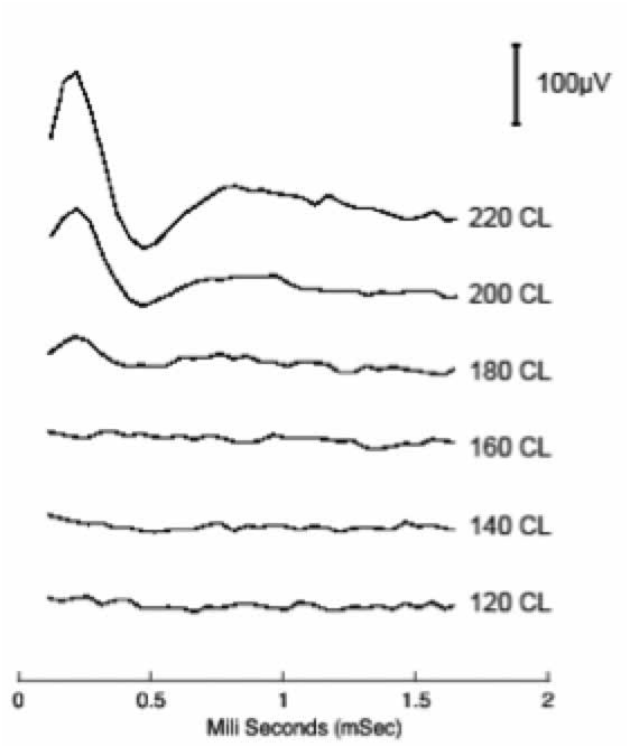

Figure 7. Comparison of stimulation rates, 70 Hz and 90 Hz, with all others parameters kept constant.

The measurement delay was evaluated in all subjects. The results showed that shorter delays were more likely to result in overloading of the measurement amplifier, producing a distorted waveform (60.0 dB gain and 80 µs delay) (Figure 6). The increase in the delay reduces the possibility of saturating the measurement amplifier, but excessive delays could result in missing features of the waveform.

The best gain values in all cases were 40 dB. The records from all subjects show saturation at 60 dB and, in most of them, at 50 dB. Therefore, 40 dB gains recorded clear neural responses also with a short delay. The optimal gain depends on the subject and the delay selected, but in our case the best combination was 40 dB measurement gain and 120 µs delay.

A comparison of stimulation rates (70 Hz and 90 Hz) was carried out in all subjects, and no difference in the resulting vestibular response was seen in any of the cases (Figure 7). The vestibular ECAP response duration in all the records was below 1 ms. So, considering that the sampling period of the cochlear implant device is fixed at 50 µs, the minimum number of samples that should be taken to be sure to obtain the full VRT response is 32 samples. In all of our cases, 32-sample recordings were made, thus taking 1.6 ms.

The best configuration was 32 samples at 40 dB gain and a delay of 120 µs, and 50, 100, and 150 repetitions were evaluated. The best result was for 150 repetitions, which gave a clear neural response.

During the VRT recordings, an eoVEMPs was also performed in order to determine the correlation between measurements. All of the

Table 4. Record eoVEMPs measurements

		Latencias		Amplitud
Subject	**Electrode**	**N1**	**P1**	**P1-N1**
S1	22	13 ms	18 ms	8.4 µV
S1	21	15 ms	17 ms	11.42 µV
S1	20	11 ms	20 ms	10.3 µV
S2	22	7 ms	13 ms	10.0 µV
S2	21	10 ms	16 ms	9.6 µV
S2	20	-	-	-
S3	22	12 ms	21 ms	10.5 µV
S3	21	14 ms	20 ms	9.9 µV
S3	20	11 ms	17 ms	8.6 µV
S4	22	14 ms	14 ms	10.9 µV
S4	21	9 ms	22 ms	7.9 µV
S4	20	-	-	-
Average		11.6 ms	17.8 ms	9.75 µV

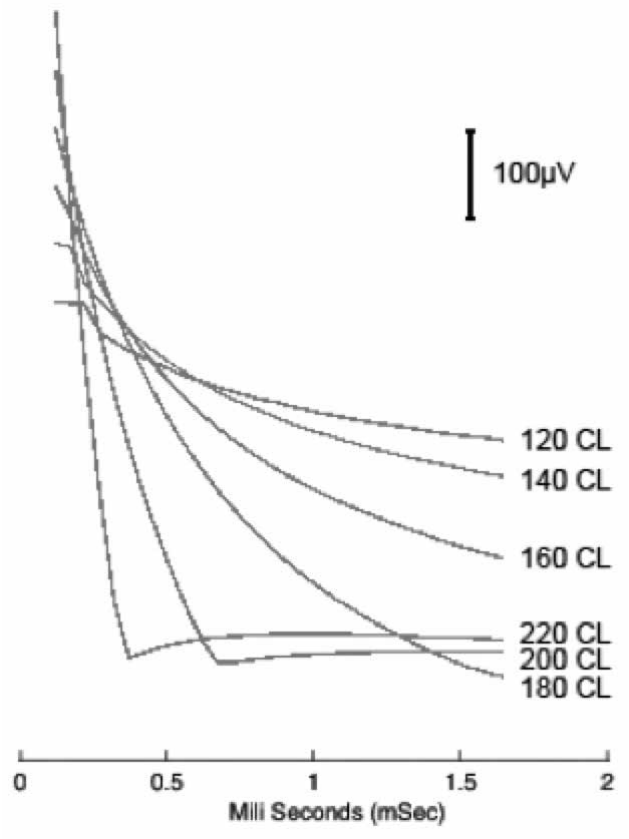

Figure 8. eoVEMPs responses in the contralateral eye electrically stimulated by an electrode in the macula region. Negative is up in this figure.

ears tested for eoVEMPs were nonresponsive to acoustic stimulation preoperatively. In all the ears, an electrically stimulated oVEMP was present when VRT was present (Figure 8). Electromyographic activity was monitored in real time. The recorded eoVEMP response was a

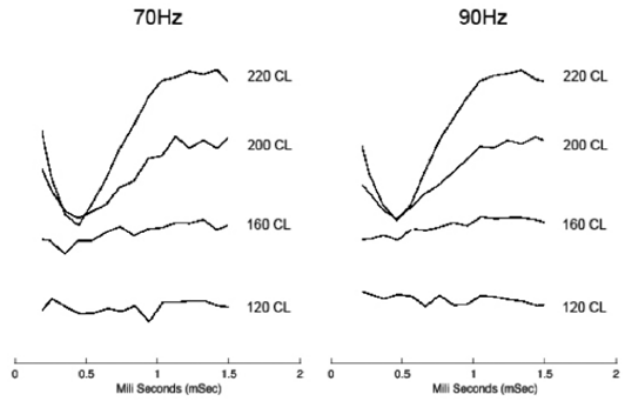

Figure 9. Detail of the electrode to stimulate the otolith organ in humans. Pat. 2015/00835. PCT/ES2016/000021

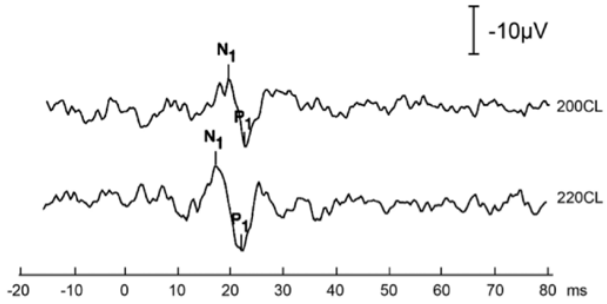

Figure 10. Voltage recordings during biphasic current-driven stimulation using one electrode of the arrays with a 5 kOhm impedance at different current levels.

biphasic waveform with an initial negative peak (N1) followed by a positive peak (P1), and as previously described by Parkes et al. [4], no statistical variability was found in eoVEMPS responses (Table 4).

DISCUSSION

In this paper, we demonstrate that vestibular ECAP responses are obtained after electrical stimulation of the otolith organ by using a similar stimulation paradigm as in cochlear implants. The VRT response, which has been recorded in the human vestibular end organ, displays many of the characteristics of the compound action potential recorded in the cochlea.

The ability to record neural responses in 83.3% of the tested electrodes supports the validity of the VRT system to measure vestibular-origin ECAPs in adult subjects.

We had already demonstrated that it was possible to generate a VRT response correlated to eoVEMPs responses through an electrode placed in the otolith organs. The ideal location of the electrode was determined by monitoring the VRT performed at slightly different places during the insertion. We observed that a minimal displacement of the electrode resulted in drastic changes in the amplitude of the responses, thus stabilization of the electrode array is necessary to obtain good responses. This also indicates that the presence of ECAP obtained from VRT and the correlation with eoVEMPs responses, when the stimulus is delivered on the otolithic organ and not when the electrode is incorrectly placed, is because it is a vestibular ECAP

and not an auditory response. Also, it is important to mention that the eoVEMPs were not obtained when the auditory neural response telemetry from the cochlear implant was performed.

The best test configuration parameters are a stimulation rate of 90 Hz, amplifier gain of 40 dB, 140 sweeps, a fixed masker level equal to the probe +10 CL, a masker advance of 400 µs, and a delay of 120 µs, and this provides the quickest and most reliable results in the tested adults.

The Vestibular Response Telemetry records collected showed consistent patterns in waveform morphology, response latency, and amplitude growth, and they were similar to previously recorded cochlear ECAPs in human patients [26, 27]. The N1 latency of the VRT and the P1 peak are both consistent with observations in cochlear ECAPs.

Animal experiments and data in humans suggest that electrical stimulation of the vestibular end organs could be used to treat loss of vestibular function [28].

Previous research suggests that the implementation of a vestibular prosthesis provides partial restitution of the vestibulo-ocular reflex (VOR) and might also improve perception and posture in the presence of bilateral vestibular hypofunction. Additionally, Perez Fornos et al. [29, 30] suggest that VOR restoration can improve the stabilization abilities with a VI.

Vestibular implants are devices designed to rehabilitate patients suffering from a dysfunction of VOR that impairs gaze stabilization and results in an abnormal loss of visual acuity in dynamic situations. Patients suffering from bilateral vestibular dysfunction can benefit from the stimulation of the otolith organ because it might have potential effects on more complex integrative behaviors such as the perception of head orientation and posture.

The results of this study provide evidence for the benefits of chronic stimulation of the otolith organ in patients suffering from bilateral vestibular dysfunction and profound sensorineural hearing loss. Development of a device for measuring the cephalic movements in three dimensions and conveying this information in a useful way to stimulate the vestibular nerve in order to replace the function of the labyrinth through the macules of the saccule and utricle is the focus of much research (Pat. 2015/00835. PCT/ES2016/000021) (Figure 9). The compliance of the current source of the stimulation circuitry of this design and the impedance of the electrode, based on size, material, and shape, can drive the electrode with charge-balance and biphasic, triphasic, or multiphase current pulses with a maximum charge injection limit of 1000 µA (Figure 10). In addition, the possibility to have an electrode disposition allows the design of several stimulation strategies (monopolar, bipolar, tripolar, multipolar, or command ground) in order to achieve functional stimulation of the utricle and saccule.

CONCLUSION

Vestibular Response Telemetry provides a method to assess peripheral neural function, and the recording technique is analogous to the ECAP recordings that are widely used in cochlear implant research and clinical practice. The VRT technique is effective for recording neural responses in the maculae region and provides us with a convenient tool to determine if the implanted electrodes are driving a neural response and, thus, to give information to help identify the optimum electrode placement during VI surgery. The weakness of this study is the small sample size, which is due to the ethical committee conditions and to the low disease prevalence. A set of default test parameters has been established to provide a relatively quick method of measuring the vestibular ECAP in our subjects. As far as we know, this is the first study that demonstrates the electrically evoked response of the directly stimulated otolith organ in humans.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of CEIC - 764 (11/06/2015).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.R.d.M., A.R.M.; Design - A.R.d.M., J.C.F.G.; Supervision - A.R.M.; Resources - A.R.M.; Materials - J.C.F.G.; Data Collection and/or Processing - A.R.d.M.; Analysis and/or Interpretation - J.C.F.G., A.R.M.; Literature Search - A.R.d.M.; Writing Manuscript - A.R.d.M., A.R.M.; Critical Review - A.R.M.

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4.3. Tercera publicación

4.3.1. Información de la publicación

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Autores: Angel Ramos Macias, Angel Ramos de Miguel, Isaura Rodriguez Montesdeoca, Silvia Borkoski Barreiro and Juan Carlos Falcón González

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Chronic Electrical Stimulation of the Otolith Organ: Preliminary Results in Humans with Bilateral Vestibulopathy and Sensorineural Hearing Loss

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Keywords
Vestibular implant · Balance · Utricle · Saccule · Bilateral vestibulopathy

Abstract
Introduction: Bilateral vestibulopathy is an important cause of imbalance that is misdiagnosed. The clinical management of patients with bilateral vestibular loss remains difficult as there is no clear evidence for an effective treatment. In this paper, we try to analyze the effect of chronic electrical stimulation and adaptation to electrical stimulation of the vestibular system in humans when stimulating the otolith organ with a constant pulse train to mitigate imbalance due to bilateral vestibular dysfunction (BVD). ***Methods:*** We included 2 patients in our study with BVD according to *Criteria Consensus of the Classification Committee of the Bárány Society*. Both cases were implanted by using a full-band straight electrode to stimulate the otoliths organs and simultaneously for the cochlear stimulation we use a perimodiolar electrode. ***Results:*** In both cases Vestibular and clinical test (video head impulse test, videonistagmography cervical vestibular evoked myogenic potentials, cVEMP and oVEMP), subjective visual vertical test, computerized dynamic posturography, dynamic gait index, Time UP and Go test and dizziness handicap index) were performed. Posture and gait metrics reveal important improvement if compare with preoperartive situation. Oscillopsia, unsteadiness, independence and quality of life improved to almost normal situation. ***Discussion/Conclusion:*** Prosthetic implantation of the otolith organ in humans is technically feasible. Electrical stimulation might have potential effects on balance and this is stable after 1 year follow-up. This research provides new possibilities for the development of vestibular implants to improve gravitoinertial acceleration sensation, in this case by the otoliths stimulation.

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Introduction

The main functions of vestibular system are to adjust head, neck, and trunk positions to maintain balance and gait and to adjust head and neck movements to maintain images at the fovea.

Bilateral vestibulopathy (BVP) or bilateral vestibular hypofunction is an important cause of imbalance that is frequently misdiagnosed. Individuals with BVP report

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experiencing chronic unsteadiness and vertigo when being in an upright position and walking, and these symptoms may become more severe with head motion and darkness. Bilateral vestibular dysfunction (BVD) has a prevalence of 16–28 cases per 100,000 individuals and is important in the elderly, as it produces more secondary effects in this group. Despite their severe impact on patients' daily life, vestibular function cannot be restored in a high number of patients, and vestibular implants (VI) improve the health state of only some patients. Many studies carried out in animals and humans lead to the concept that restoring vestibular function by electrically stimulation of the vestibule can be useful. At this point, most of the research has been focused on developing VI to be placed in the semi-circular canal ampullae. However, no attempt has been made to chronically stimulate the otolith organs in humans [Sprinzl and Riechelmann, 2010; Ward et al., 2013; Della Santina et al., 2017; Hedjoudje et al., 2019].

The clinical management of patients with bilateral vestibular loss remains difficult, as there is no clear evidence of an effective treatment. Additionally, it must be considered that many dizzy patients may suffer from different conditions that must be considered during their evaluation and treatment.

The otolith organ consists of 2 areas: the utricular sac and the saccular sac. Each of these sacs contains a plate of specialized receptor hair cells and connective tissue called macula. The utricular and saccular maculae are placed approximately perpendicular to each other. The saccule and utricle respond to linear acceleration and to gravity: the saccule senses acceleration in the sagittal plane and the utricle senses acceleration in the horizontal plane. With the head erect (head-up position), the utricular macula is tilted by about 30 degrees (open anterior) with respect to the horizontal plane of the head, whereas the saccular macula is nearly vertical. The spontaneous activity of the primary otolithic afferents is highly regular in some afferents, whereas it is highly irregular in others. In addition, there is a continuum of regularity between these extremes. Physiological responses are closely related to this dimension of regularity. Irregular neurons show a strong response to changes in linear accelerations, while regular neurons show a faithful response to maintained linear accelerations [Goldberg and Fernandez, 1984; Curthoys et al., 2018].

The superior vestibular nerve carries impulses from the utricle and semicircular canals to the vestibular nucleus, and then, these impulses travel through the medial longitudinal fasciculus mainly to the oculomotor nucleus. It stimulates mainly the oculomotor nucleus and the medial rectus and inferior oblique. The inferior vestibular nerve carries impulses from the saccule to the medial vestibular nucleus and is related to the vestibulospinal tract, which carries these impulses to the spinal accessory nucleus. This nucleus innervates the sternocleidomastoid and the vestibulo-collic reflex related to maintain neck musculature in relation to head position [Brodal, 1974].

For the purpose of this study, and focusing on surgical aspects, it is also important to understand the anatomical relation of the otolith organ and the stapedial footplate. With respect to the distances from the stapedial footplate to the vestibular end organs and cochlear duct, they range from 1.9 to 2.4 mm to the utricle, and from 1.7 to 2.1 mm to the saccule, while the distance between the cochlear duct and the inferior border of the footplate is around 0.2 mm [Pauw et al., 1991].

The vestibular electrical stimulation tries to produce "artificial" neural patterns to the central nervous system that are similar to those coded by the normal system. In healthy subjects, the vestibular nerves fire spontaneously at a rate of about 90 action potentials per second in the absence of movement (15, 16). Electrical stimulation of the utricular nerve in cats causes a distinct pattern of eye movement: a torsion of both eyes in which the upper poles of the eyes roll away from the side being stimulated because of the activation of the contralateral inferior oblique and ipsilateral superior oblique muscles. Complementary, studies have shown that unilateral section of the vestibular nerve causes torsion of both eyes toward the operated side. In natural head movements, the otoliths are activated and generate compensatory eye and postural responses [Curthoys et al., 1991].

Another interesting aspect of this VI research is to generate evidences on vestibular function research, particularly by providing selective and direct access to the otolith end organs structures.

Objective

The objective is to analyze the effect of chronic electrical stimulation and the adaptation to electrical stimulation of the vestibular system in humans when the otolith organ is stimulated with a constant pulse train to mitigate imbalance due to BVD.

Preliminary results will be presented regarding vestibular testing and clinical aspects, and mainly focused on spatial orientation, balance, posture and gait of 2 patients with otolith chronic electrical stimulation.

Table 1. Clinical data of both vestibular implanted patients

Patient	Gender	Aetiology	Onset age, years	Age at VI	Side	N elect	Contralat. CI
VI/CI-1	Male	Meningitis	45 (2017)	46	OI	3	Nucleus® Profile™ Contour Advance® – CI512, (2017)
VI/CI-2	Male	Meningitis	29 (2002)	45	OI	3	Nucleus 24M (2006)

Material and Methods

The current study was conducted with the approval of the Ethics Committee of our hospital (CEIm-CHUIMI 2017/956) and performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients provided written informed consent before participating. All the procedures involving human participants were in accordance with the ethical standards of our institutional research committee.

Two patients matching the following criteria were included in our study: being older than 18 years, presenting BVD according to *Criteria Consensus of the Classification Committee of the Bárány Society*. In both cases, supervised rehabilitation sessions, in addition to a daily home exercise program, were used before their implantation for more than 1 year. Both cases failed to the adequate vestibular rehabilitation program and also in both cases, a profound hearing loss was found.

The exclusion criteria for this study were the following: being unable to provide consent personally, not matching cochlear implantation criteria, ossification or other inner ear anomalies that prevent full insertion of electrodes, retrocochlear or central origins of hearing impairment, medical contraindications for surgery, chronic depression, dementia and cognitive disorders, cerebellar ataxias without BVP, downbeat nystagmus syndrome, peripheral neuropathies, Parkinson's disease, atypical Parkinson's syndromes, multiple system atrophies, central gait disorders due to normal pressure hydrocephalus, frontal gait disorders, lower-body Parkinson, subcortical vascular encephalopathy or multiple sclerosis.

Subject 1 (vi/ci-1) is a man who had meningococcal meningitis for 1 year before surgery and the implantation was performed at the age of 46 in the left ear. Subject 2 (vi/ci-2) was a man who had meningitis for 15 year before surgery and received the implant in the left ear at the age of 45.

The first patient received a cochlear implant (CI) in the contralateral ear to be treated 14 months before (CI532®), and the second, 14 years before (Cochlear CI24M®). In both cases, the left side was implanted with a Cochlear CI532® for cochlear stimulation (CI; although the results are out of the focus of this study) and a Straight Cochlear 24RE ST® for Otolith organ stimulation (VI), in the same surgical procedure simultaneously. The first implantation was performed in July 2018 and the second one in November 2018 (Table 1).

Inclusion Criteria

Both cases had BVP. For the diagnosis of BVP, we followed the *Diagnostic Criteria Consensus document of the Classification Committee of the Bárány Society* (21). For the diagnosis of BVP, the horizontal angular vestibulo-ocular reflex (VOR) gain on both sides should be <0.6 (angular velocity 150–300°/s). For the diagnosis of probable BVP, the above-mentioned symptoms and a bilaterally pathological bedside HIT are required.

Radiological Evaluation

Computed tomography (CT): images were acquired by cone beam CT (RayScan M., Ray Co Ltd., Korea). Cone beam CT has been previously validated as a valuable tool for the assessment of electrodes post-cochlear implantation, as it requires less irradiation than a regular CT and shows less sensitivity to metallic artifacts. Thus, it represents a better method to identify electrode placement in the cochlea and otolith organ. We use this technique in both patients to measure the vestibule size. OsiriX software was used to collect all the images, in the DICOM file format, of the vestibule. A MatLab script was developed to extract and reconstruct the volume of the vestibule. The vestibule depths were 2.79 mm for 1 patient and 2.53 mm for the other patient.

An MRI-scan, T1 and T2 images of the cerebellopontine angle, with intravenous gadolinium contrast was performed in order to evaluate the patency of the labyrinth and nerve structure analysis. Inner ear fluid space images and positive perilymph/positive endolymph images were acquired by using a 1.5-tesla unit. Removal of the magnet of the contralateral side was not required.

Three-dimensional (3-D) images were constructed semiautomatically by using both anatomical and tissue information and by fusing the 3-D images of the inner ear fluid space. Custom made software was developed to construct semi-automatically 3-D meshes of the inner ear of the patient and the vestibular electrode array. The reconstruction procedure was based on the following 5 stages:

1. Inner ear location.
2. Volumetric reconstruction of bonny structures.
3. Volumetric reconstruction of electrode.
4. Cleaning mesh manually.
5. Superimpose anatomical structures and electrode array.

For that proposal, OsiriX MD [Rosset et al., 2004] software was used for the volumetric reconstructions of the different structures. MeshLAB [MeshLab 2008] software was used to clean the meshes.

Surgical Procedure

Stimulation Technique and Surgical Approach

A full-band straight electrode, CI24RE (ST), from Cochlear Ltd (Lane Cove, NSW, Australia) was used. This electrode array has a diameter of 0.4 mm on the apical part. Each electrode has a cylindrical band of 0.3 mm width and 0.4 mm diameter on the tip. The interelectrode space is 0.2 mm on each lead. Full-band electrodes were selected to assure that the electrodes were facing the closest area of neural tissue related to the saccular area. For the cochlear stimulation, a Cochlear CI532® (Cochlear Ltd., Sydney, NSW, Australia)

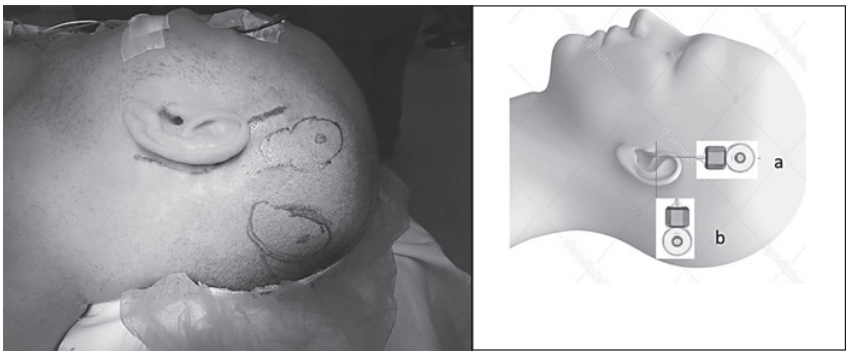


Fig. 1. Surgical approach and position of both receptors: vestibular and cochlear implant. Incision and anatomical situation of both receptors. **a** Vestibular implant. **b** Cochlear implant.

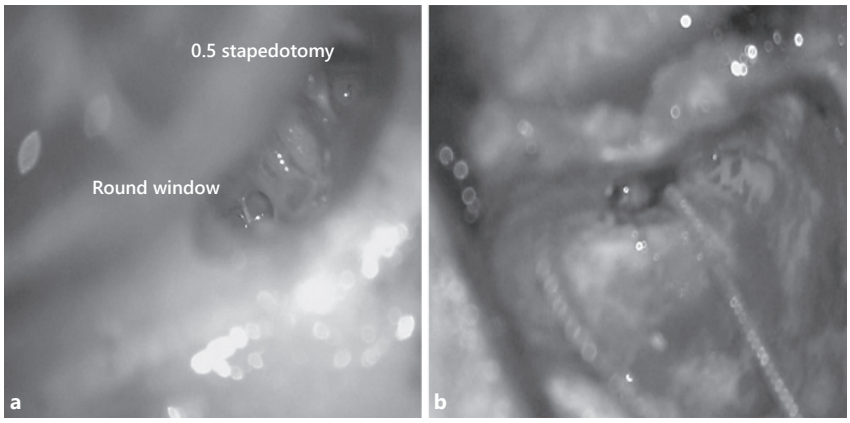


Fig. 2. Anatomical landmarks for vestibular and cochlear implant insertion. Posterior tympanotomy view. **a** Stapedotomy for VI insertion and Round Window approach for CI. **b** Vestibular and cochlear implants arrays insertion.

perimodiolar electrode with a diameter of 0.35–0.4 mm at the tip and 0.45–0.5 mm at the base was used. It has 22 half banded platinum contacts and 3 white markers to control insertion depth (Fig. 1).

The same surgeon performed all procedures (A.R.M.). Enlarge retroauricular approach was performed. Then, after identifying the temporalis muscle, a flap was developed following the same principles as in standard CI surgery. Cortical mastoidectomy extended to the attic was performed. As anatomical landmarks sigmoid sinus, incus and lateral semicircular canal were identified. As cochlear implantation is performed simultaneously, posterior tympanotomy is performed at this time with a clear exposure of the long process of incus, stapes and oval window.

Two different and independent subperiosteal pockets were performed: one at 90° of the pinna and the second at 180°. In both cases, a CI532® CI was inserted first. Once it was inserted and tested, VI was inserted. Opening of the vestibule was performed by performing a 0.5 mm stapedotomy with CO_2 laser just medial and inferior to the anterior crura of the stapes in order to reach the closest area to inferior vestibular nerve afferent near the saccule macula. Saccule macula is located on the antero-inferior region, presenting a mean distance from the oval window of 1.4 mm (minimum of 0.8 mm). Utricle is located on the postero-superior region 1.4 mm form the oval window (minimum distance of 0.2 mm). A maximum insertion depth of 2.2 and 2.3 mm in each case was performed, inserting the 3 first contact of the vestibular component (Fig. 2).

During the surgical procedure, the facial nerve was monitored with the Nerve Integrity Monitor 2tm system (Medtronic, Minneapolis, MN, USA).

Fixation of both implants was made independently, and a "Three-point fixation" of the VI electrode array (Stapedotomy, *fossa incudes*, and cortical edge of mastoidectomy) was performed. No immediate postsurgical vertigo was observed. The postsurgical hospital stay was not longer than that after CI surgery. During the postsurgical stay, CT scans and 3-D reconstruction were performed to check the placement and orientation of both implants, aiming at the proximity to the lower vestibular nerve (Fig. 3).

Intraoperative Testing

As previously described [Ramos de Miguel et al., 2017] a "vestibular response telemetry" (VRT) software was designed by using the nucleus implant communicator library (Cochlear LTD) for Python (Python Software Foundation, version 2.4) in order to obtain electrically evoked action potentials (ECAPs) from the vestibular nerve. The software automatically evaluates all of the configurations available to find the best ECAP response. On average, total acquisition takes 10 min. The software communicates then with the speech processor to capture, process, and store the measurement data on a computer. The VRT software controls the parameters of the stimulus used to evoke and record the response to be measured intraoperatively.

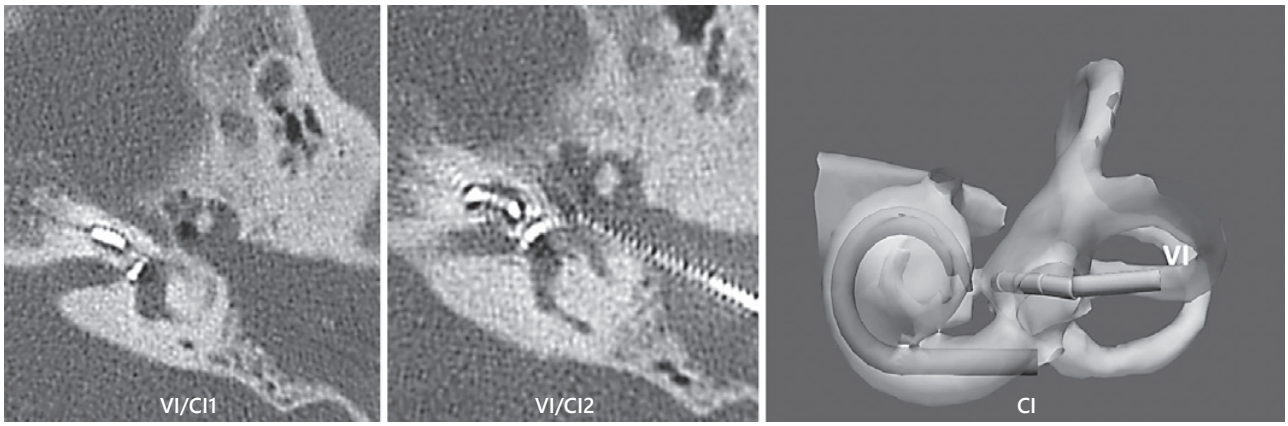
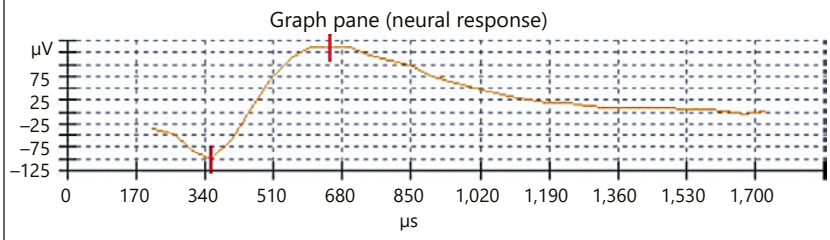


Fig. 3. Final position of the cochlear and vestibular implant in the CT images and 3D reconstruction. CT scan showing the insertion of vestibular and cochlear electrode arrays in both patients (VI/CI1 and VI/CI2). Also, it shows a 3 D reconstruction of the final situation in VI/CI2 subject. VI, vestibular implant; CI, cochlear implant.



Patients	Active electrode	N1–P1 Amplitude	N1	P1
VI/CI1	20	68.31	405.2	649.2
VI/CI1	21	237.7	356.4	649.2
VI/CI1	22	171.45	356.4	649.2
VI/CI2	20	57.57	179.33	374.2
VI/CI2	21	108.26	374.2	764.6
VI/CI2	22	93.58	423	813.4

Fig. 4. Vestibular-evoked potential. Neural response in the electrodes. The intraoperative ECAP response obtained in both patients.

The VRT measurements were done after insertion of the 3 electrodes into the vestibule, and the 2 reference electrodes were correctly placed and covered by tissue. An extracochlear ball electrode on a flying lead was placed under the temporalis muscle (MP1), and a plate electrode was placed on the receiver-stimulator (MP2). Monopolar stimulation (MP) was used in all tests. We then studied the effect of different test parameters, including stimulation rate, number of repetitions, measurement delay, masker level, and masker advance. The specific test (stimulation and recording) parameters studied were the following: (1) measurement delay (80–120 ìs); (2) stimulation rate (90 or 70 Hz); (3) number of samples; and (4) number of averages (50, 100, or 150). The setup consists of a lap computer, cochlear POD interface, Nucleus Freedom processor (Cochlear Corp., Sydney, NSW, Australia), and CI24RE (ST).

Additionally, electrically ocular vestibular evoked myogenic potentials (eoVEMP) responses were recorded by using a recording system (Eclipse Interacoustic, EP25). This test was included in order to confirm the stimulation of the vestibular pathway by recording electrically eoVEMPs, by using a trigger system.

To minimize the stimulation artifacts, the developed software implements the forward-masking paradigm and involves a sequence of conditions: probe-only (A), masker followed- by-probe (B), masker-only stimuli (C), and no stimulation (D). The probe-only condition yields the desired neural response plus an artifact from the probe. The masker-and-probe condition with an appro-

priate masker advance yields stimulus artifacts for both masker and probe, and the neural responses to the probe are absent or decreased because of the forward masking. The masker-only condition yields only the masker artifact. After the recordings of each of these 4 stimulation conditions were performed, extraction of the ECAP from the stimulus artifact was accomplished by using the subtraction method (A, [B, (C, D)]) to cancel the large masker stimulus artifacts found in each condition, and this allows one to extract the relatively small neural response.

In order to obtain the neural responses, a second test using Cochlear's Custom Sound Evoked Potential Software tool (version 5.2) was used. The basic parameters used to create the stimulus in channels 20–21 and 22 of the electrode beam were the following: Recording active electrode Prb Act E + 2; Probe Indifferent Electrode MP1; Probe current level (CL) ≥200; Probe Pulse Width 40 μs; Probe Rate 40 Hz; Recording Indifferent Electrode MP2; Gain 50 dB; Delay 122 μs; Number of Sweeps 50; and Measurement Windows 1,600 μs (Fig. 4).

Electrically Ocular Vestibular Evoked Myogenic Potentials

In order to record eoVEMPs (responses attributed to the utricular-ocular reflex pathway) simultaneously with the vestibular ECAP, electrical oVEMPs were performed intraoperatively. A trigger synchronized both systems. In this study, ocular vestibular-evoked myogenic potentials were obtained from both participants by using Eclipse EP 15/EP25/VEMPS (Interacoustics AS, Assens, Denmark system). Responses were collected and analyzed by using a 2-channel surface electrode montage and Eclipse Interacoustic EP25 4.4 VEMP 4.3 recording platform. In order to determine the accuracy of the calibration method, the active electromyogram (EMG) electrode was placed over the medial inferior oblique muscle edge contralateral to the stimulated ear, and the reference electrode was placed on the cheek 1 cm below. Then montage ground electrode was placed on the mid-forehead. Impedance was kept below 5 kOhms.

EMG signals were band pass filtered (1–3,000 Hz) and recorded in a 25–50 ms window relative to stimulus onset. No online artifact rejection was used. For all eoVEMPs tests, 2 or more trials (100 sweeps each) were obtained. When such responses were not identified after 2 trials, testing was ended. The maximum intensity levels were set from 120 to 220 CL, with a 20 CL stepsize, for both single 57 ìs biphasic electric pulses (25 ìs/phase with a 10 ìs interphase gap). The eoVEMPs tests were first conducted by using electrode 22 and then were repeated by using the other inserted electrodes 21 and 20.

The facial nerve was monitored in all the subjects, and no cross stimulation of the facial nerve was observed in any of these cases.

Postsurgical Measurement and Processor Activation

During the activation process, both patients described a feeling of surprise, then a sensation of comfort and stability while they stay seated when the activation process was performed. When the increase of the stimulation sensation was excessive, they felt unexpected motion sickness without nausea.

Vestibular stimulation is composed of a constant pulse train of the 3 inserted electrodes. This makes the use of external sensor unnecessary even when the patient is in dim light. The objective of this stimulation is to provide a vestibular activity that masks the absence of stimulus consistent with the forces perceived by the patient and allows the rest of the balance system (vision and proprioception) to maintain balance.

Table 2. Data of first programming session in both patients

Patient	Active electrode	NRT	C level	T level	Maxima
VI/CI1	20	182	130	129	8
VI/CI1	21	182	130	129	8
VI/CI1	22	179	130	129	8
VI/CI2	20	223	195	194	8
VI/CI2	21	241	195	194	8
VI/CI2	22	244	195	194	8

We use a monopolar stimulation of the electrodes ICE22, ICE21, and ICE20 against ECE1 + 2. The stimulus is a biphasic pulse of 25 us per phase and 8 us of Inter-Phase gap at a stimulation frequency of 900 pps. The dynamic range for each patient is 1 CL (as it will be described afterwards) to achieve a constant stimulation in the 3 electrodes involved. AutoNRT measurement was carried out with the basic parameters of the Cochlear Custom Sound Evoked Potential Software version 5.2.

As standard, an ACE (RE) coding strategy, an MP1 + MP2 stimulation and a maximum of 8 were used, so 8 channels activated (from 15 to 22) were kept, maintaining channels from 15 to 19, CL values threshold (T) = 1, dynamic range (RD) = 1, and comfort level (C) = 3. The channels in which responses were obtained were those used to provoke the stimulus. In both patients, channels 20–21 and 22 were selected, assigning as threshold T the minimum value of subjective perception of the patient RD = 1 and C = +1, speed of stimulus of 900 Hz although we considered changing later to 1,200 Hz given that in both patients the neural responses were above 200 CL, which allowed us to low C levels. In both patients, with respect to channel 22, 205 Hz was assigned to the frequency allocation table.

The same "C" and a RD of 1 value were used in all 3 channels 20–22. The stimulation was started with a value of 70% of the value of the postsurgical neural response (this percentage oscillated between 70 and 90%) monitoring the patient's nystagmus through the Videonystagmography testing. The 3 channels were increased simultaneously in 2 CL step keeping always an RD of 1, until observing with the monitoring the decrease or abolition of the nystagmus. The first MAP was recorded at this level of stimulation, creating 3 MAPS with an increment of +2 CL consecutively in the 3 channels. These MAPs were the ones that the patient had been changing every week during the study period. The 3 channels in both patients were evaluated individually, alternating them by active pairs (22–20, 22–21, 21–20) and all 3 at the same time. And it was observed that the best selection of channels (where the best results have been obtained) was when 3 channels have been used simultaneously.

The values obtained were used as a reference of indicator of perception of the minimum stimulus perceived by the patient to initiate levels C in the Programming MAP (Table 2).

CP950 Processor (Kanso Cochlear®) was used by the patients for daily use (16 h/day) and CP910 processor (Cochlear®) was used during programming and measurements sessions in the hospital.

For the CI, we used the SD method. In both cases, a CP950 Processor (Kanso Cochlear®) was used.

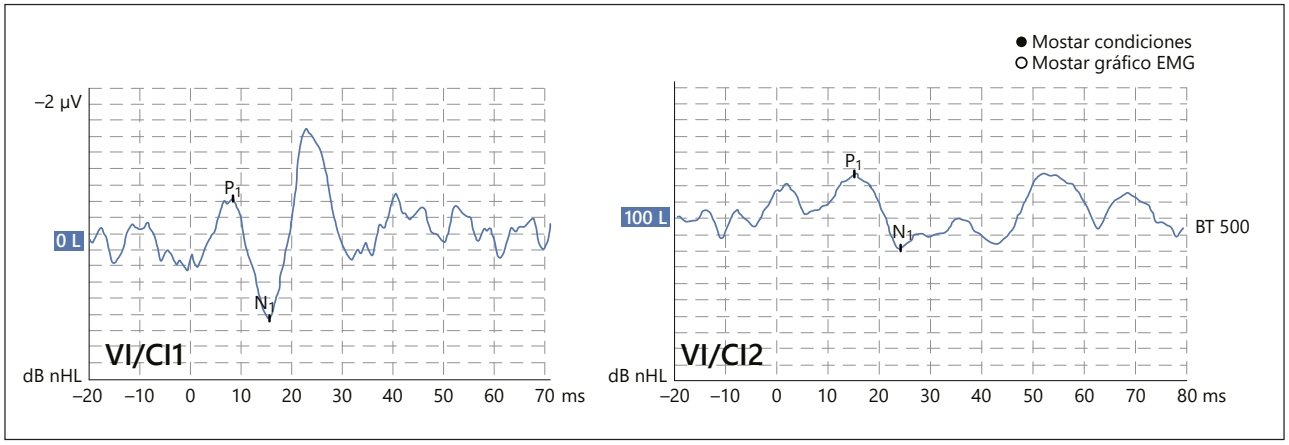


Fig. 5. Vestibular-evoked myogenic potentials. ecVEMPs were obtained from both patients. Results after 1 month postsurgery are presented. VI, vestibular implant; CI, cochlear implant.

Results

Posture and gait metrics of the patients reveal a mean improvement with respect to their pre-surgery situation. Oscillopsia, unsteadiness, independence, and the resulting quality of life remarkably improved, reaching values close to normality.

Clinical Evaluation

One month after the surgical procedure was performed, the vestibular and CI were alternately activated. Both subjects showed an immediate response (in a few seconds) after the activation of their VI. After continued use, they reported a perception of change 5 min after VI turned off and a residual effect for at least 5 h. The tests were re-evaluated to check the results reproducibility with a frequency of a month between sessions. With respect to side effects, only Subject 1 reported a slight increase in his previous tinnitus during VI turned on, but that disappeared after 1 month.

Vestibular Test

Video Head Impulse Test

Horizontal angular VOR gain on both sides semicircular canals. Bilaterally reduced or absent angular VOR function by bilaterally pathological horizontal angular VOR gain <0.66, measured by the video-HIT (ICS Impulse type 1085 from GN Otometrics A/S). Although, predictably, there were no expectations of changes in the VOR gain, as the stimulus was focused on the otolith organ, better VOR gain in the semicircular canals of the implanted side was observed in one of the patients. However, this was not enough to reach a normal value in normal situation, but this data must be analyzed as probably it, together with the excellent clinical response, must be considered in future research.

Videonistagmography

(VisualEyes™ 515/525 by Interacoustics) was used to test spontaneous nystagmus. This test was conducted with the vision-denied cover attached to the front of the mask, eliminating any possibility of fixation. In the second patient, a decrease in the average slow phase velocity using VI (from 2.3 to 0.3) was obtained. As an important weakness we missed the initial data of the first patient after activation.

Vestibular Evoked Myogenic Potentials

Measurements of the vestibular evoked myogenic potentials (VEMPs) allow for an evaluation of the function of otolith organs and are therefore a useful addition to the neurotologic test battery. Two subtypes have been increasingly used in clinical practice as well as in research over the last years: cervical VEMP (cVEMP) and ocular VEMP (oVEMP). Both generated in response to air or bone conduction stimulus. The cVEMP is recorded by EMG electrodes over the tensed sternocleidomastoid muscles, and consists of a short-latency (13 ms from stimulus onset to response peak) positive EMG potential called the cVEMP p13-n23. The oVEMP is a small (5–10 ìV) negative potential recorded by electrodes on the skin beneath the eyes when the person looks up. VEMPs can be used to assess otolith integrity

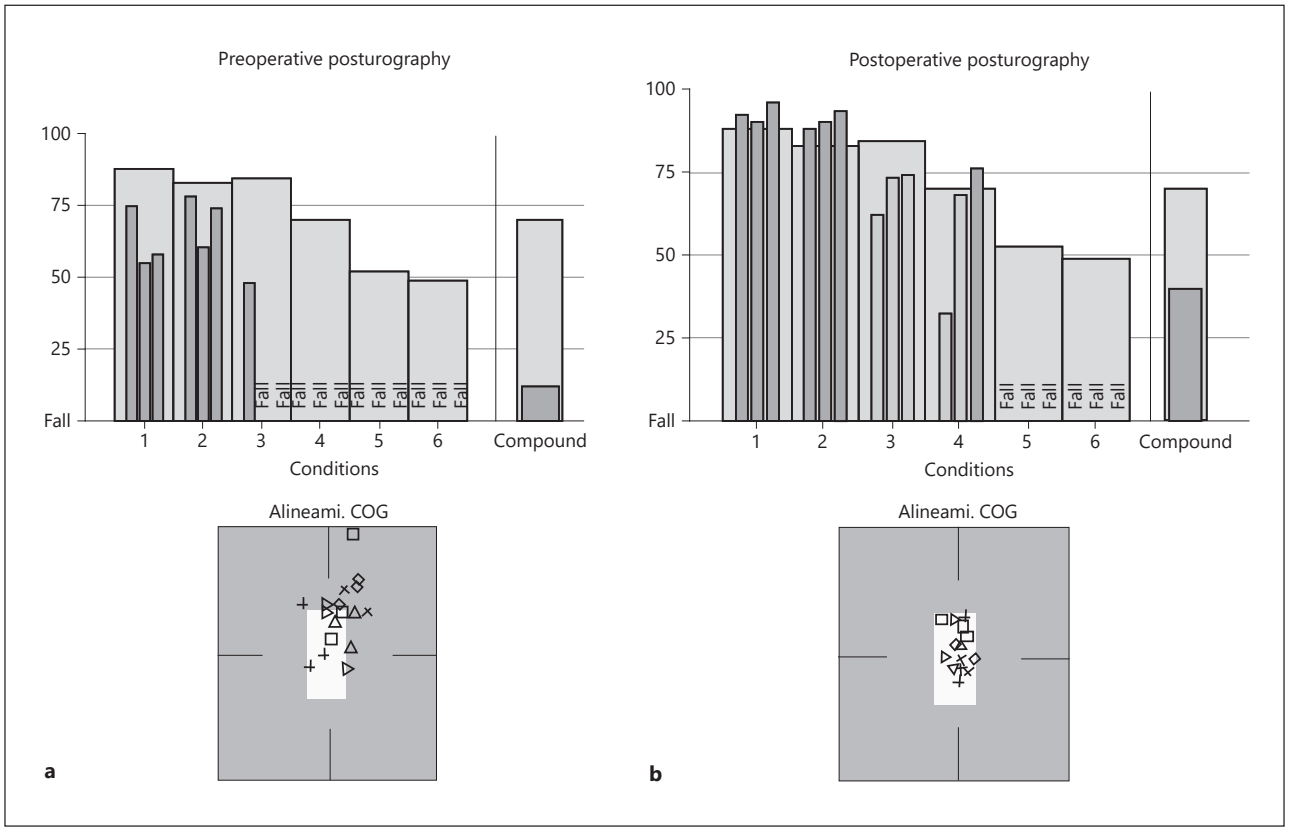


Fig. 6. Response preoperative (**a**) and postoperative (**b**) posturography. CDP: LOS with better directional control and increase in maximum excursion. SOT with an improvement in Conditions 1–4 and increase in composite score and center of gravity more centered adaptation test with evident improvement of the reaction control.

as well as vestibulo-collic and vestibulo-ocular pathways [Curthoys, 2010].

Cervical and oVEMPs are reflexes mediated by the saccule and utricle respectively. There are data confirming that oVEMPs to 500 Hz probe utricular function and cVEMPs to 500 Hz probe saccular function come from the pattern of responses of patients with vestibular neuritis, in which hearing is not affected, but vestibular function is affected [Halmagyi et al., 2010].

In this study, cervical and ocular vestibular-evoked myogenic potentials were obtained from all participants using bilateral air conduction tone bursts with stimulus frequencies of 500 Hz. In our 2 patients VEMPs were absent before surgery and, 1 month after surgery, electrical cVEMPs in the implantation side were obtained. P1 and N1 latencies were in 8–15 and 15–24 s, respectively. These results were present 6 months after that, being a testing of the activation of the vestibulo-collic reflex and, consequently, of the activation of the saccular part of the otolith organ (Fig. 5).

Subjective Visual Vertical

Subjective visual horizontal (SVH) or subjective visual vertical (SVV): In human subjects with the eyeball in a rolled position, visual perception changes in accordance with this new torsional. Systematic deviations in SVV or SVH greater than about 2 degrees, in patients with peripheral vestibular dysfunction, are taken to indicate static otolith dysfunction. Standardized measurement of the SVH, with a dim light-bar in an otherwise totally darkened room, can give valuable diagnostic information. SVV: The visual vertical application offers the quickest and easiest to measure SVV in patients. Static SVV will be measured using the visual vertical TM (Clear Health Media, Wonga Park, VIC, Australia) application on an iPhone (Apple, Cupertino, CA, USA). The normal range of deviation is set to 2.3° in either direction of the true vertical.

In this study, Static SVV was measured by using the visual vertical TM (Clear Health Media, Wonga Park, VIC, Australia) application on an iPhone (Apple, Cupertino, CA,

USA). The normal range of deviation is set to 2.3° in either direction of the true vertical. In Subject 1, a considerable improvement, (pre-surgery: –9.6° and post-surgery: –1.3°) was obtained, with a normal value. In subject 2, although he showed a better pre-surgery score, he also reached better results 1 month after the surgery (1.1 and 0.6°)

Computerized Dynamic Posturography

Computerized dynamic posturography (CDP) is an objective method of differentiating sensory, motor, and central adaptive functional impairments of balance. CDP includes the sensory organization test (SOT), the adaptation test and the limits of stability (LOS).

CDP was performed with the SMART EquiTest® CDP 8.1 version (NeuroCom®, USA). It allows differentiating sensorial, motor, and central adaptive functional impairments of balance including the SOT, the adaptation test and the LOS. These tests were probably the most accurate tools to evaluate functional results of VI in real life. In both patients, immediately after activate VI, they perform better in all condition obtaining, observing a progression to normal ranges or near normal level in both cases. We can check better directional control and an increase in maximum distance excursion end point, center of gravity more centered, and evident improvement of the reaction control in both patients (Fig. 6).

Dynamic Gait Index

Dynamic gait index was developed as a clinical tool to assess gait, balance, and fall risk. It evaluates steady-state walking and also walking during more challenging tasks. In both patients, they were reaching maximum values, especially subject 1 experienced a great evolution from the beginning, going from a figure of 8/24 before intervention to obtain the maximum value in the test after it (24/24). The second patient reached initial values of 16/24, and he also obtained the maximum value after the intervention (24/24).

The Time UP and Go test

Time UP and Go test measures the time that take to stand up from a standard armchair, walk 3 meters, turn around, walk back to the chair, and sit down again. If we consider a cutoff score of 11 s, the duration improved after surgery with normal ranges reaching a maximum of 7 s in both patients.

Dizziness Handicap Index

Dizziness handicap index measures the self-perceived level of handicap associated with the symptom of dizziness. In Subject 1, a clear improvement in the perception of his disability was observed, going from a severe to a mild grade. Subject 2 started from a better situation, but and also noticed a progression to better results.

With the results described above, an evident improvement in patients' quality of life was observed after a 1-year follow-up in the first patient and 7 months in the second patient. They had improved their values in the dizziness handicap index, gait in dim light and difficult spaces, and spatial orientation reaching normal ranges in tests like the dynamic gait index and Time UP and Go test. Other improvements were also observed, such as in SOT, and its static position, obtaining an adequate center of gravity in the posturography, as well as, extending the LOS.

It is also important to consider interesting details of their daily life as relevant: Both patients restored their normal activities such as walking on unlevelled terrain (beach sand), abandoning the use of walking sticks or help from other people, being able to walk on narrow sidewalks, walking in the dark, being able to carry weight, tight shoes and complete recover the daily activities without any support. Both patients used their system 24 h/day.

However, there are still aspects to be studied, such as the role played by the otolithic stimulus in the restoration of VOR, since a certain modulation in the results of the video head impulse test, as well as, in the spontaneous nystagmus in one of our patients was observed.

Audiological Results

Although this is not a matter of this study, both patients obtained good responses with the CI532® CI. The subjects used alternatively both systems due to interference in the processors, and they used every day the VI system and the contralateral CI, and only used both CI when stay seated (e.g., watching TV, etc.).

Discussion

Our balance system may be activated when there is a concern for movement, but it is not active only when someone is moving, but also while maintaining a balanced posture or gait. The vestibular organ senses linear and rotational acceleration of the head during active and passive motion. These signals are necessary for bipedal locomotion, navigation, and for the coordination of eye and head movements in 3-D space. The temporal dynamics of vestibular processing in cortical structures has been poorly studied in humans. Natural otolith stimulation in subjects accelerated along the main axis shows that the

source localization gave the cingulate sulcus visual area and the opercular-insular region as the main origin of the evoked potentials, and it is essential in the processing of acceleration intensities as sensed by the otolith organs [Ertl et al., 2017].

VI are research devices designed to rehabilitate patients with a dysfunction that impairs gaze and balance mainly in dynamic situations. Patients with BVD have a quality of life that is significantly impaired, and they can benefit from the stimulation of the otolith organ because it might have potential effects on more complex integrative behaviors, such as posture. In this research, it has been shown that a multichannel vestibular (otoliths stimulator) prosthesis can restore the vestibular sensation, as evidenced by improvements in the spatial orientation, gaze stabilization, posture, and gait. However, a key challenge is to optimize the propagation of the current beyond the otolith organ itself to the nerve branch. The otolith stimulation was performed by placing 3 electrodes in proximity of the vestibular nerve in addition to a CI.

Previous studies suggest that the implementation of a vestibular prosthesis provides partial restitution of the VOR and might also improve perception and posture in the presence of bilateral vestibular hypofunction. Good results have been reported in patients implanted with modified CI with a trifurcating array incorporating different number of electrodes per array inserted into the ampullae. Some devices were purely vestibular and others included a cochlear electrode array.

Some of these devices were conceived to act as a pacemaker that could be activated during a Meniere's crisis to regulate vestibular function in patients suffering from intractable diseases. In addition, there are new techniques that try to preserve residual hearing and, although we cannot rule out of that principle, more technical innovations must be done [Fridman et al., 2010; Golub et al., 2014; Phillips et al., 2015; Perez Fornos, 2017].

In this study, vestibular ECAP responses were obtained after electrical stimulation of the otolith organ by using a similar stimulation paradigm as in CI. The vestibular ECAP response, which has been recorded in the human vestibular end organ, displays many of the characteristics of the compound action potential recorded in the cochlea.

It was also observed that it is possible to correlate the vestibular ECAP response with the electrically oVEMPs responses through an electrode placed in the otolith organs. The ideal location of the electrode was determined by monitoring the vestibular ECAP at slightly different places during the insertion. We observed that a minimal displacement of the electrode resulted in drastic changes in the amplitude of the responses, thus stabilization of the electrode array is necessary to obtain good responses. This also indicates that the presence of vestibular ECAP correlates with electrically eoVEMPs responses, and could be used as a sign of vestibular stimulation [Ramos de Miguel et al., 2017].

Regarding the stimulation, although it is not well known how the stimulus in the vestibular organ can provide an effective response in the afferent vestibular nerve, many studies have been presented with different researches on this topic. A model of the primate labyrinth has been recently made from 3-D reconstruction images to study the spread of prosthetic current in the inner ear and to facilitate design of electrode arrays and stimulation protocols for a VI system, which offers important data of the spread and the effect of the stimulation [Hedjoudje et al., 2019].

The role of the otoliths in human (utricle and saccule) in the global function of the vestibular function has not been widely studied and it is difficult to determine [Curthoys, 2010; Curthoys et al. 2018].

Nystagmus can be affected by gaze positions. However, there are still doubts to be solved, such as the role played by the otoliths stimulus in the restoration of VOR, since a certain modulation in the results of the video head impulse test and in the spontaneous nystagmus in one of our patients was observed. With respect to the relation with the VOR, a recent study examining the role of the otoliths in adaptation of the VOR in an animal model shows that otoliths do not contribute to the adaptation of the normal angular VOR, as it has been shown during the activation in our patients. However, the otoliths provide the main cue for gravity context-specific VOR adaptation, and also may have some effect in the spontaneous nystagmus, that also has been observed in our study [Khan et al., 2019].

In addition, it is important to consider that many authors confirmed that imbalance is a common cause of morbidity following CI. In most cases, it is not correlated with reductions in VOR gain and suggests that the underlying lesion may be isolated to other vestibular end organs as otolith organs [Rubinstein et al., 2012; Shute et al., 2018; Imai et al., 2019].

Future Work

These results indicate that electrical stimulation of the vestibular nerve, by using an otolith stimulation approach, has a significant functional impact on balance and everyday tasks such as walking, and fall prevention. The concept presented in this research has the potential to restore

the vestibular function and could have a central role in improving the quality of life of BVL patients, but future research is needed in order to improve our knowledge:

- A new multicentre study using a new device in order to stimulate simultaneously cochlear and otolith organ will be developed in the next months (Horizon2020 Fet Open. Grant Agreement No. 8 0 1 1 2 7. Project Acronym: BionicVEST).
- Preservation of the vestibular and hearing function will be a crucial issue and substantial efforts must be put into the design of new electrodes and surgical approaches
- Analyze the specificity of stimulation targeting the different branches of the vestibular nerve, including the saccular, utricular and semicircular canals
- Improve the specificity of the stimulus and the sensors to provide a better result.

Weakness

This study has been conducted on a much reduced number of patients, as the authorization of new procedure had to be obtained, and it was limited to 2 patients. Now, our group is authorized to include a third patient in this preliminary study and also, with a new research prototype device, a multicenter study will include 12 more patients.

Conclusion

Prosthetic implantation of the otolith organ in humans is technically feasible. Electrical stimulation might have potential effects on balance and this is stable after 1 year follow-up. This research provides new possibilities for the development of VI to improve the gravito-inertial acceleration sensation, in this case, by the otoliths stimulation.

Statement of Ethics

The current study was conducted with the approval of the Ethics Committee of our hospital (CEIm-CHUIMI 2017/956) and performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients provided written informed consent before participating. All the procedures involving human participants were in accordance with the ethical standards of our institutional research committee.

Disclosure Statement

All authors declare that they have no conflicts of interest.

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Author Contributions

A.R.M.: design of the work; final approval of the manuscript; surgeries. A.R.dM. and J.C.F.G.: intraoperative and postoperative neurophysiological testing; analysis of data; drafting the manuscript. I.R.M. and S.B.B.: clinical tests; analysis of data; drafting the manuscript.

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4.4. Cuarta publicación

4.4.1. Información de la publicación

Título: The vestibular implant: Opinion statement on implantation criteria for research.
Autores: Raymond van de Berg, Angel Ramos, Vincent van Rompaey, Alexandre Bisdorff, Angelica Perez-Fornos, Jay T. Rubinstein, James O. Phillips, Michael Strupp, Charles C. Della Santina and Nils Guinand
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The vestibular implant: Opinion statement on implantation criteria for research

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Abstract. This opinion statement proposes a set of candidacy criteria for vestibular implantation of adult patients with bilateral vestibulopathy (BVP) in a research setting. The criteria include disabling chronic symptoms like postural imbalance, unsteadiness of gait and/or head movement-induced oscillopsia, combined with objective signs of reduced or absent vestibular function in both ears. These signs include abnormal test results recorded during head impulses (video head impulse test or scleral coil technique), bithermal caloric testing and rotatory chair testing (sinusoidal stimulation of 0.1 Hz). Vestibular implant (VI) implantation criteria are not the same as diagnostic criteria for bilateral vestibulopathy. The major difference between VI-implantation criteria and the approved diagnostic criteria for BVP are that *all* included vestibular tests of semicircular canal function (head impulse test, caloric test, *and* rotatory chair test) need to show significant impairments of vestibular function in the implantation criteria. For this, a two-step paradigm was developed. First, at least one of the vestibular tests needs to fulfill stringent criteria, close to those for BVP. If this is applicable, then the other vestibular tests have to fulfill a second set of criteria which are less stringent than the original criteria for BVP. If the VI-implantation is intended to excite the utricle and/or saccule (otolith stimulation), responses to cervical and ocular vestibular evoked myogenic potentials must be absent in addition to the above mentioned abnormalities of semicircular canal function. Finally, requirements for safe and potentially effective stimulation should be met, including implanting patients with BVP of peripheral origin only, and assessing possible medical and psychiatric contraindications.

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Keywords: Vestibular implant, vestibular prosthesis, implantation criteria, bilateral vestibulopathy, bilateral vestibular hypofunction, electrical stimulation, vestibular system, vestibulo-ocular reflex, VOR, bilateral vestibular loss, bilateral vestibular areflexia

1. Introduction

Bilateral vestibulopathy (BVP) is a disorder most often resulting from reduced peripheral vestibular function [1, 2]. Patients can suffer from many disabling symptoms, like imbalance and oscillopsia (illusory visual movement of the environment) [3]. BVP leads to reduced mobility, up to 30 times higher risk of falling, significant loss of quality of life, and an increased socio-economic burden on individuals and on society [4]. The etiologies of BVP are heterogenous and vary from ototoxicity, e.g., from exposure to gentamicin or streptomycin, to genetic factors, e.g., DFNA9, CANVAS or spinocerebellar ataxia, infectious causes, e.g., meningitis, auto immunity, e.g., Cogan's syndrome, trauma, and neurodegenerative diseases [2, 5, 6]. However, in up to 51–75% of patients with BVP, the etiology remains unclear [2–4, 7]. In some patients there may be a transition from presbyvestibulopathy to BVP due to aging or neurodegeneration [8].

A diagnosis of BVP can be made using the diagnostic criteria consensus document of the classification committee of the Bárány Society [9]. However, clinical reality shows that establishing a diagnosis of BVP is challenging in many cases [10]. Pitfalls in diagnosis of BVP include: 1) different clinical pictures with and without dizziness, postural imbalance, vertigo, or oscillopsia, 2) falsely normal clinical bedside head impulse test (HIT) results due to covert compensatory saccades, and 3) frequently normal appearing test results with rotatory chair testing, especially in the higher frequencies around 5 Hz [2, 11–13]. Finally, there is no agreement on normative data for laboratory testing of vestibular function [14]. These challenges can often lead to misdiagnoses or a delay in diagnosis, on average a delay of 33 months, up to more than 8 years [10]. Therefore, prevalence rates for BVP which vary from 28 to 81 per 100.000 people, are very likely to be an underestimation [15, 16]. If so, neurotologists are likely to encounter more of these patients in their daily clinic than previously reported, especially in older patients.

Unfortunately, the prognosis is poor for recovery of vestibular function in patients with BVP [17]. Furthermore, symptoms often do not resolve despite participation in vestibular rehabilitation therapy and cessation of vestibular-suppressant medications. Currently available treatment options have a low likelihood of benefit, especially for unpredictable and high-frequency movements [18, 19].

In the last decade, multiple research groups have proposed the concept of a vestibular implant (VI) to partially restore vestibular function in patients with BVP [20–23]. The VI, which is currently still considered a research device, is in concept analogous to the cochlear implant. It captures head movements with motion sensors and processes them into electrical signals. These electrical signals are then conveyed to the vestibular nerve by electrodes that are implanted near the vestibular nerve branches that innervate the semicircular canals, i.e. the anterior, lateral and posterior canal ampullary nerves, or otolith organs, i.e. the utricular and saccular nerves, collectively called macular nerves [23–26]. Research in humans has demonstrated feasibility of the VI to partially restore vestibular function. First, it was reproducibly shown that it is possible to increase the vestibulo-ocular reflex (VOR) gain with a VI [27–30], and to influence the vestibulocollic and vestibulospinal reflexes [31, 32]. Secondly, functional benefits were demonstrated by restoring the dynamic visual acuity in close-to-reality situations and in the high-frequency range [33, 34]. Therefore, it was concluded that the VI could become a clinically useful device for treatment of patients with BVP, and possibly for other vestibular disorders like chronically uncompensated unilateral vestibulopathy [35]. Patients also have indicated the need for VI research; their main expectation is improvement of their overall mobility (van Stiphout et al., submitted).

Currently, one of the main current questions in the field of VI research is: Whom should be implanted for research? Until now, no uniform implantation criteria for research have been established and as a consequence, research groups have applied different criteria [21, 29, 36]. Therefore, in order to facilitate better comparison between future clinical trials regarding efficacy, safety, and other outcome measures, there is a need for establishing uniform criteria for the selection of patients appropriate for implantation of a VI.

The classification committee of the Bárány society previously described the diagnostic criteria for

BVP, which is also called bilateral vestibular failure, -deficiency, -areflexia, -hypofunction and -loss [9]. These criteria comprise a combination of symptoms and quantitative VOR measures of the lateral semicircular canal. However, function of vertical semicircular canals and otolith organs are not included [9]. The criteria for VI-implantation should go beyond the existing criteria for BVP, in order to demonstrate significant impairment of all canals in all frequency ranges, and (on indication) the otolith organs, since:

1) VI-implantation is practically irreversible for the vestibular system: the diagnosis should therefore be verified by more than one vestibular test;
2) VI-implantation is not restricted to the lateral semicircular canals, but can also involve the other semicircular canals and the otolith organs: the function of these structures should therefore be evaluated before implantation;
3) VI-implantation can impair residual vestibular function, e.g. by surgical plugging of the semicircular canals: the VI should not damage the vestibular system more than it can help restore it.

Furthermore, VI-implantation is a unilateral procedure and may in the future not be restricted to BVP: indications might evolve to include second-side implantation or otherwise to treat chronically uncompensated unilateral vestibulopathy [35]. Although this document only focuses on BVP, other indications for VI-implantation should not be excluded from future research.

The objective of this opinion statement is to provide clear and, as far as possible, evidence-based criteria for VI-implantation in adult patients with BVP in a research setting. Since research regarding this subject is an ongoing process, it is not the aim to define criteria that are "set in stone". To the contrary, this document aims to provide a basis for the first preclinical VI-implantations, and to lay the foundation for future development of VI-implantation [2, 37–40].

2. Methods

Members from all four research groups currently investigating vestibular implantation in humans were invited to participate in this opinion statement by the first author. All four groups participated. In addition, other research collaborators and members of both the Bárány Society and Politzer Society were included. This opinion statement was developed according to the template established by the Classification Committee of the Bárány Society [41], although this is not an official document of the Bárány society. A literature search was performed and draft criteria were developed. These criteria were supported by notes and comments. An iterative process of discussion and refinement by all authors resulted in the final opinion statement.

3. VI-implantation criteria

The diagnostic criteria of BVP according to the Bárány Society were modified and extended, since they are a necessary but not sufficient prerequisite. Therefore, the following more precise criteria are recommended as provisional criteria for the selection of patients appropriate for implantation with a VI[1]. To be eligible for VI-implantation, patients must meet all of the following criteria:

A. Chronic vestibular syndrome with the following disabling[2] symptoms:
   - Unsteadiness when walking or standing plus at least one of the following:
     - Movement-induced blurred vision or oscillopsia during walking or quick head/body movements, and/or
     - Worsening of unsteadiness in darkness and/or on uneven ground
B. Symptoms greatest during head movement
C. Bilaterally reduced or absent angular VOR function documented by *at least one of the following major criteria*:
   - Bilaterally pathological horizontal angular VOR gain ≤ 0.6 *and at least bilaterally one vertical angular VOR gain* < 0.7, measured by the video-HIT or scleral-coil technique[3]
   - Reduced caloric response (sum of bithermal max. peak SPV on each side $\leq 6^\circ$/sec for 30 sec water stimuli or $<10^\circ$/sec for 60 sec water or air stimuli)[4]
   - Reduced horizontal angular VOR gain ≤ 0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax = 50°/sec) and a phase lead $>68^\circ$ (time constant <5 sec)

C'. Obligatory only in case of implantation of otolith structures: Bilaterally absent cVEMP and oVEMP responses[5]

D. In case only one or two criteria from C are matched (and also criterion C' is matched in case of otolith stimulation), the remaining test(s) should comply with *the following minor criteria*:
   - Bilaterally pathological VOR gains of at least two semicircular canals <0.7, measured by the video-HIT or scleral-coil technique
   - Reduced caloric response (sum of bithermal max. peak SPV on each side <10°/sec for water and air stimuli of ≥30 sec)
   - Reduced horizontal angular VOR gain <0.2 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax = 50°/sec)

E. Symptoms are not better accounted for by another disease

F. Fitting the additional requirements relevant to initial preclinical trials
   - Age 18 years and above
   - BVP results most likely from a peripheral origin[6]
   - Vestibular function and symptoms are unlikely to significantly improve, according to the duration of symptoms and clinicians' estimations[7]
   - Patent vestibular end-organ and intact vestibular nerve[8]
   - Ability to use the device and follow a personalized rehabilitation program[9]
   - Ability to undergo the surgery[10]

G. No current psychological or psychiatric disorder that could significantly interfere with use or evaluation of the VI[11]

4. Notes

1. It is advised to become familiar with the notes and comments of the diagnostic criteria for BVP established by the Bárány Society [9] because patients meeting diagnostic criteria for BVP might also meet these candidacy criteria for vestibular implantation.
2. Disabling is considered as "interfering with activities of daily living". It is up to the patient and clinician to decide whether symptoms are disabling in each specific case. A Dizziness Handicap Inventory total score of >30 would be preferred [42].
3. vHIT should be performed and analyzed by a trained examiner, using a validated vHIT device and taking precautions to minimize vHIT goggle slip with respect to the skull, which is common and typically results in artifacts that influence vHIT VOR gain. VOR gain is the ratio between angular eye velocity and angular head velocity. For these implantation criteria, two options are possible to calculate the VOR gain: 1) the ratio of the area under the curve of angular eye velocity over time, divided by the area under the curve of angular head velocity over time, or; 2) angular eye velocity at a fixed time (typically around 60 ms after onset of the impulse), divided by angular head velocity at the same time [9]. It is advised to calculate the VOR-gain of each canal using a minimum of seven artifact-free impulses. Head impulses should have a peak acceleration of at least 1000°/sec^2 [11].
4. The caloric test should preferably be performed using cold and warm (30° and 44° respectively) irrigations of water, lasting for ≥30 seconds, with a total volume of at least 250 ml. Alternatively, warm and cool air insufflation (8 liters/min) can be used instead of water. Air caloric tests should only be performed with a 60 sec stimulus to be able to comply with criterion C. Precautions should be used to ensure that VOR responses to a prior stimulus are not falsely recorded as responses to a subsequent stimulus due to persistence of the previous response. Therefore, techniques designed to minimize persistence of caloric effects from one stimulus trial that could confound measurements during a subsequent trial, such as interposing a stimulus interval of five minutes between successive monothermal irrigations, should be used [11].
5. Criterion C' only applies when otolith implantation is considered. If only semicircular canal implantation is considered, VEMPs do not have to be absent in the candidate ear. However, relative function of the left and right utricle and saccule as quantified by VEMP responses, should be considered along with pre-operative semicircular canal and cochlear function when deciding whether and which side to implant.
6. A disorder of peripheral origin is defined by having an etiology localized to the inner ear (e.g. hair cell loss or dysfunction due to gentamicin

ototoxicity, a genetic abnormality, infection, ischemia, trauma or other labyrinthine injury). No persistent central vestibular involvement can be present, e.g., no tumors of the vestibular nerve, no brainstem lesions, and no cerebellar ataxia. An idiopathic BVP without any central vestibular signs on physical examination including ocular motor testing and with a normal MRI of the brain and internal auditory canals, can be regarded as "most likely from a peripheral origin." Disorders with clear signs of structural nerve pathology, e.g., vestibular schwannoma or after vestibular neurectomy, and disorders with indications that the vestibular nerves might not be functioning properly, e.g., after radiotherapy of the cerebellopontine angle, should not be considered for VI-implantation.

7. The clinician should estimate that it is very unlikely vestibular function will recover to values higher than the criteria mentioned above, and that vestibular symptoms will significantly improve. In cases that do not require early implantation (see "Comments - Timing of implantation and rehabilitation"), it is preferred to have a "wait and see period" of at least six months from onset of symptoms, including an adequate vestibular rehabilitation program with the patient off all vestibular suppressant medications for at least three months. After that, it is up to the clinician to estimate whether vestibular implantation can be considered. If there is a delay in diagnosis of BVP, and a patient has already experienced symptoms typical of BVP for more than 6 months [10], vestibular implantation can be considered without an additional "wait and see period" as long as adequate treatment, e.g., rehabilitation off vestibular suppressants, has already been provided. In cases that require early implantation (e.g. meningitis with concern for impending labyrinthitis ossificans), it is up to the clinician to estimate whether vestibular function and symptoms are likely to recover or not. If the probability is low, vestibular implantation can be considered.
8. Prior to intralabyrinthine electrode insertion, the structures to be implanted (semicircular canals and/or otolith organs) should be determined to be patent for surgical insertion as determined by high resolution temporal bone CT. In conditions with an increased risk of a non-patent labyrinth, e.g. meningitis with concern for development of labyrinthitis ossificans, patency should be checked with MRI and/or CT. Patients without a patent labyrinth are not yet considered for intralabyrinthine electrode insertion. There should be no clear signs of structural nerve pathology or indications that the nerve could not be functioning properly (see note 6).
9. Factors for successful use of a VI system and accomplishment of a personal rehabilitation program include, among others: ability to understand and use the system, ability to tolerate the external device and implant, e.g. no allergy for the components of the device, ability to tolerate repeated activation and deactivation of the device, ability to fulfill the rehabilitation program with respect to physical condition and logistic factors, e.g. travel distance, willingness to avoid vestibular suppressant medications that can interfere with central nervous system compensation after sudden onset of asymmetry in vestibular input from the two ears.
10. The whole vestibular implant team should agree on the operability of the patient. This includes considering co-morbidities, e.g. American Society of Anesthesiologists Physical Status Classification System [43], and the status of the middle ear on the side to be implanted, e.g. no chronic otitis media.
11. If a psychological or psychiatric disorder, e.g., depression, anxiety disorder, borderline personality disorder, is present and considered likely to hinder thorough evaluation and treatment of the VI recipient according to the clinician, VI-implantation should be avoided. Persistent Postural Perceptual Dizziness (PPPD) is not considered an exclusion criterion, nor is a history of psychological or psychiatric disorders that are not currently present or are judged not likely to relapse during the research trial.

5. Comments

5.1. Vestibular implantation criteria differ from bilateral vestibulopathy criteria

In its current forms, vestibular implantation surgery can irreversibly impair any residual vestibular function. Since a vestibular test is never infallible, e.g. the caloric test results can be subject to anatomical variabilities leading to false positive outcomes [11], a two-step paradigm for vestibular testing was imple-

mented. This implies that one abnormal vestibular test is not enough to confirm implantation eligibility: a double confirmation from the other two vestibular tests is needed. In contrast to BVP diagnostic criteria, all vestibular tests mentioned above are suggested to screen for implantation eligibility. However, not all patients suffering from severe BVP who might be candidates for vestibular implantation show consistently low vestibular test results on all vestibular tests. For example, a subject might have a caloric response of $\leq 6^{\circ}$/sec but an angular vHIT VOR gain of >0.6 instead of $\leq$0.6 [42]. Therefore, for the confirmation step, criteria for vestibular test results are less strict (see point D of the criteria). Due to this double confirmation, the vestibular test results under point C were changed from "<" to "$\leq$". Whether all these values are still low enough to prevent clinically relevant damage of useful sensory function by vestibular implantation, should still be investigated.

Criteria in point F were included to increase the likelihood that VI-implantation will be safe and effective.

5.2. Disabling symptoms

No questionnaires are available currently that are specifically designed to determine the level of disability in BVP patients. Therefore, it was decided to defer to clinician expertise and opinion regarding the disability due to BVP in each specific case. A total score on the Dizziness Handicap Inventory of >30 would be preferred, since this could show at least moderate handicap [44, 45]. It was decided not to make this score obligatory since in a cohort of 90 patients with bilateral vestibulopathy, more than 40% of the patients scored below 31, while still a subset of them reported significant complaints [42]. This could imply that the Dizziness Handicap Inventory might not be the best tool to quantify the handicap in bilateral vestibulopathy patients. However, it could still help guide some clinicians in their judgment.

5.3. Types of surgery and implantation criteria

For vestibular implantation, two types of surgery are possible: intralabyrinthine, i.e., fenestrating the semicircular canals and/or vestibulum and inserting the electrodes, and extralabyrinthine, i.e., not intentionally opening the semicircular canals and/or vestibulum and trying to place the electrodes directly on the nerves close to the semicircular canals or the internal auditory canal [46]. The intralabyrinthine approach modifies the biomechanical properties of the canals and can lead to loss of the residual inner ear function including hearing loss. Theoretically, the extralabyrinthine approach might reduce this risk. However, the full risks of the extralabyrinthine approach are not yet fully determined, and the facial nerve is exposed to a higher risk with the extralabyrinthine approach [47]. Therefore, it was decided to consider both techniques as being associated with a risk of inducing vestibular hypofunction.

Tests of otolith function were not included in the diagnostic criteria for bilateral vestibulopathy. Since implantation of otolith structures [23] is almost certain to cause otolith hypofunction due to mechanical disruption of the membranous labyrinth during implantation, oVEMPS and cVEMPS were included in the implantation criteria when the otolith structures are being considered for implantation (see C').

5.4. Video head impulse testing

Based on previous findings in BVP patients, it was chosen to set the angular VOR gain of the vertical semicircular canals and the gain of the lateral semicircular canal in those patients whose caloric test or rotatory chair test already fit the implantation criteria to <0.7 [42]. This value might be subject to change, depending on new insights. Only one vertical semicircular canal on each side needs to fulfill the criterion of an angular VOR gain <0.7, since it was shown that selective sparing of a single semicircular canal is possible [48] while a clinically relevant BVP is still present, making the patient probably eligible for implantation. It should be noted that artifacts frequently occur [49] when using the Video Head Impulse Test to assess the lateral and especially the vertical semicircular canals. Therefore, test results that are noisy, distorted by artifacts, or otherwise unreliable, should not be included in the analysis [2].

Non-quantitative head impulse testing (HIT), i.e., a physical examination without a means of high speed eye movement recording, was not included in the implantation criteria, due to its limited sensitivity and specificity in the setting of covert corrective saccades [12]. Bedside HIT also is not able to quantify precisely the effect of the vestibular implant after implantation, in contrast to vHIT or scleral coil oculography.

The suppression head impulse paradigm (SHIMP) was not included in the criteria, since vHIT has already been shown to be effective in demonstrat-

ing the vestibular deficit. The clinical relevance of SHIMPs in BVP should still be determined [50].

5.5. The caloric test

Since not all laboratories are able to use water irrigations, e.g., due to regulations, it was decided to also include the air caloric test in the VI-implantation criteria. When using the air caloric test, it is advised to irrigate at 8 liters/min for at least 60 seconds to be able to comply with criterion C, since air might be a less strong stimulus than water. This paradigm is advised based on the experience with the air caloric test in patients following VI-implantation [29]. In case of a 60 sec stimulus (water or air), $<10^\circ$/sec is used as a criterion rather than $\leq 6^\circ$/sec because stimulation for an additional 30 sec beyond the initial 30 sec of stimulation is very likely to increase the magnitude of the response.

Caloric test values for implantation are defined in point D as the sum of bithermal caloric irrigations $<10^\circ$/sec on each side using irrigations for $\geq$30 seconds. This criterion is based on previous reports in which patients with a sum of all bithermal irrigations $<20^\circ$/sec still reported significant imbalance and/or oscillopsia [2, 39]. This might make these patients candidates for vestibular implantation. However, these values might still be subject to change, depending on new insights. In both criteria C and D, water and air stimuli have the same cut-off value when irrigating for 60 sec (criterion C) and $\geq$30 sec (criterion D). The committee is aware that these different stimuli probably do not lead to equal results. However, experience with caloric test results as an inclusion criterion for vestibular implantation only exists with 30 sec water stimuli and 60 sec air stimuli. In order to facilitate centers who might use 60 sec water stimuli, this stimulation paradigm was added to the criteria although specific values for vestibular implantation when using 60 sec water stimuli are not available.

Ice water caloric irrigations are not required in the implantation criteria since a sum of bithermal max. peak SPV on each side $\leq 6^\circ$/sec for $\geq$30 sec water stimuli or $<10^\circ$/sec for 60 sec stimuli, was judged to be adequate as a major criterion (point C of criteria) for vestibular implantation.

5.6. Rotatory chair testing

The criterion for horizontal angular VOR gain measured with sinusoidal stimulation on a rotatory chair is defined in point D as <0.2. This value is higher than the one used in the diagnostic criteria for BVP. It has been shown that patients with BVP with a horizontal VOR gain $\geq$0.1 at a stimulus frequency of 0.1 Hz still experienced significant imbalance and/or oscillopsia, making them possible candidates for vestibular implantation [2]. The upper value of <0.2 is based on expert opinion only, and should still be investigated further in the future. For very low VOR responses, the calculation of VOR gain, and especially of VOR phase and VOR time constants may be unreliable. Results should therefore be evaluated critically and interpreted with caution [2].

5.7. Vestibular evoked myogenic potentials

It is preferred to test cVEMP and oVEMP responses before and after vestibular implantation. VEMP responses must be compared to normative values established for the system used by the particular laboratory [51]. In case of implantation of otolith structures, cVEMP and oVEMP responses should be absent bilaterally. Although the otolith system can probably have a gradual decline in function and does not work as an "on-off" system [52], VEMPS are not currently clinically suited to detect subtle changes in otolith function or define "minimal residual otolith function". It was decided therefore that otolith implantation should only be performed in patients with bilaterally absent VEMP responses and not take into account other parameters, e.g. increase of thresholds. More specifically, both cVEMP and oVEMP responses should be absent, since otolith implantation might interfere with the function of both otolith organs. With absent cVEMP and oVEMP responses, it is expected that the benefit of vestibular implantation will be higher than the drawbacks of the potential iatrogenically induced vestibular hypofunction due to vestibular implantation of the otolith endorgans. This criterion is subject to change, depending on new insights. Note that in case of otolith endorgan implantation, VEMPs are used in addition to the other criteria; that is, the other criteria should also be fulfilled. These patients should also have bilaterally impaired semicircular canal function and, therefore, patients suffering from so-called "dissociated bilateral vestibulopathy" are currently not candidates for VI-implantation [53].

VEMP responses do not need to be absent when only implanting the semicircular canals. Many symp-

tomatic patients with BVP can have preserved otolith responses [37, 54–56]. The presence of VEMP responses indicates that on an aggregate basis some otolithic signal is present, but it does not demonstrate useful otolith function. Furthermore, correct implantation of semicircular canals and electrical stimulation does not necessarily lead to destruction of the otolith organs [57]. Nevertheless, the committee strongly advises to always measure VEMP responses before and after vestibular implantation, to investigate the influence of vestibular implantation on otolith structures and their responses.

5.8. Implantation criteria include only adults

At this moment, evidence regarding the effects of BVP in the pediatric population is considered to be too scarce to consider implanting the pediatric population. It is advised by the committee to first investigate this subject further in adults, and extend this knowledge to the development of outcome measures for vestibular implantation specifically tailored to the pediatric population.

5.9. Implanting only BVP of peripheral origin

The VI replaces the vestibular organ by capturing head motion and sending electrical signals to the vestibular nerves. A VI-implantation attempts to serve as an artificial replacement of the peripheral vestibular organ and it does not replace the whole vestibular nerve or central vestibular system. Only few human implantations have been performed until now [21, 23, 29, 36] and the influence of deficits of the vestibular nerve and central vestibular system on performance of the VI have not been studied yet. However, it is expected that with current techniques, the VI will not effectively treat a deficit of the vestibular nerve or the central vestibular system. Currently, it is therefore preferred to implant a patient only when symptoms mainly result from an inner ear deficit. In the future, it should be investigated whether BVP not only or not mainly resulting from an inner ear deficit, can be treated with a VI.

5.10. Timing of implantation and rehabilitation

The prognosis of BVP is poor in most cases [11]. Most patients do not show significant recovery from their vestibular function loss. In addition, six months after a vestibular nerve injury, recovery is probably complete [58]. Therefore, a "wait and see" period of at least 6 months after the onset of symptoms was chosen before considering vestibular implantation. In cases with a possible reversible etiology or that require early implantation (e.g. labyrinthitis ossificans), the "wait and see" period is tailored to the prognosis of the disorder comparable to cochlear implantation. Due to lack of sufficient tools to predict the prognosis for each specific case, it was decided to value the clinicians' expertise and opinion regarding the prognosis of recovery.

Data are not yet available on the effectiveness of VI-implantation and the influence of etiology and duration of the disease on efficacy. It is hypothesized that "dying back" of the vestibular nerve could compromise effective vestibular stimulation, although long standing vestibular losses have also shown promising results with a VI [29, 30, 35, 36]. For now, it is preferred to avoid a "wait and see" period of more than six months, if possible. Therefore, if BVP already exists for more than six months without any improvement, the "wait and see" period of six months is not applicable. The "wait and see" period of six months after onset of the disease also facilitates time for an adequate vestibular rehabilitation program. An adequate vestibular rehabilitation program should include once a week supervised rehabilitation sessions for three months, in addition to a daily home exercise program, as advised by the American Physical Therapy Association [59]. If symptoms are present for more than six months, it should be decided for each individual case whether vestibular rehabilitation is still indicated.

5.11. Imaging

An MRI-scan of the internal auditory canals and cerebellopontine angle is advised in the vestibular implantation work-up for two reasons: 1) to evaluate the presence or absence of vestibular nerves, and to evaluate the patency of the labyrinth in cases with an increased risk of a non-patent labyrinth (see note 8). Conditions with an absent vestibular nerve preclude VI-implantation on the side with the absent nerve. Conditions without a patent labyrinth, e.g., labyrinthitis ossificans, are not now considered for intralabyrinthine electrode insertion although in the future a "vestibular drill-out" might be considered; and 2) to screen for additional findings in cases without a definite etiology. Significant findings on MRI have been reported in 14% of BVP-cases. Some of these findings might hinder vestibular implantation

or influence the sidedness of implantation, e.g. unilateral vestibular schwannoma [2]. It is preferred to use high resolution (<1 mm) T1 and T2 images of the cerebellopontine angle, preferably with intravenous gadolinium contrast, to be able to detect extralabyrinthine and intralabyrinthine disorders, e.g., an intralabyrinthine vestibular schwannoma. A CT scan of the mastoid region is helpful for surgical planning, to assess labyrinth patency, and to rule out middle ear or mastoid disease that could prevent safe and successful vestibular implantation.

5.12. Hearing and vestibular implantation

Hearing status has explicitly not been incorporated in the vestibular implantation criteria. Hearing might be preserved in the acute phase after intralabyrinthine implantation, although this is not always the case [60]. The extralabyrinthine approach was developed in hopes of reducing the risk of hearing loss or creating vestibular hypofunction [47, 61]. However, at the present time, only deaf patients have been implanted with the extralabyrinthine approach. The safety for hearing has therefore not yet been determined.

Two versions of the vestibular implant are available: the vestibular implant aimed at only restoring vestibular function and the vestibulo-cochlear implant aimed at restoring vestibular and hearing function by incorporating also a cochlear implant. Taking the available evidence into account, it was decided that in case of a vestibular implant only, it is too early to develop formal auditory criteria. Hearing status is therefore not a determining factor for implantation, although the hearing status of both ears should be taken into account. The better hearing ear should not be implanted. Furthermore, it is advised to only implant patients in whom, according to the clinician, coping mechanisms and the hearing status of the contralateral ear are sufficient to be able to successfully cope with a possible single sided deafness on the implanted side. With a vestibulo-cochlear implant, criteria for cochlear implantation in the ear to be implanted are applicable, in addition to the criteria for vestibular implantation.

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4.5. Patente

4.5.1. Información de la patente

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Inventores: Angel Ramos Macias, Angel Ramos de Miguel, Koen Erik Van den Heuvel and Mattheus Johannes Petrus Killian

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(54) **VESTIBULAR STIMULATION PROSTHESIS**

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(21) Appl. No.: **16/816,965**

(22) Filed: **Mar. 12, 2020**

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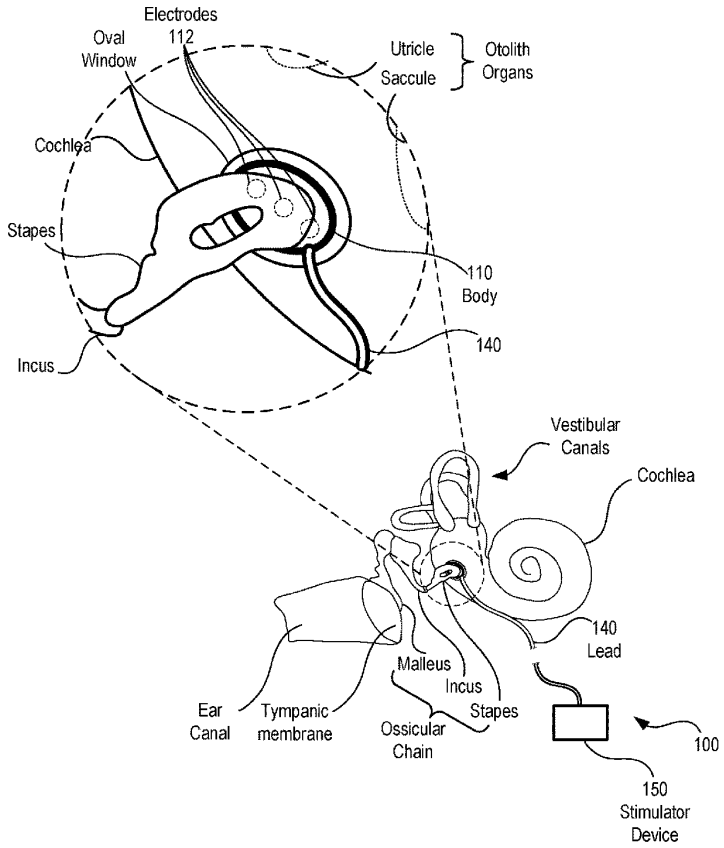
A61N 1/05	(2006.01)
A61N 1/372	(2006.01)

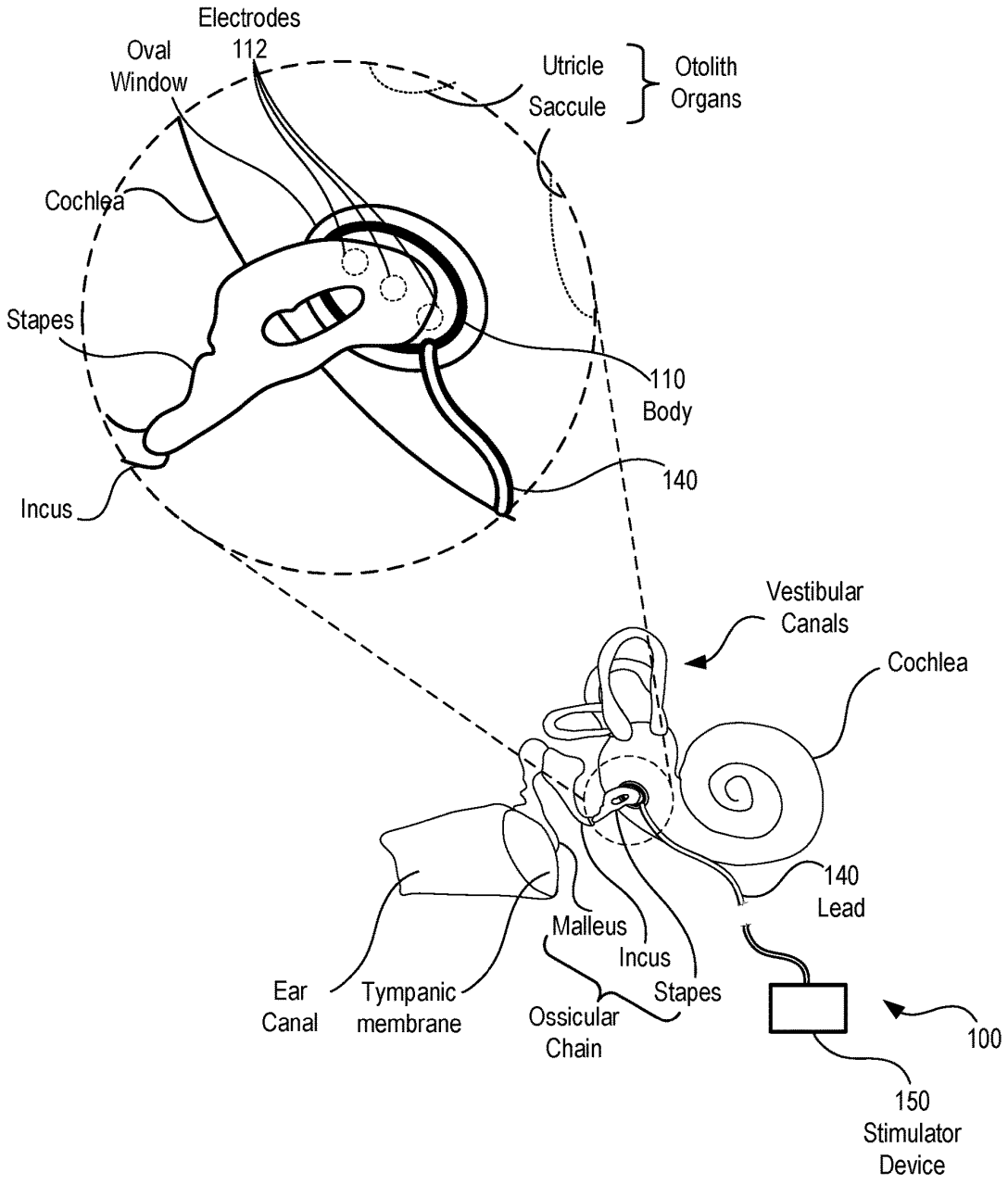
(52) **U.S. Cl.**

CPC ***A61N 1/3606*** (2013.01); ***A61N 1/36142*** (2013.01); ***A61N 1/372*** (2013.01); ***A61N 1/0541*** (2013.01)

(57) **ABSTRACT**

A vestibular stimulation prosthesis can restore vestibular function in recipients having vestibular deficiency. In an example, a body is appended onto or within the recipient's ossicular chain such that the body directly interfaces with an oval window of an inner ear of the recipient. Electrical stimulation is provided using one or more electrodes of the body to stimulate the vestibular system and thereby restore vestibular functioning. In an example, a stimulator device connected to the body via a lead is also implanted. The stimulator device can have a small and convenient form factor. In some instances, the stimulator device is a stand-alone device that is configured to provide stimulation to the recipient's vestibular system without respect to signals received from devices external to the recipient. In some implementations, the stimulator device is a component of a sensory prosthesis (e.g., a cochlear implant or bionic eye) or another medical device.

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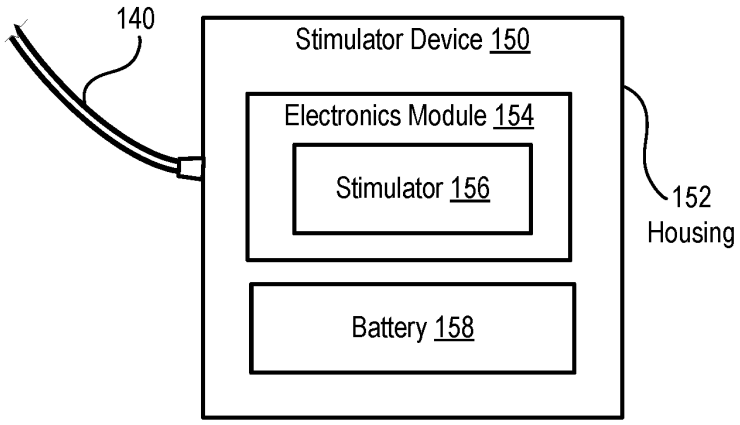
Stimulator
Device

FIG. 1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Electronics Module 154
Stimulator 156
Battery 158
152
Housing

FIG. 2

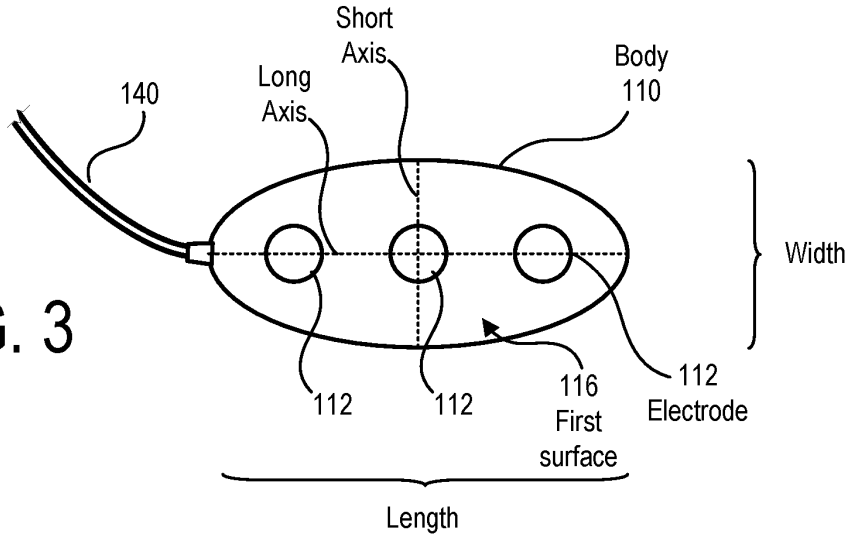
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FIG. 3

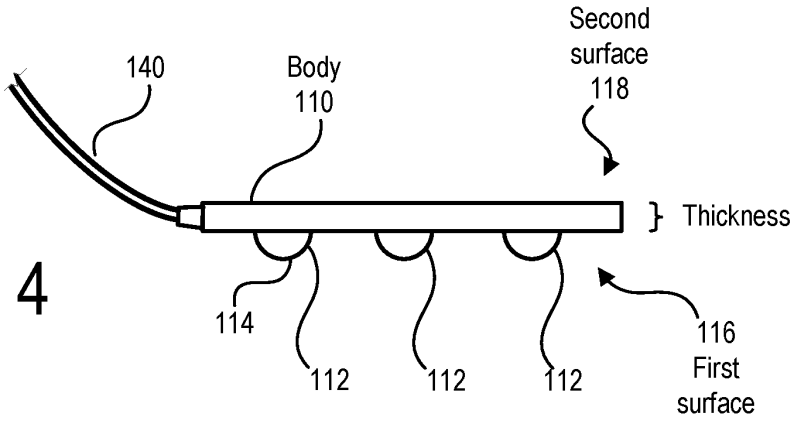
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FIG. 4

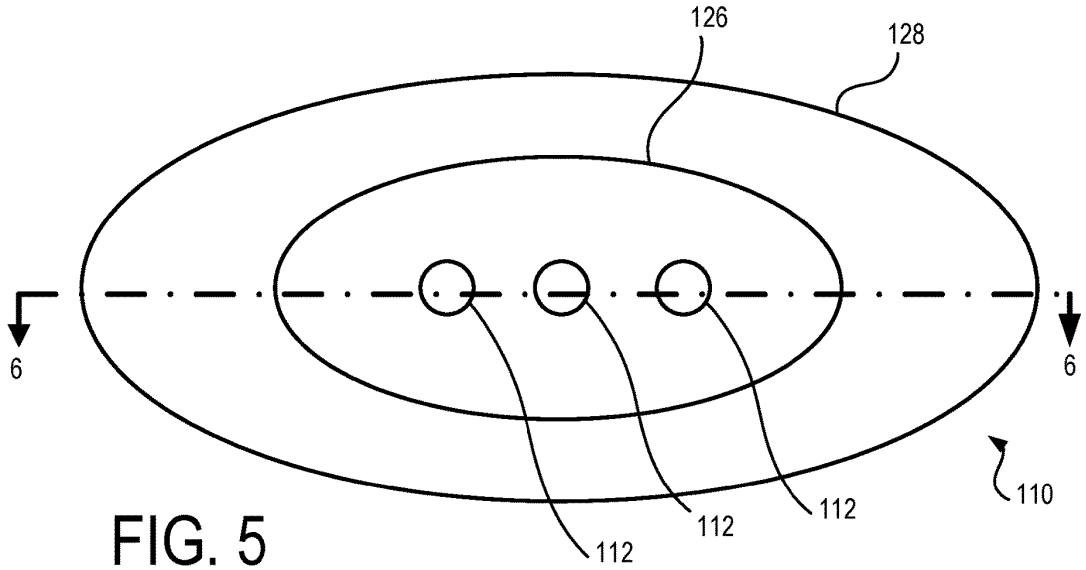


FIG. 5

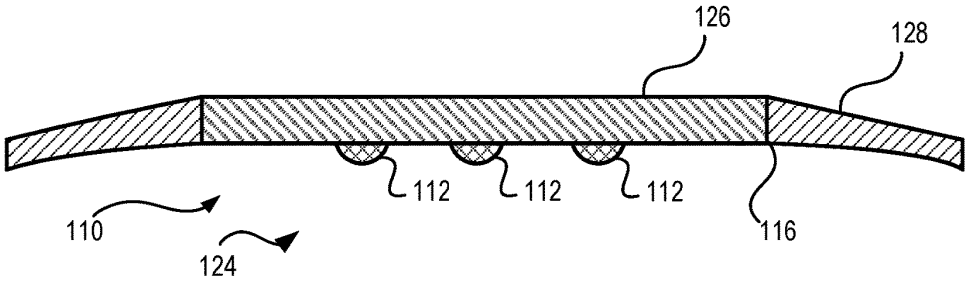


FIG. 6

FIG. 7

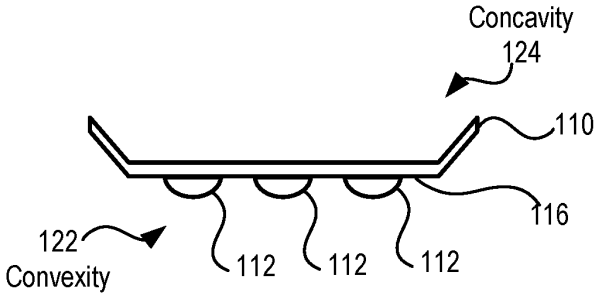


FIG. 8

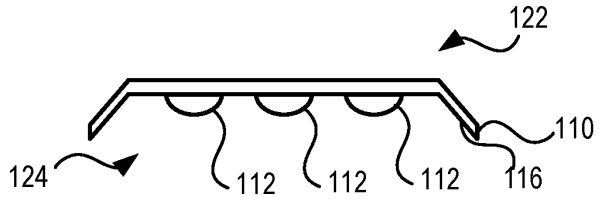


FIG. 9

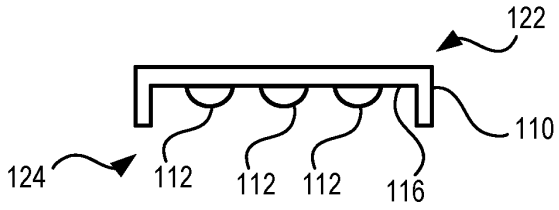


FIG. 10

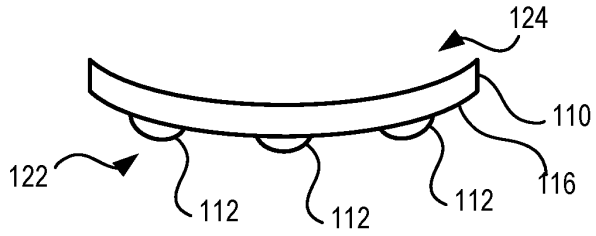
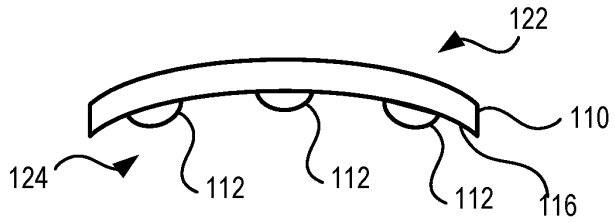


FIG. 11



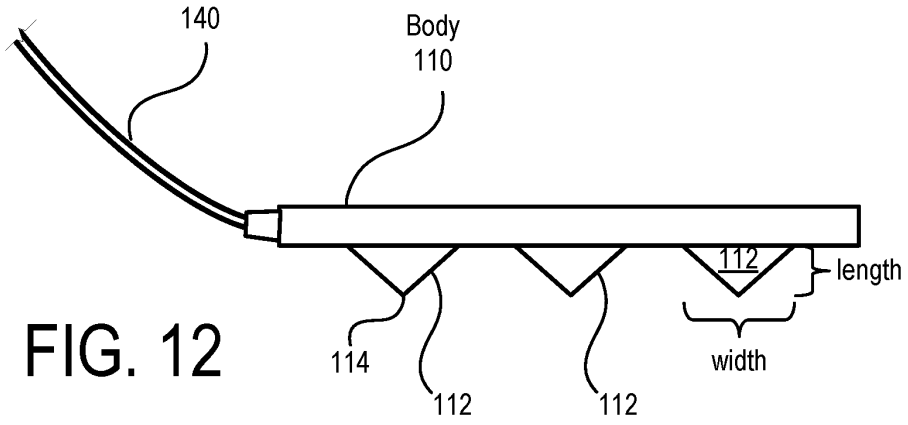

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FIG. 12

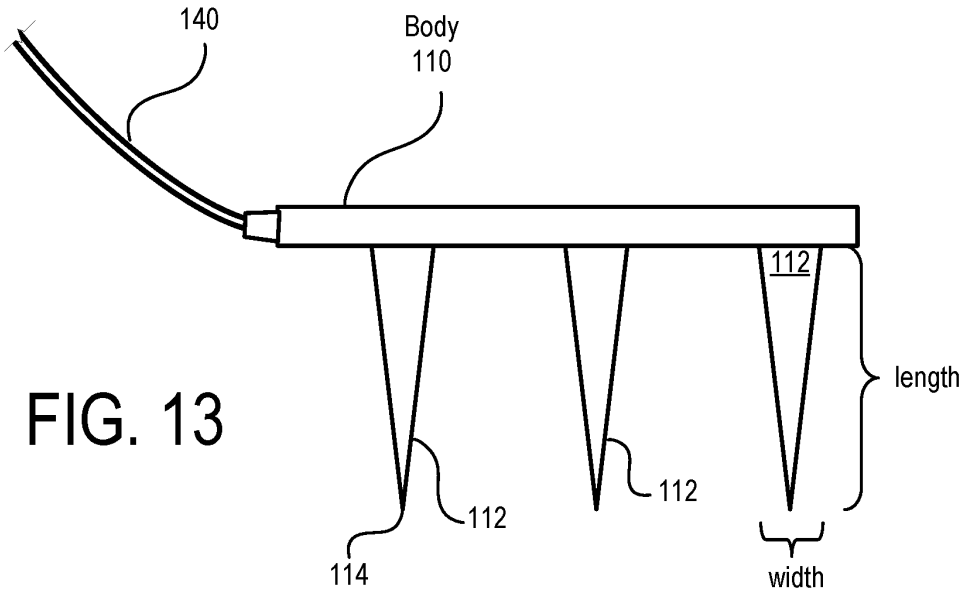
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FIG. 13

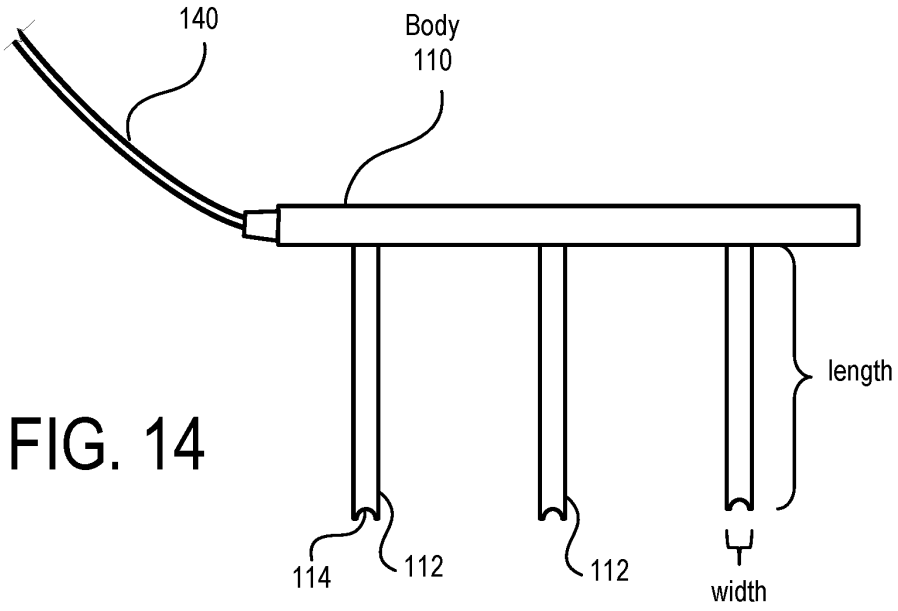
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FIG. 14

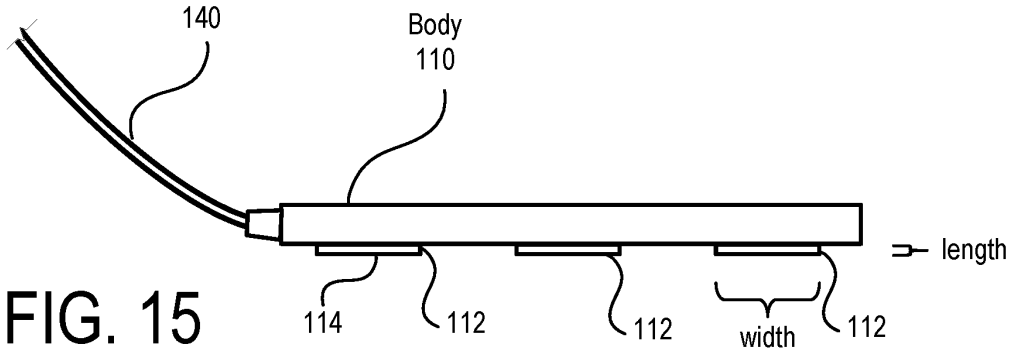
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FIG. 15

FIG. 16

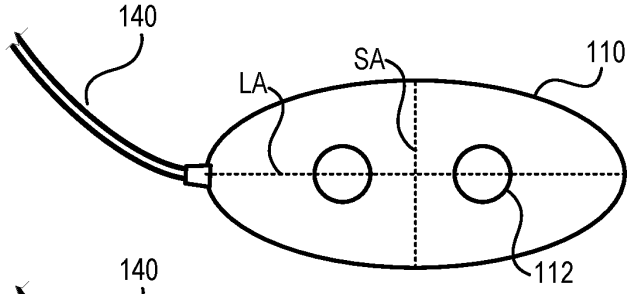


FIG. 17

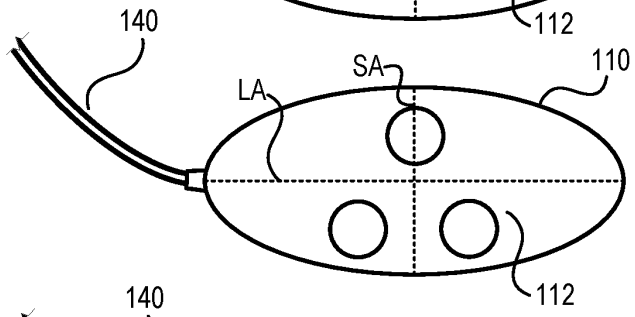


FIG. 18

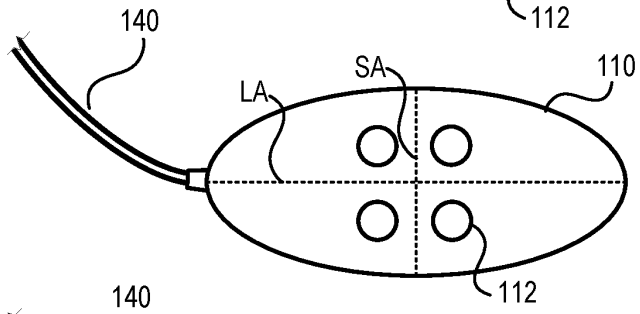


FIG. 19

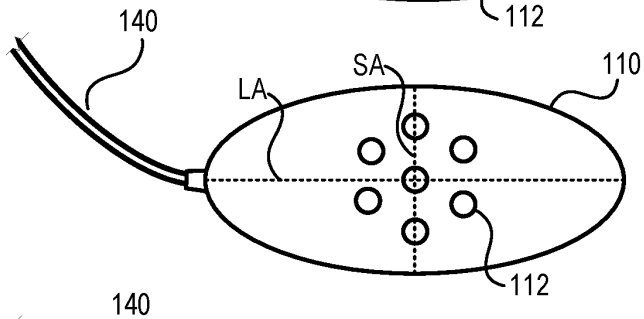
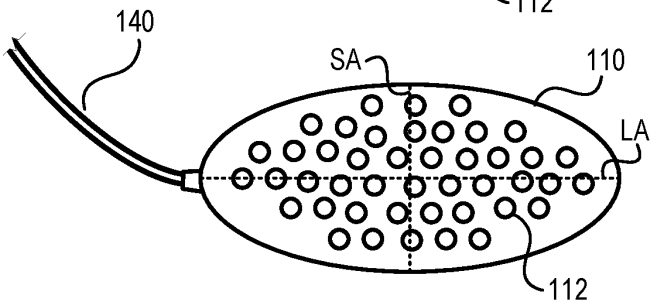


FIG. 20



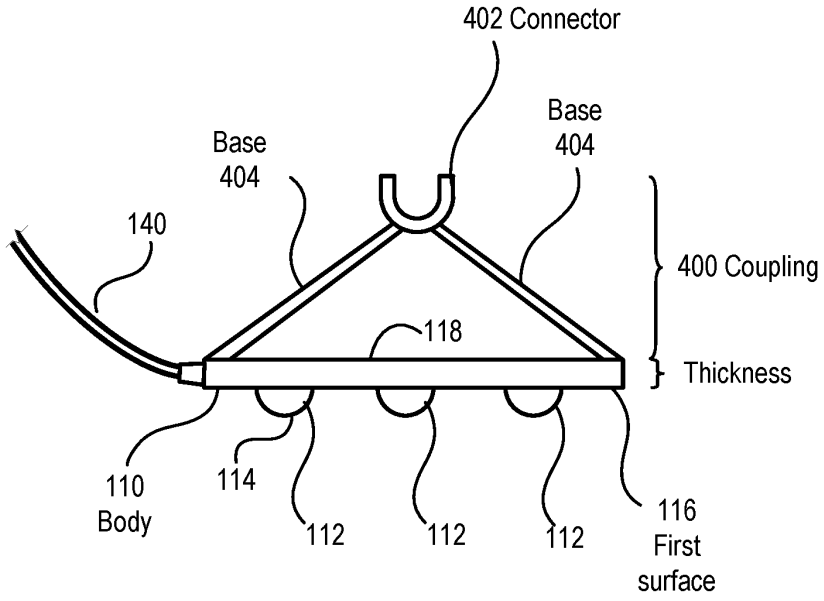

402 Connector
Base
404
Base
404
140
400 Coupling
118
Thickness
110
Body
114
112
112
112
116
First
surface

FIG. 21

FIG. 22

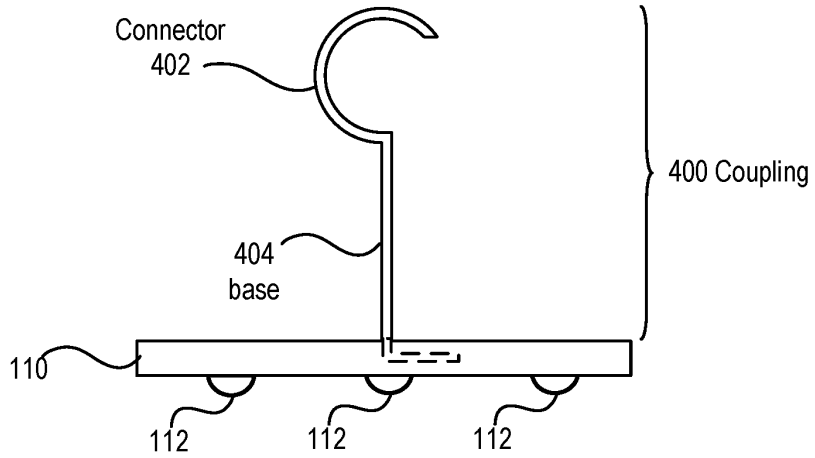

Connector
402
400 Coupling
404
base
110
112
112
112

FIG. 23

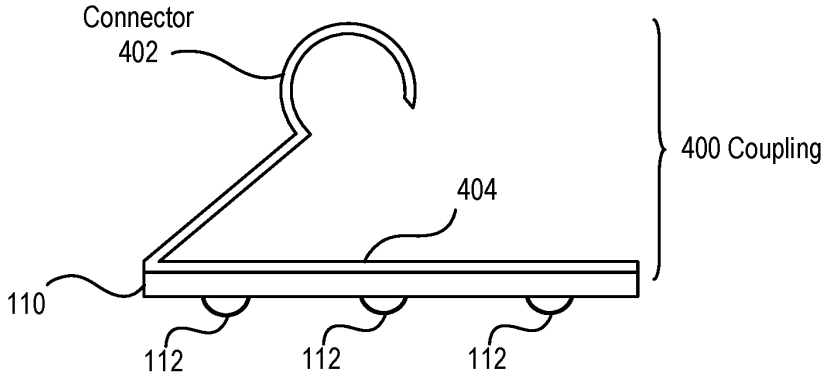

Connector
402
400 Coupling
404
110
112
112
112

FIG. 24

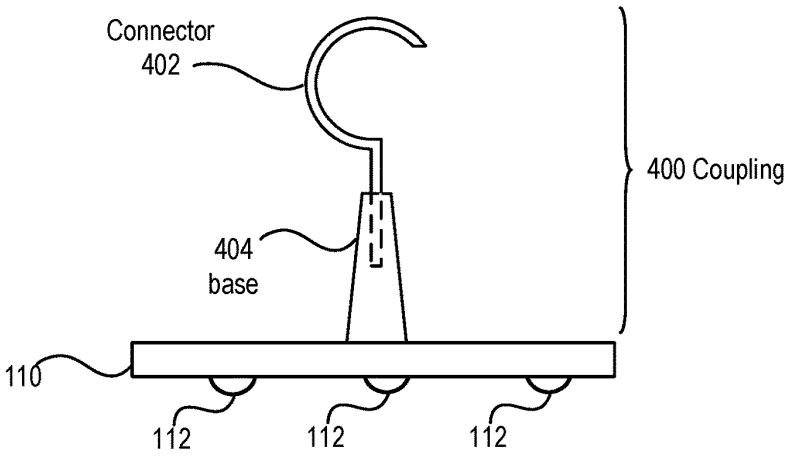
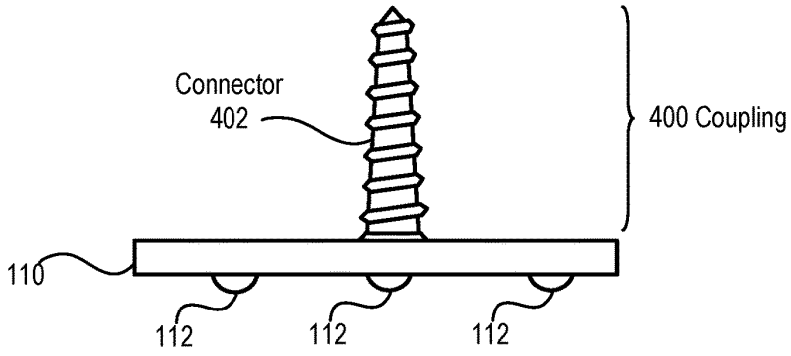

Connector
402
400 Coupling
404
base
110
112
112
112

FIG. 25


Connector
402
400 Coupling
110
112
112
112

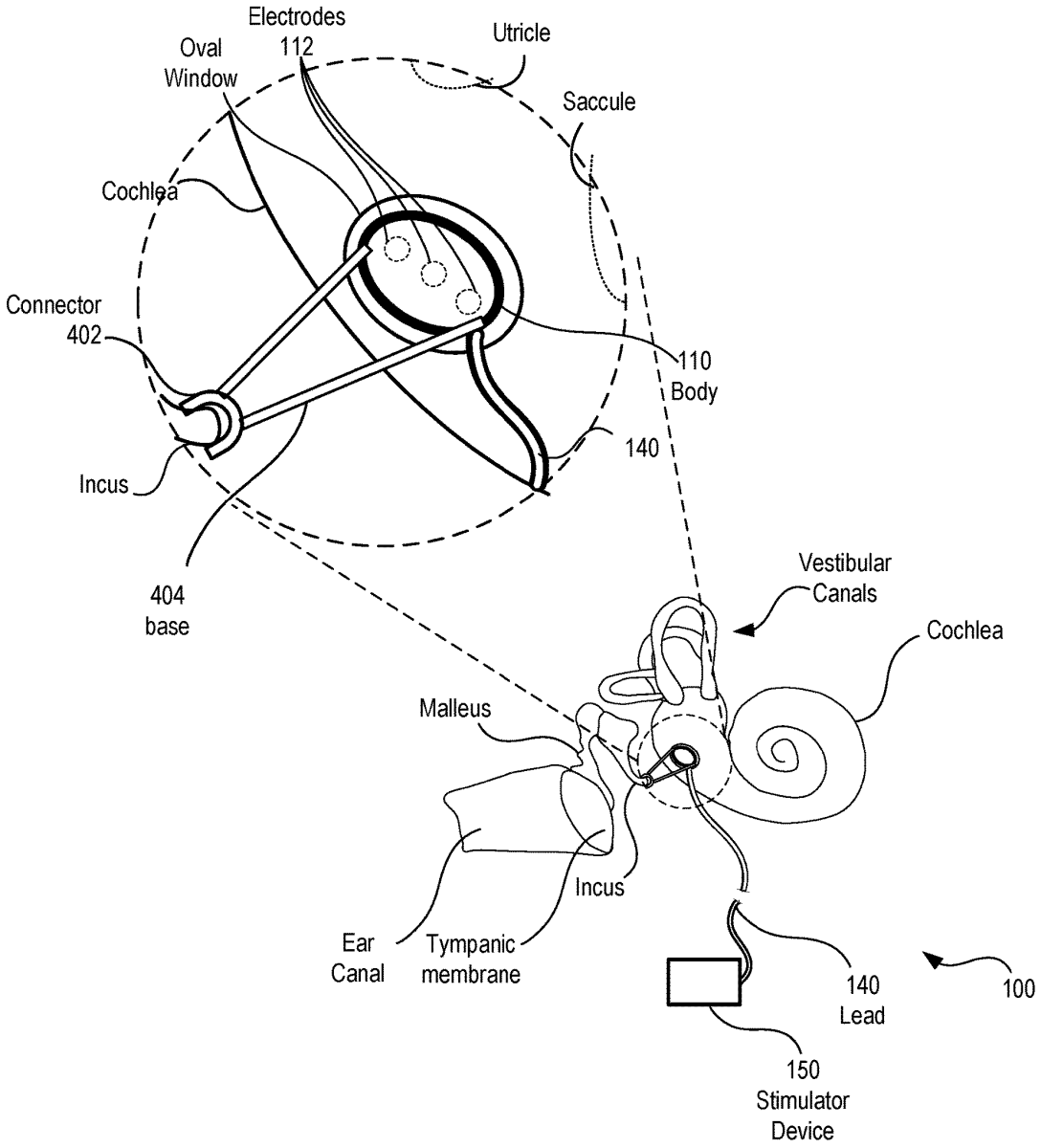

Electrodes
112
Oval
Window
Utricle
Saccule
Cochlea
Connector
402
110
Body
140
Incus
404
base
Vestibular
Canals
Cochlea
Malleus
Incus
Ear
Canal
Tympanic
membrane
140
Lead
100
150
Stimulator
Device

FIG. 26

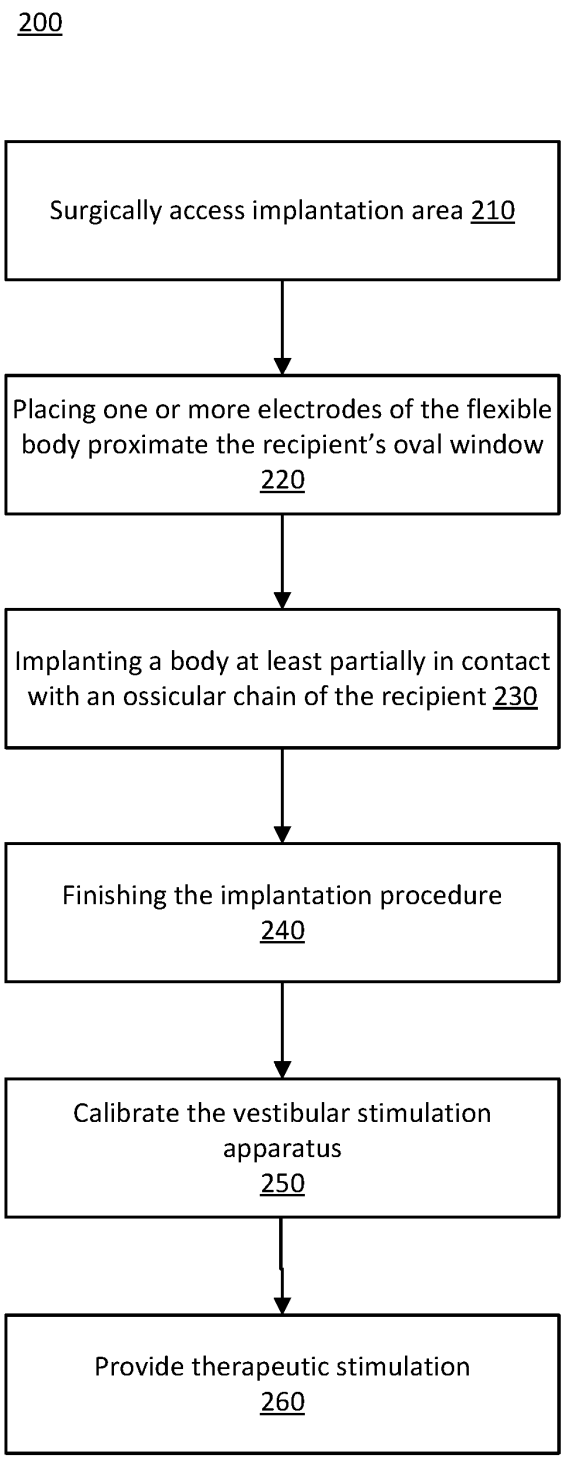

200
Surgically access implantation area 210
Placing one or more electrodes of the flexible body proximate the recipient's oval window 220
Implanting a body at least partially in contact with an ossicular chain of the recipient 230
Finishing the implantation procedure 240
Calibrate the vestibular stimulation apparatus 250
Provide therapeutic stimulation 260

FIG. 27

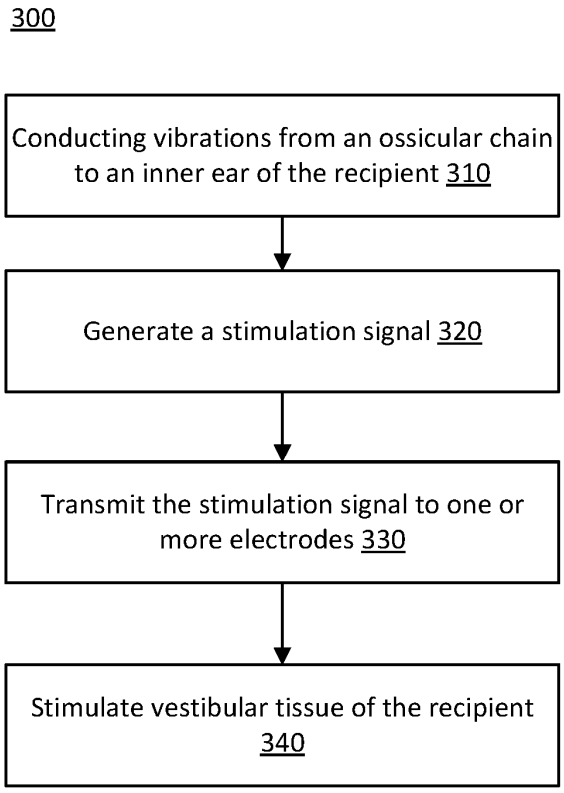

300
Conducting vibrations from an ossicular chain to an inner ear of the recipient 310
Generate a stimulation signal 320
Transmit the stimulation signal to one or more electrodes 330
Stimulate vestibular tissue of the recipient 340

FIG. 28

FIG. 29

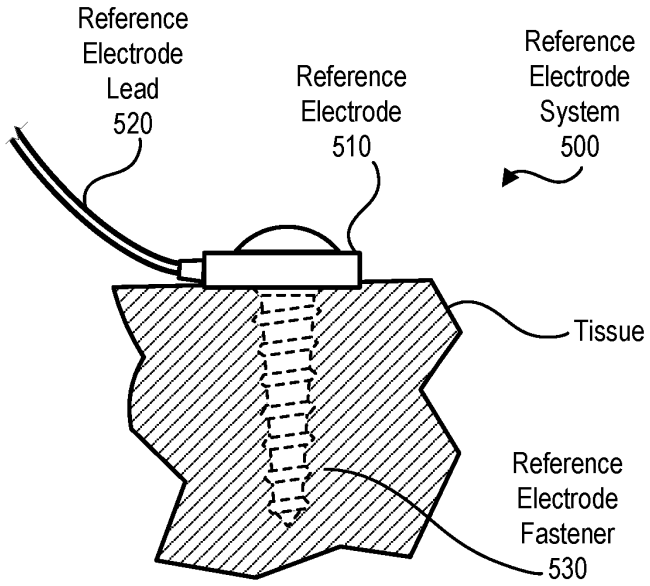


FIG. 30

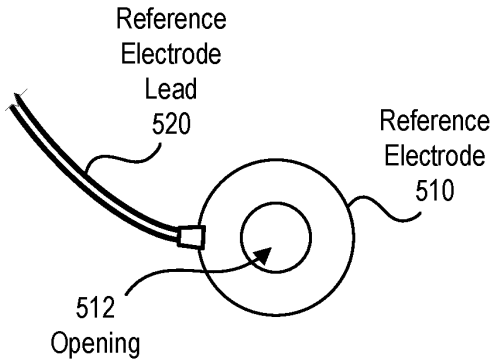
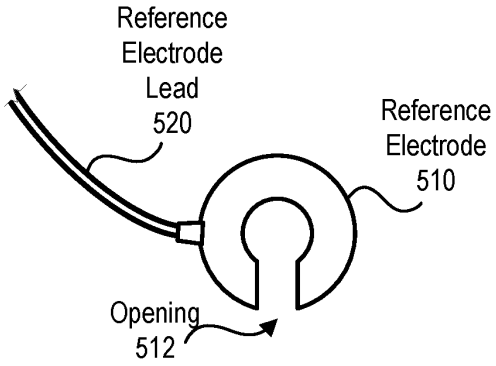


FIG. 31



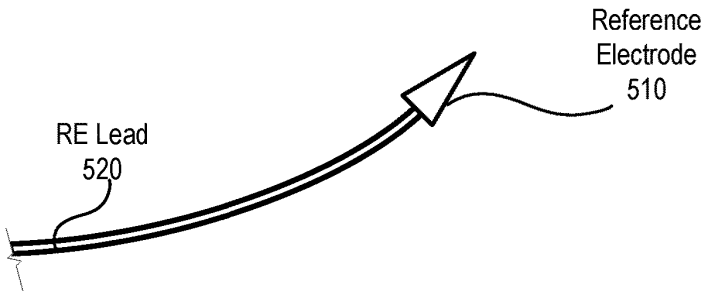


FIG. 32

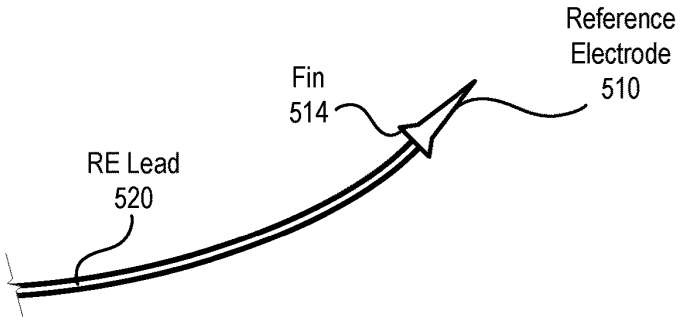


FIG. 33

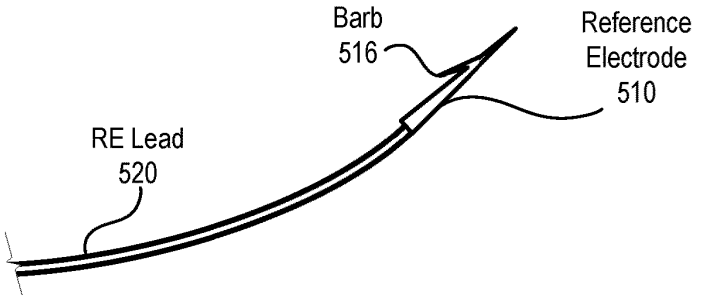


FIG. 34

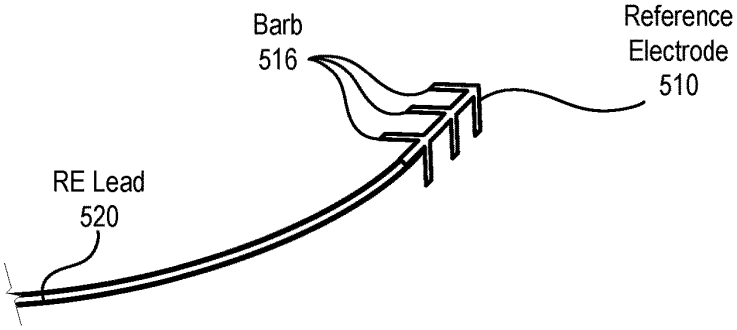


FIG. 35

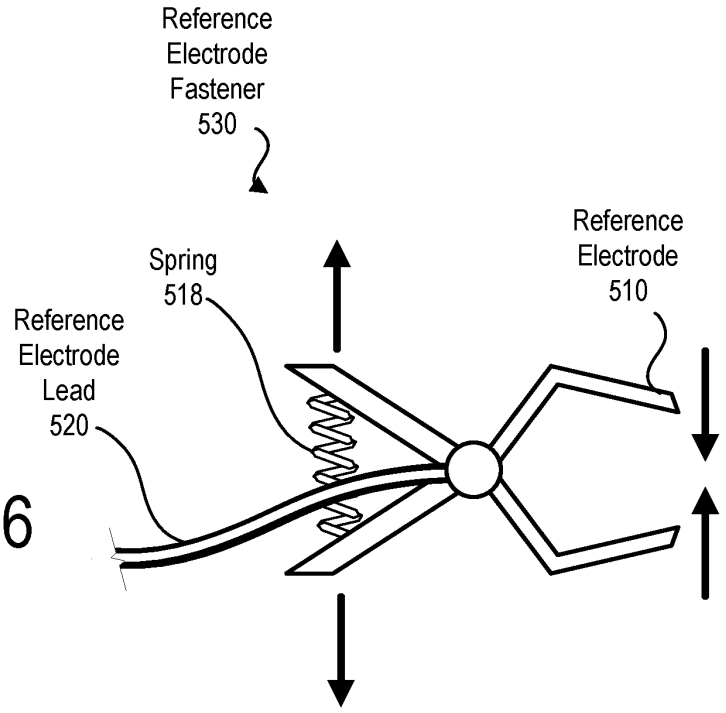

Reference
Electrode
Fastener
530
Spring
518
Reference
Electrode
510
Reference
Electrode
Lead
520

FIG. 36

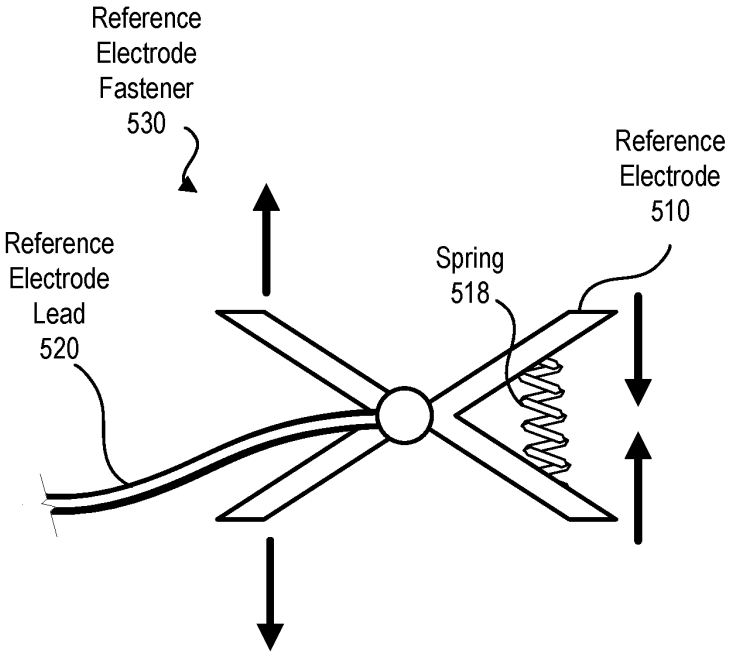

Reference
Electrode
Fastener
530
Reference
Electrode
510
Reference
Electrode
Lead
520
Spring
518

FIG. 37

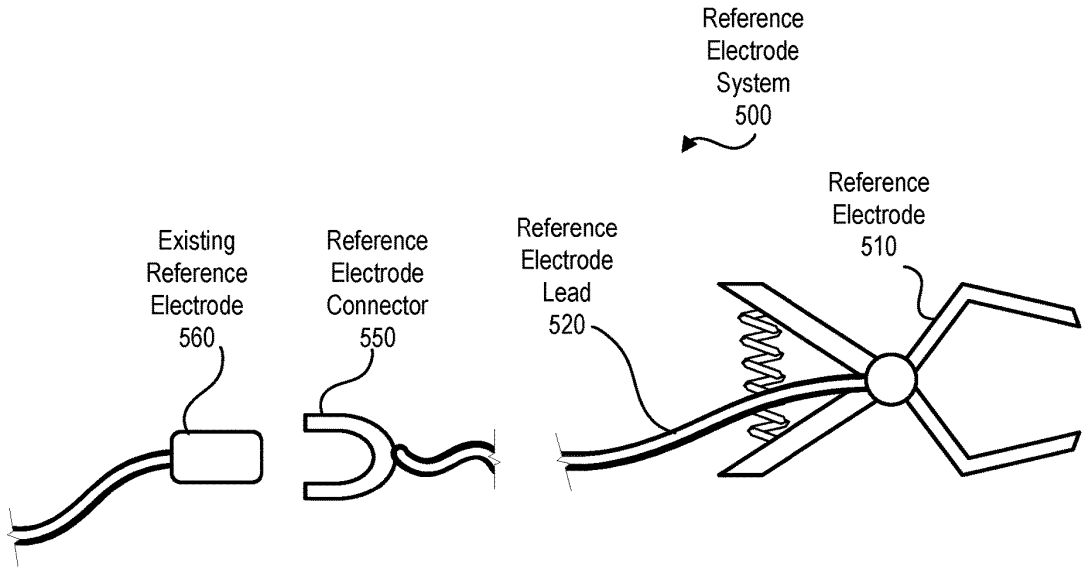

Reference
Electrode
System
500
Reference
Electrode
510
Existing
Reference
Electrode
560
Reference
Electrode
Connector
550
Reference
Electrode
Lead
520

FIG. 38

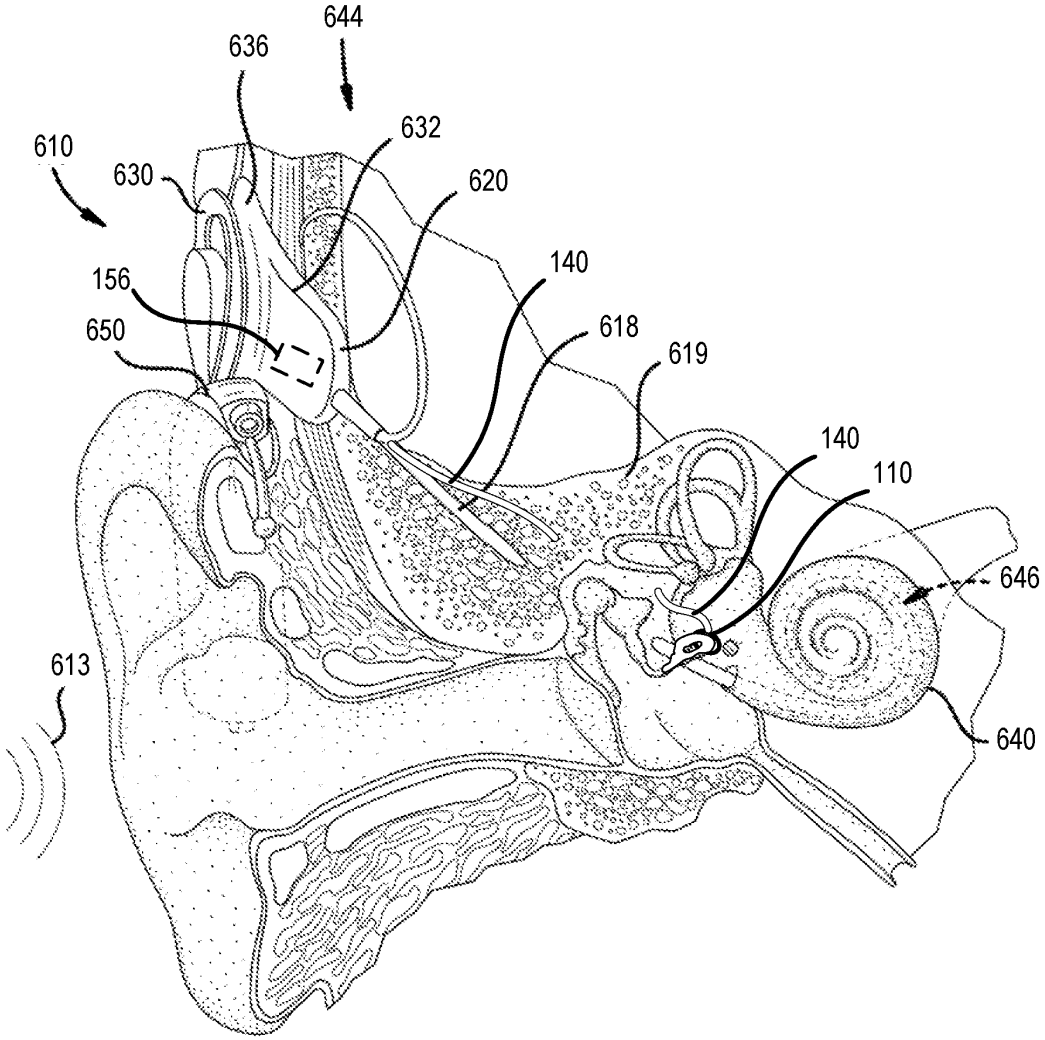


FIG. 39

VESTIBULAR STIMULATION PROSTHESIS

RELATED APPLICATION

[0001] This application claims the benefit of European Patent Application No. 19382629.4, which was filed Jul. 24, 2019, and which is hereby incorporated herein by reference in its entirety. To the extent appropriate, a claim of priority is made to the above disclosed application.

BACKGROUND

[0002] Medical devices having one or more implantable components, generally referred to herein as implantable medical devices, have provided a wide range of therapeutic benefits to recipients over recent decades. In particular, partially or fully-implantable medical devices such as hearing prostheses (e.g., bone conduction devices, mechanical stimulators, cochlear implants, etc.), implantable pacemakers, defibrillators, functional electrical stimulation devices, and other implantable medical devices, have been successful in performing lifesaving and/or lifestyle enhancement functions and/or recipient monitoring for a number of years.

[0003] The types of implantable medical devices and the ranges of functions performed thereby have increased over the years. For example, many implantable medical devices now often include one or more instruments, apparatus, sensors, processors, controllers or other functional mechanical or electrical components that are permanently or temporarily implanted in a recipient. These functional devices are typically used to diagnose, prevent, monitor, treat, or manage a disease/injury or symptom thereof, or to investigate, replace or modify the anatomy or a physiological process. Many of these functional devices utilize power and/or data received from external devices that are part of, or operate in conjunction with, the implantable medical device.

SUMMARY

[0004] In an example, there is an apparatus comprising: a flexible body having one or more electrodes; an implantable housing remote from the flexible body; a stimulator disposed in the implantable housing and configured to deliver stimulation to vestibular tissue of a recipient through an oval window of the recipient via the one or more electrodes; and a lead for electrically connecting the one or more electrodes to the stimulator.

[0005] In another example, there is a method comprising: surgically accessing an implantation area in a recipient; placing one or more electrodes of a flexible body of a vestibular stimulation prosthesis proximate an oval window of the recipient; implanting the flexible body at least partially in contact with an ossicular chain of the recipient; and finishing implantation.

[0006] In another example, a method comprising: via a flexible body disposed in a recipient: conducting vibrations from an ossicular chain to an inner ear of the recipient; and electrically stimulating vestibular tissue of the recipient.

[0007] In another example, an ossicular chain prosthesis comprising: one or more electrodes; a body configured to be disposed proximate an oval window of a recipient to deliver stimulation to vestibular tissue of a recipient through the oval window via the one or more electrodes; and a coupling configured to couple the body with a bone of the recipient's auditory ossicles.

[0008] In another example, there is an apparatus comprising: a reference electrode; a lead coupled to the reference electrode for electrically coupling the reference electrode to another component; and a reference electrode fastener configured to fasten the reference electrode to middle ear anatomy.

[0009] This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The same number represents the same element or same type of element in all drawings.

[0011] FIG. **1** illustrates an example view of a vestibular stimulation prosthesis implanted relative to inner ear anatomy in accordance with certain embodiments herein.

[0012] FIG. **2** illustrates an example implementation of a stimulator device of the vestibular stimulation prosthesis in accordance with certain embodiments herein.

[0013] FIG. **3** illustrates an example front view of a body of a vestibular stimulation prosthesis in accordance with certain embodiments herein.

[0014] FIG. **4** illustrates a side view of the body of FIG. **3** in accordance with certain embodiments herein.

[0015] FIG. **5** illustrates an example front view of the body having an inner portion and an outer portion in accordance with certain embodiments herein.

[0016] FIG. **6** illustrates a cross-section view of FIG. **5** taken along the line **6-6** of FIG. **5** in accordance with certain embodiments herein.

[0017] FIG. **7** illustrates an example side view of the body with electrodes disposed proximate a convex portion of the body having substantially straight sides in accordance with certain embodiments herein.

[0018] FIG. **8** illustrates an example side view of the body having electrodes disposed proximate a concave portion of the body having substantially straight sides in accordance with certain embodiments herein.

[0019] FIG. **9** illustrates an example side view of the body with a rectangular shape defining a concavity and a convexity in accordance with certain embodiments herein.

[0020] FIG. **10** illustrates an example side view of the body in a curved configuration with electrodes disposed proximate a convex portion of the body in accordance with certain embodiments herein.

[0021] FIG. **11** illustrates an example side view of the body in a curved configuration with electrodes disposed proximate a concave portion of the body in accordance with certain embodiments herein.

[0022] FIG. **12** illustrates an example side view of an example body with electrodes extending therefrom having a width greater than a length in accordance with certain embodiments herein.

[0023] FIG. **13** illustrates an example side view of an example body with electrodes extending therefrom with a length greater than a width in accordance with certain embodiments herein.

[0024] FIG. **14** illustrates a side view of an example body with electrodes extending therefrom tips with a convex shape in accordance with certain embodiments herein.

[0025] FIG. **15** illustrates a side view of an example body with electrodes extending therefrom having a flat tip in accordance with certain embodiments herein.

[0026] FIG. **16** illustrates a front view of an example body with two electrodes in accordance with certain embodiments herein.

[0027] FIG. **17** illustrates a front view of an example body with three electrodes in accordance with certain embodiments herein.

[0028] FIG. **18** illustrates a front view of an example body with four electrodes in accordance with certain embodiments herein.

[0029] FIG. **19** illustrates a front view of an example body with seven electrodes in accordance with certain embodiments herein.

[0030] FIG. **20** illustrates a front view of an example body with many electrodes in accordance with certain embodiments herein.

[0031] FIG. **21** illustrates a side view of an example body having a coupling extending from the second surface of the body.

[0032] FIG. **22** illustrates an example coupling having a form of a hook and a base in accordance with certain embodiments herein.

[0033] FIG. **23** illustrates an example coupling having a form of a hook and a base with the base in the form of an elongate section extending from the hook in accordance with certain embodiments herein.

[0034] FIG. **24** illustrates an example coupling having a form of a hook and a base with the base in the form of a pedestal in accordance with certain embodiments herein.

[0035] FIG. **25** illustrates an example coupling having a form of a screw. in accordance with certain embodiments herein

[0036] FIG. **26** illustrates an embodiment of an ossicular-bone-replacement configuration of the body in accordance with certain embodiments herein.

[0037] FIG. **27** illustrates an example process for implanting and using a vestibular stimulation prosthesis in accordance with certain embodiments herein.

[0038] FIG. **28** illustrates an example process for stimulating vestibular tissue of a recipient in accordance with certain embodiments herein.

[0039] FIG. **29** illustrates a side view of an example reference electrode system affixed to tissue in accordance with certain embodiments herein.

[0040] FIG. **30** illustrates a first example top view or bottom of the reference electrode system of FIG. **29** with the tissue and reference electrode fastener omitted in accordance with certain embodiments herein.

[0041] FIG. **31** illustrates a second example top view or bottom of the reference electrode system of FIG. **29** with the tissue and reference electrode fastener omitted in accordance with certain embodiments herein.

[0042] FIG. **32** illustrates an example implementation of reference electrode having a triangular shape in accordance with certain embodiments herein.

[0043] FIG. **33** illustrates an example implementation of reference electrode having an arrowhead-like shape in accordance with certain embodiments herein.

[0044] FIG. **34** illustrates an example implementation of reference electrode having a harpoon-tip-like shape in accordance with certain embodiments herein.

[0045] FIG. **35** illustrates an example implementation of reference electrode having a barbed-arrowhead-like shape in accordance with certain embodiments herein.

[0046] FIG. **36** illustrates an example implementation of a reference electrode having a reference electrode fastener configured as a clip in accordance with certain embodiments herein.

[0047] FIG. **37** illustrates an example implementation of a reference electrode having a reference electrode fastener configured as a clip in accordance with certain embodiments herein.

[0048] FIG. **38** illustrates an example configuration of the reference electrode system in which the reference electrode system can extend an existing reference electrode in accordance with certain embodiments herein.

[0049] FIG. **39** illustrates an example cochlear implant system that can benefit from use of the technologies disclosed herein.

DETAILED DESCRIPTION

[0050] Sensory impulses relating to balance and spatial orientation are generated by the human vestibular system. These sensory impulses are perceived by the brain via the vestibulocochlear nerve and provide a sense of balance and spatial orientation. But disorders affecting the vestibular system (e.g., Meniere's disease, other bilateral vestibular disorders, or inflammation of vestibular anatomy) can cause vestibular deficiency by interfering with these sensory impulses, thereby negatively affect one's sense of balance and spatial orientation. Vertigo can also result.

[0051] Disclosed embodiments include vestibular stimulation prostheses for restoring vestibular function in recipients having vestibular deficiency. In an example, a body (e.g., a flexible a mesh-like body) is appended onto or within the recipient's ossicular chain such that the body directly interfaces with an oval window of an inner ear of the recipient. Electrical stimulation is provided using one or more electrodes of the body to stimulate the vestibular system (e.g., the otolith organs thereof) and thereby restore vestibular functioning. In an example, a stimulator device connected to the body via a lead is also implanted. The stimulator device can have a small and convenient form factor. In some instances, the stimulator device is a stand-alone device that is configured to provide stimulation to the recipient's vestibular system without respect to signals received from devices external to the recipient. In some implementations, the stimulator device can be a component of a sensory prosthesis (e.g., a cochlear implant or bionic eye) or another medical device.

[0052] The body of the vestibular stimulation prosthesis can interface directly with a recipient's oval window. In one example, the body is configured to be placed between the stapes and the oval window. In another example, the body also acts as a stapes prosthesis. For instance, the body can connect to the incus. In addition, the body can be configured to preserve inner ear anatomy. For instance, the body and the components thereof (e.g., the electrodes thereof) can be configured to avoid penetrating into the inner ear. This placement of the body within the ossicular chain can result in approximately 10 Decibels or less of hearing loss for the recipient due to attenuation of vibrations conducted to the oval window. However the hearing loss can be preferable in many instances compared to the potentially worse outcomes

that can result from alternative approaches penetrating the inner ear (e.g., damaging hearing or vestibular anatomy).

[0053] Positioning the body proximate to the oval window can provide several advantages. First, the oval window is sufficiently close to the otolith organs to provide relatively easy targeting of stimulation to the otolith organs. Additionally, the stimulation signals from the electrodes can more easily penetrate through the oval window than other bony structure within the middle ear cavity (e.g., the temporal bone). This can allow for the use of relatively lower intensity stimulation and relatively lower collateral damage to tissue. Further, the placement proximate the oval window can be performed transtympanically, which is less invasive than traditional approaches through the temporal bone.

[0054] Disclosed embodiments further include particular electrode and body arrangements and designs for use with vestibular stimulation prostheses (see, e.g., FIGS. **3-20**), particular coupling arrangements and designs for connecting the body with anatomy of the recipient (see, e.g., FIGS. **21-26**), processes for implanting the vestibular stimulation prosthesis and providing therapeutic stimulation (see, e.g., FIGS. **27** and **28**), example reference electrode configurations (see, e.g., FIGS. **29-38**), and an example implementation of the vestibular stimulation prosthesis with a sensory prosthesis (see, e.g., FIG. **39**).

[0055] As should be appreciated, while particular examples are illustrated and discussed herein, the disclosed vestibular stimulation prostheses and processes described herein can be integrated in any of a variety of ways in accordance with many embodiments of the invention. The discussion is not meant to suggest that the disclosed vestibular stimulation examples are only suitable for implementation within systems akin to that illustrated in and described herein. In general, additional configurations can be used to practice the methods and systems herein and/or some aspects described can be excluded without departing from the processes and systems disclosed herein.

Vestibular Stimulation Prosthesis

[0056] FIG. **1** illustrates a view of an example vestibular stimulation prosthesis **100** implanted relative to inner ear anatomy in accordance with certain embodiments herein. The vestibular stimulation prosthesis **100** is an apparatus configured to provide therapeutic stimulation to a vestibular system of a recipient. In the illustrated configuration, the vestibular stimulation prosthesis **100** includes a body **110** having one or more electrodes **112**. The body **110** is connected to a stimulator device **150** via a lead **140**. Other configurations of the vestibular stimulation prosthesis **100** are also possible.

[0057] The body **110** can be a carrier for one or more components of the vestibular stimulation prosthesis **100**. In particular, the body **110** be a carrier for one or more components for providing stimulation to the vestibular system, such as the one or more electrodes **112**. The body **110** can be configured to be placed proximate the oval window. The body **110** can include other components, such as one or more components for connecting the body **110** to the ossicular chain (e.g., the stapes, incus, or malleus thereof). Such connectors are described in more detail in relation to FIGS. **20-25**. The body **110** can further include one or more sensors (e.g., for sensing the vestibular system).

[0058] The body **110** can take any of a variety of forms. In an example, the body **110** is formed as a mesh. In an example, the mesh is relatively flexible. In an example, the body is formed with an elastomer, such as silicone. In an example, the body **110** is configured to conduct vibrations from the ossicular chain to the oval window. The body **110** can be configured to interface with the oval window. The body **110** can be configured to cover part of or the entirety of the oval window. The body **110** can be configured to cover the oval window in such a manner that one or more electrodes **112** are positioned to target vestibular anatomy of the recipient.

[0059] The one or more electrodes **112** are electrically-conductive components via which stimulation can be provided. The one or more electrodes **112** can have any of a variety of different shapes, sizes, profiles, and configurations. Example configurations of the electrodes **112** are shown in FIGS. **3-17**. Generally, the one or more electrodes **112** can be advantageously configured to resist penetrating the oval window when the body **110** is properly implanted. IN other examples, the one or more electrodes **112** can be configured to penetrating the oval window to a predetermined depth, avoiding anatomical damage of otolith organ.

[0060] The lead **140** is a component that electrically connects two or more components of the vestibular stimulation prosthesis **100**. In many examples, the lead **140** is a cable having one or more wires disposed within an insulated sheath. In the illustrated configuration, the lead **140** connects the stimulator device **150** to the body **110**. In such a configuration, the lead **140** can convey electrical stimulation signals from the stimulator device **150** to the body **110** (e.g., to the electrodes **112** thereof).

[0061] The stimulator device **150** can be a component of the vestibular stimulation prosthesis **100** that generates the stimulation signals that are to be applied to the vestibular system. The stimulator device **150** often includes a housing in which one or more components are disposed. An example, configuration of the stimulator device **150** is shown in FIG. **2**.

[0062] The figure further shows the vestibular stimulation prosthesis **100** disposed in relation to vestibular and auditory anatomy. Among the anatomy shown, is the ear canal, which is part of the auditory anatomy. Acoustic pressure or sound waves can be channeled into and through ear canal. Disposed across an end of ear canal is a tympanic membrane which vibrates in response to the sound wave. This vibration is coupled to oval window (also known as the fenestra ovalis), which is adjacent round window (not shown), through the bones of the middle ear. The bones of the middle ear are the malleus, the incus, and the stapes, collectively referred to as the ossicles or the ossicular chain. The ossicles are positioned in the middle ear cavity and serve to filter and amplify the sound wave **103**. The ossicles cause the oval window to articulate (e.g., vibrate) in response to the vibration of tympanic membrane. This vibration of the oval window sets up waves of fluid motion of the perilymph within cochlea. Such fluid motion, in turn, activates tiny hair cells (not shown) inside of cochlea. Activation of the hair cells causes appropriate nerve impulses to be generated and transferred through the spiral ganglion cells (not shown) and auditory nerve (not shown) to the brain (also not shown) where they are perceived as sound.

[0063] In addition to the auditory anatomy, vestibular anatomy is also shown: the vestibular canals (also known as the semicircular canals) and the otolith organs. The vestibular canals are three canals (known as the horizontal canal,

the superior canal, and the posterior canal) that allow rotational movement to be sensed. The otolith organs, which include the utricle and saccule, allow linear movement to be sensed. Rotational and linear movement cause appropriate nerve impulses to be generated via the vestibular anatomy and transferred through the auditory nerve (not shown) to the brain (also not shown) where they are perceived as motion.

[0064] The human skull is formed from a number of different bones that support various anatomical features. These bones are omitted from FIG. **1** to aid the viewer. The temporal bone is situated at the side and base of the recipient's skull. The temporal bone is covered by a portion of the recipient's skin, muscle, and fat, which can collectively be referred to as tissue. The temporal bone can be referred to as having a superior portion and a mastoid portion. The superior portion comprises the section of the temporal bone that extends superior to the auricle. That is, the superior portion is the section of the temporal bone that forms the side surface of the skull. The mastoid portion is positioned inferior to the superior portion and is the section of the temporal bone that surrounds the middle ear.

[0065] The various components of the vestibular stimulation prosthesis **100** can be disposed with reference to this anatomy. In particular, the illustrated configuration shows the body **110** (and thus the one or more electrodes **112**) disposed at least partially between the stapes and the oval window of a recipient's left or right auditory anatomy. In this position, the body **110** is further proximate the otolith organs to which stimulation can be delivered through the oval window. As illustrated, the body **110** covers only a portion of the oval window. In other examples, the body **110** can entirely cover the oval window. In addition, while the stimulator device **150** is illustrated as being located inferior to the cochlea, the stimulator device **150** can be located in any of a variety of locations. The stimulator device **150** is described in more detail in relation to FIG. **2**.

Stimulator Device

[0066] FIG. **2** illustrates an example implementation of the stimulator device **150**. As illustrated, the stimulator device includes an electronics module **154** and a battery **158** disposed within a housing **152**.

[0067] The housing **152** can be an encasement that surrounds and hermetically seals one or more components of the stimulator device **150**. In examples, the housing **152** comprises a biocompatible material. In examples, the housing **152** includes a header providing an interconnection between the lead **140** and one or more components within the stimulator device **150** (e.g., the electronics module **154** thereof).

[0068] The electronics module **154** can include one or more other components to provide vestibular stimulation functionality. In some examples, the electronics module **154** includes one or more components for receiving a signal from an external device and converting the signal into a stimulation signal. But in many examples, the electronics module **154** generates a stimulation signal without regard to a signal from an external device. In many examples, the stimulation signal is generated according to a predetermined stimulation schedule that defines when and at what intensity the stimulation is to be applied.

[0069] In some examples, the electronics module **154** includes one or more processors (e.g., central processing units) coupled to memory components (e.g., flash memory) storing instructions that when executed cause performance of an operation described herein. In examples, the electronics module **154** generates and monitors parameters associated with generating and delivering the stimulus (e.g., output voltage, output current, or line impedance). In examples, the electronics module **154** generates a telemetry signal that includes telemetry data based on one or more of the parameters. The electronics module **154** can send the telemetry signal to an external device or store the telemetry signal in memory for later use or retrieval.

[0070] As illustrated, the electronics module **154** can include a stimulator **156**. The stimulator **156** generates electrical stimulation signals for use in stimulating tissue. The stimulator **156** can use stimulation control signals generated by the electronics module **154** (e.g., based on a stimulation schedule) to generate electrical stimulation signals (e.g., current signals) for delivery to the recipient's vestibular anatomy via the one or more electrodes **112**. In this way, the vestibular stimulation prosthesis **100** electrically stimulates the recipient's vestibular anatomy (e.g., nerve cells thereof), in a manner that causes the recipient to perceive vestibular percepts. The stimulation can be bipolar stimulation or monopolar stimulation.

[0071] The battery **158** is a component configured to store power. The battery **158** includes, for example, one or more rechargeable or non-rechargeable batteries. In some examples, the stimulator device **150** can be configured to receive power from another device, such as an external device or another implanted device. The power stored by the battery **158** can be distributed to the other components of the stimulator device **150** as needed for operation.

[0072] The stimulator device **150** can be a standalone vestibular stimulation prosthesis. In other examples, the vestibular stimulation prosthesis **100** can be part of another implanted medical device to add vestibular stimulation capabilities to the device. For instance, the implanted medical device can be a sensory prosthesis relating to one or more of the recipient's senses. For example, the sensory prosthesis can be a prosthesis relating to one or more of the five traditional senses (vision, hearing, touch, taste, and smell) and/or one or more of the additional senses. The sensory prosthesis can be an auditory prosthesis medical device configured to treat a hearing-impairment of the recipient. Where the sensory prosthesis is an auditory prosthesis, the sensory prosthesis can take a variety of forms including a cochlear implant, an electroacoustic device, a percutaneous bone conduction device, a passive transcutaneous bone conduction device, an active transcutaneous bone conduction device, a middle ear device, a totally-implantable auditory device, a mostly-implantable auditory device, an auditory brainstem implant device, a hearing aid, a tooth-anchored hearing device, a personal sound amplification product, other auditory prostheses, and combinations of the foregoing (e.g., binaural systems that include a prosthesis for a first ear of a recipient and a prosthesis of a same or different type for the second ear). In examples, the sensory prosthesis can be or include features relating to bionic eyes. Technology disclosed herein can also be relevant to applications with devices and systems used in for example, sleep apnea management, tinnitus management, and seizure therapy. Technology disclosed herein can be used with sensory devices such as consumer auditory devices (e.g., a hearing aid or a personal sound amplification product).

Additional details regarding implementation of the vestibular stimulation prosthesis **100** with another implanted medical device is described in relation to FIG. **39**.

[0073] The stimulator device **150** can be connected via the lead **140** to the body **110** for providing stimulation via the electrodes **112**. The body **110** and the electrodes can take any of a variety of different configurations, including those described in relation to FIGS. **3-20**.

[0074] In some examples, the stimulator device **150** (and the vestibular stimulation prosthesis **100** as a whole) can include one or more aspects of the devices, methods, and computer programs for generating one or more signals for the electrical stimulation of the saccule and utricle of a patient as described in WO 2017/081335, which is hereby incorporated by reference in its entirety for any and all purposes.

Body and Electrodes

[0075] FIG. **3** illustrates a front view of an example body **110**, and FIG. **4** illustrates a side view of the example body **110** of FIG. **3**. In the illustrated configuration, the body **110** has an oval shape with a long axis being longer than a short axis. The thickness of the body **110** is less than the width of the body **110**, which is less than the length of the body **110**. The body **110** includes three electrodes **112** disposed linearly along the long axis. The three electrodes **112** protrude from the body **110** and have a dome shape. The electrodes **112** each have respective tips **114**, which are rounded. The roundness of the respective tips **114** contributes to the electrodes **112** resisting penetration into the oval window when the body **110** is implanted proximate the oval window. The lead **140** extends laterally from the body **110**. The illustrated configuration is just one example implementation and others are also possible.

[0076] As illustrated, the body **110** can define a first surface **116** and a second surface **118**. The first surface **116** can be a surface (e.g., a side or face of the body **110**) configured to be disposed proximate (e.g., configured to contact) oval window tissue of a recipient when the body **110** is implanted in the recipient. In many examples, the first surface **116** is the surface of the body **110** at which the electrodes **112** are disposed. The second surface **118** can be a surface of the body **110** configured to be disposed proximate (e.g., configured to contact) an ossicular chain of the recipient. In examples, the second surface **118** is a surface at which a coupling for connecting the body **110** to the ossicular chain is disposed (see, e.g., coupling **400** shown in FIGS. **21-26**).

[0077] The body **110** can take any of a number of different shapes. In examples, the body **110** can have the shape of an n-sided polygon, where n is an integer three or greater (e.g., a triangle, quadrilateral, pentagon, etc.), when viewed from the front of the body **110**. In examples, the body **110** can have the shape of an n-pointed star polygon, where n is an integer five or greater (e.g., a pentagram, a hexagram, heptagram, etc.), when viewed from the front of the body **110**. The corners of the body **110** can be rounded or sharp. In the elevation view of FIG. **4**, the body **110** is flat. In other examples, the body **110** can have concavities, convexities, ridges, waves, or other structural features. In an example, a flexible body **110** is a body sufficiently flexible to conform to a shape of a recipient's oval window when implanted. The body **110** can be constructed using any of a variety of materials, such as elastomers (e.g., silicone).

[0078] Generally, the configurations of the body **110** can be selected to properly position the electrodes **112** to target vestibular anatomy to deliver therapeutic stimulation. For example, the body **110** can be sized and shaped to facilitate placement of the electrodes **112** proximate target tissue. The body **110** can be sized and shaped to facilitate useful contact between the body **110** and the oval window. In addition or instead, the configurations of the body **110** can be selected to facilitate the conduction of vibrations from the ossicular chain to the oval window. For instance, the body can be sized and shaped to do so. Further, the materials of the body **110** can be selected to have sufficient stiffness or other properties to be conducive to the transmission of vibrations to the oval window. Further, the body **110** can be configured to preserve inner ear anatomy of the recipient. For example, the body **110** can be configured to resist damaging inner ear anatomy (e.g., by having rounded or blunt shapes or protrusions). Example configurations of the body **110** (and its components) are shown in FIGS. **5-11**.

Body Configurations

[0079] FIG. **5** illustrates an example front view of the body **110** having an inner portion **126** and an outer portion **128**, and FIG. **6** illustrates a cross-section view of FIG. **5** taken along the line **6-6** of FIG. **5**. For ease of understanding, additional internal features of the body **110** are omitted from FIGS. **5** and **6** (e.g., the lead **140** is omitted, as are internal wiring components connecting the lead to the electrodes **112**). In the illustrated example, the outer portion **128** surrounds the perimeter of the inner portion **126** (e.g., the outer portion **128** circumferentially surrounds the inner portion **126**). In other examples, the outer portion **128** can extend from (e.g., but need not necessarily surround) the inner portion **126**. The outer portion **128** can include fixation features to facilitate attaching the body **110** to the oval window or the ossicular chain. The inner portion **126** and the outer portion **128** can be formed from the same or different materials. In examples, the outer portion **128** can be formed from a softer material than the material of the inner portion **126**. In examples, the outer portion **128** has a decreased thickness compared to the inner portion **126**. In an example, the inner portion **126** can have a region (e.g., extending from a top of the inner portion **126** to a bottom of the inner portion **126**) having a thickness of approximately 3 mm or less, 2 mm or less, or 1 mm or less. The outer portion **128** can have a region (e.g., extending from a top of the outer portion **128** to a bottom of the outer portion **128**) having a thickness of approximately 2 mm or less 1.5 mm or less, 1 mm or less, or 0.5 mm or less.

[0080] As can be seen in FIG. **6**, the outer portion **128** can define a concavity **124** of the body **110**. The electrodes **112** can be disposed within the concavity **124**. In an example, the concavity **124** has a depth approximately equal to the height of the electrodes **112**. In an example, the concavity **124** is configured to form a seal with the oval window, the oval window niche, the temporal bone, other tissue, or combinations thereof In examples, the body **110** can act as a diaphragm that vibrates in response to vibrations conducted from the ossicular chain and conducts the vibrations to the oval window.

[0081] FIGS. **7** and **8** illustrate side views of an example body **110**. In an example, the body **110** can have a shape like that of FIG. **7** or FIG. **8** in cross section along a width or a length of the body **110**. As illustrated, the body **110** has a

trapezoidal shape defining a concavity **124** and a convexity **122**. The sides of the body **110** defining the concavity **124** and the convexity **122** are substantially straight. The base of the concavity **124** and convexity **122** are also substantially straight. FIG. **7** shows the electrodes **112** disposed at the convex portion of the body **110**. In such an example, the concavity **124** can facilitate a connection between the body **110** and the ossicular chain. For example, the stapes can be configured to at least partially fit within the concavity **124**. FIG. **8** shows the electrodes **112** disposed at the concave portion of the body **110**. In an example, the concavity **124** can facilitate a connection between the body **110** and the oval window.

[0082] FIG. **9** illustrates a side view of an example body **110**. In an example, the body **110** can have a shape like that of FIG. **9** in cross section. As illustrated, the body **110** has a rectangular shape defining a concavity **124** and a convexity **122**. The sides of the body **110** defining the concavity **124** and the convexity **122** are substantially straight and are approximately perpendicular to a base of the concavity **124**. The base of the concavity **124** and the base of the convexity **122** are also substantially straight. As illustrated, the electrodes **112** are disposed at the concavity **124** of the body **110**. In another configuration, the electrodes **112** can be disposed at the convexity **122** of the body **110**. In an example, the concavity **124** can facilitate a connection between the body **110** and the oval window.

[0083] FIGS. **10** and **11** illustrate example side view of an example body **110**. In an example, the body **110** can have a shape like that of FIG. **10** or FIG. **11** in cross section. As illustrated, the body **110** has a curved shape defining a concavity **124** and a convexity **122**. FIG. **10** shows the electrodes **112** disposed at the convexity **122** of the body **110**. In such an example, the concavity **124** can facilitate a connection between the body **110** and the ossicular chain. For example, the stapes can be configured to at least partially fit within the concavity **124**. FIG. **11** shows the electrodes **112** disposed at the concavity **124** of the body **110**. In an example, the concavity **124** can facilitate a connection between the body **110** and the oval window.

Electrode Configurations

[0084] Just like the body **110** can take any of a variety of configurations, so too can the electrodes **112** take any number of shapes. Further, the electrodes **112** can be disposed in any of a variety of configurations on the body **110**. Such shapes and configurations can be selected to facilitate targeting particular vestibular anatomy, such as otolith organs, when the body **110** is implanted. The electrodes **112** can be embedded in the body **110**, can be disposed flush with a surface of the body **110**, can extend a surface of the body **110** (e.g., such as perpendicular to the surface of the body **110** or at an angle relative to the surface), can take other configurations, or can take combinations of multiple configurations. The electrodes **112** can be affixed to the body **110**. The electrodes **112** can also have any of a variety of different shapes or combinations of shapes. The electrodes **112** can be formed as part of an n-sided polygon or an n-pointed star polygon in shape or in cross-section where n is an integer three or greater. The electrodes **112** can each have a respective tip **114** having a particular configuration. For example, the tip **114** can be configured to resist penetrating oval window tissue, such as by having a blunt shape, thereby being configured to resist penetrating the oval window tissue when the body **110** is implanted proximate the oval window. In other examples, the tip **114** can be configured to penetrate the oval window tissue, such as by having a sharp shape configured to penetrate the oval window tissue when the body **110** is implanted proximate the oval window. In examples, the tip **114** can have a concavity or a convexity. Example configurations of the electrodes **112** are shown in FIGS. **12-20**.

[0085] FIGS. **12** and **13** illustrate side views of an example body **110** with electrodes **112** extending therefrom. In the illustrated configurations, the electrodes **112** have a triangular shape when viewed from at least one side. In examples, the electrodes **112** can be conical or shaped like pyramids having an n-sided base, where n is an integer three or greater (e.g., a triangular base pyramid, a square base pyramid, a pentagonal base pyramid, etc.). In examples, the electrodes **112** can be shaped like a triangular prism. The electrodes **112** are illustrated as having a pointed tip **114**. Such a tip **114** can be relatively sharp and configured to penetrate tissue. In other examples, the tip **114** can be relatively rounded and configured to resist penetrating tissue. In FIG. **12**, the electrodes **112** have a width greater than a length. In such a configuration, the electrodes **112** can be configured to resist penetrating tissue. In other examples, the electrodes **112** can be blade-like and have a relatively small depth such that the electrodes **112** are configured to penetrate tissue to a depth. In FIG. **13**, the electrodes **112** have a length greater than their width. In such a configuration, the electrodes **112** can be configured to penetrate tissue. In an example, the length of the electrodes is selected to resist penetrating the oval window, damaging auditory anatomy, damaging vestibular anatomy, damaging other tissue, or combinations thereof. In an example, the length of the electrodes is selected to penetrate the oval window to a depth of 2.5 mm or less, 2 mm or less, 1.5 mm, or less, 1 mm or less, or 0.5 mm or less. In addition, although the figures are described with reference to electrodes **112**, any one or more of the electrodes **112** described herein can be replaced with or operate as a sensor configured to obtain data relating to stimulation or other measurable data.

[0086] FIG. **14** illustrates a side view of an example body **110** with electrodes **112** extending therefrom. In the illustrated configuration, the electrodes **112** have a substantially rectangular shape when viewed from at least one side. The length of the electrodes **112** is longer than a width of the electrodes **112**. In examples, the electrodes **112** can be cylindrical or rectangular. As illustrated, the tip **114** of the electrodes **112** has a convex shape. The tip **114** can take the form of a bident (e.g., has a bifurcated tip) with two tines extending from the body of the electrode. In examples, each of the two tines can be separate electrodes **112**.

[0087] FIG. **15** illustrates a side view of an example body **110** with electrodes **112**. In the illustrated configuration, the electrodes **112** have a substantially rectangular shape when viewed from at least one side. In examples, the electrodes **112** can be cylindrical or rectangular. The length of the electrodes is shorter than a width of the electrodes. As illustrated, the tip **114** of each of the electrodes **112** is flat. The flat tip **114** can resist penetrating the oval window, damaging auditory anatomy, damaging vestibular anatomy, damaging other tissue, or combinations thereof.

[0088] FIGS. **16-20** illustrate example arrangements of electrodes **112** relative to a surface of the body **110**. The

arrangement of the electrodes **112** can be selected to target vestibular anatomy with stimulation.

[0089] FIG. **16** illustrates a front view of an example body **110** with two electrodes **112**. In the illustrated configuration, the electrodes **112** are linearly disposed along the long axis of the body **110**. The electrodes **112** are disposed in locations equidistant from the short axis of the body **110**. In other examples, the electrodes **112** can be linearly disposed along the short axis of the body **110**. In examples, the electrodes **112** can be disposed in a line rotated along any angle relative to the long axis.

[0090] FIG. **17** illustrates a front view of an example body **110** with three electrodes **112**. In the illustrated configuration, the electrodes **112** are disposed in such a way to from vertexes of an equilateral triangle centered on the body **110** (e.g., an equilateral triangle centered where the long and short axes meet). The electrodes **112** can be disposed in such a way as to form any other kind of triangle on the body **110** (e.g., an isosceles triangle, a scalene triangle, a right tringle, an obtuse triangle, or an acute triangle). The triangle can be centered elsewhere on the body **110** and rotated to any angle (e.g., any angle θ, where θ is an integer between 0 and 360 degrees, inclusive) relative to the long axis.

[0091] FIG. **18** illustrates a front view of an example body **110** with four electrodes **112**. In the illustrated configuration, the electrodes **112** are disposed in such a way to from vertexes of a square centered on the body **110**. The electrodes **112** can be disposed in such a way as to form any other kind of rhombus on the body **110** (e.g., rectangles, squares, parallelograms or trapezoids). The rhombus can be centered elsewhere on the body **110** and can be rotated to any angle (e.g., any angle θ, where θ is an integer between 0 and 360 degrees, inclusive) relative to the long axis.

[0092] FIG. **19** illustrates a front view of an example body **110** with seven electrodes **112**. In the illustrated configuration, the electrodes **112** are disposed in such a way to from vertexes of a hexagon centered on the body **110** with an additional electrode **112** disposed at the center of the hexagon. While the illustrated electrodes **112** are disposed to form an equilateral and equiangular hexagon, the electrodes **112** can be disposed to form a non-equilateral and non-equiangular hexagon. The illustrated hexagon is centered at a center of the body **110** but can be centered elsewhere on the body **110** and can be rotated to any angle (e.g., any angle θ, where θ is an integer between 0 and 360 degrees, inclusive) relative to the long axis.

[0093] FIG. **20** illustrates a front view of an example body **110** with many electrodes **112**. The electrodes **112** can be disposed on the body in any of a variety of ways, such as at vertices of an n-sided polygon where n is an integer three or greater. The electrodes **112** can be disposed in other locations as well. For example, the electrodes **112** can be disposed to fill a region of the body **110** with electrodes a predetermined distance apart. In an example, the total surface area of the electrodes visible in a front view is greater than a total surface area of the body **110** visible in the front view.

[0094] As described above, the shapes and configurations of the electrodes **112** and the body **110** can be selected to facilitate targeting particular vestibular anatomy, such as otolith organs, when the body **110** is implanted. In many implementations, the body **110** further includes a coupling to facilitate the implantation of the body **110**, positioning of the electrodes **112**, and the targeting of vestibular anatomy.

Coupling

[0095] Examples of the vestibular stimulation prosthesis **100** can further include a coupling **400** configured to couple the body **110** with tissue of the recipient (e.g., the temporal bone or a bone of the recipient's auditory ossicles, such as one or more of the malleus, the incus, and the stapes). The coupling **400** can be further configured to receive and conduct vibrations from the ossicular chain to the body **110** for transmission to the oval window.

[0096] FIG. **21** illustrates a side view of an example body **110** having a coupling **400** extending from the second surface **118** of the body **110**. The coupling **400** can be a component configured to couple the body **110** with a bone of the recipient's auditory ossicles. The coupling **400** can take any of a variety of forms. In the illustrated configuration, the coupling **400** includes a connector **402** and one or more bases **404**.

[0097] The connector **402** can be the portion of the coupling **400** that couples with the bone or other tissue of the recipient. The connector **402** can take any of a variety of different forms, such as one or more clips, screws, hooks, clamps, fasteners, adhesives, cements (e.g., bone cement), other kinds of couplings, or combinations thereof. In an example, the connector **402** comprises a metal, such as titanium.

[0098] The base **404** can be the portion of the coupling **400** that links the body **110** with the connector **402**. In examples, the base **404** can facilitate the positioning of the connector proximate tissue (e.g., the ossicular chain) with the first surface **116** of the body **110** positioned proximate the oval window. In examples, the base **404** is adjustable to facilitate such positioning. For instance, the angle between the base **404** and the connector can be adjustable. Likewise, the angle between the base **404** and the body **110** can also be adjustable. Further, a length of the base **404** can be adjustable. Further still, the base **404** can include an adjustable or fixed bend to facilitate angling the body **110** relative to the connector **402**. In some examples, the base **404** is sized and shaped to mimic one or more portions of the ossicular chain. In some examples, the base **404** is configured to conduct vibrations form the connector **402** to the body **110** for transmission to the oval window. In an example, the connector **402** comprises an elastomer, such as silicone.

[0099] FIG. **22** illustrates an example coupling **400**. In the illustrated configuration, the coupling **400** has a connector **402** in the form of a hook and a base **404** in the form of an elongate section extending from the hook and terminating in the body **110**. In an example, the connector **402** and the base can be integral with each other. The connector **402** and the base **404** can be formed from the same material, such as a metal (e.g., titanium). As illustrated, the base **404** extends from the second surface **118** and is substantially perpendicular to the second surface **118**. The base **404** extends from a middle of the body **110** but could be disposed elsewhere. The hook of the connector can be configured to attach directly to a bone of the ossicular chain or a fixation element coupled to the bone (e.g., a screw disposed within the bone). In examples, the hook can be configured to pierce into the bone. The hook can form its own path through the bone or follow a pre-excavated path.

[0100] FIG. **23** illustrates an example coupling **400**. As in FIG. **22**, the coupling **400** has a connector **402** in the form of a hook and a base **404** in the form of an elongate section extending from the hook. But in the configuration illustrated

in FIG. **23**, the base **404** extends from an area proximate an edge of the body **110** at a non-perpendicular angle to the body **110**. As illustrated, the base **404** further includes a section extending from the edge of the body **110** along at least a portion of the body **110**. In the illustrated configuration, the base **404** extends along the second surface **118** without being disposed within the body **110**. In an example, the base **404** can be welded, adhered, or otherwise fastened to the body **110** without the base **404** being disposed within the body **110**.

[0101] FIG. **24** illustrates an example coupling **400**. As in FIGS. **22** and **23**, the coupling **400** has a connector **402** in the form of a hook. But in the configuration illustrated in FIG. **24**, the base **404** takes the form of a pedestal extending from the second surface **118**. As illustrated, the base **404** is trapezoidal or frustoconical but can take other forms. Further, a section of the connector **402** extends into the base **404** for support. In an example, the base **404** can be integral with the body **110** or discrete from the body. In an example, the base **404** can be formed from the same material as the body **110**. In an example, the connector **402** is formed from a metal (e.g., titanium) and the base **404** is formed from an elastomer (e.g., silicone).

[0102] FIG. **25** illustrates an example coupling **400**. In the illustrated configuration, the coupling has a connector **402** in the form of a screw extending from the body **110**. In an example, such a configuration can be considered to lack a base **404**.

[0103] FIG. **26** illustrates an embodiment of an ossicular-bone-replacement configuration of the body **110**. In particular, as illustrated, the body **110** is implanted in the ossicular chain replacing the stapes (but in one or more other examples, one or more other bones of the ossicular chain can be partially or wholly replaced). The body **110** includes a coupling **400** sized and shaped to replace the stapes. In particular, the coupling **400** is sized to place the electrodes **112** proximate the oval window when the body **110** is implanted with the connector **402** of the coupling connected to the incus. For instance, the base **404** can be sized and shaped to reach from the incus to the oval window. In this configuration, the body **110** can be configured to conduct vibrations from the incus to the oval window.

Example Processes

[0104] FIG. **27** illustrates an example process **200** for implanting and using a vestibular stimulation prosthesis. The process **200** can begin with operation **210**.

[0105] Operation **210** includes surgically accessing an implantation area in a recipient. For instance, a clinician can form an incision in tissue proximate a location where the vestibular stimulation prosthesis **100** is to be implanted and remove tissue to expose an implantation area. The incision can be sized and shaped to allow for the performance of operations **220** and **230** through the incision. In some examples, surgically accessing the implantation area includes performing a mastoidectomy. The operation can further include enlarging a posterior tympanotomy, which can include exposing the oval window, such as by enlarging superiorly the posterior tympanotomy. In some examples, surgically accessing the implantation area includes identifying the stapes, as well as the anterior and posterior crura of the stapes and the footplate of the stapes, which contacts the oval window. The facial nerve of the recipient proximate the oval window can also be identified.

[0106] In some examples, operation **210** further includes excavating ossicular chain tissue form a location for implanting a body **110**. For instance, using an excavating tool (e.g., a carbon dioxide laser) or a surgical drill, some or all of the footplate of the stapes is removed to make room for the body **110**. In some instances, the incus is removed to make room to place the body **110**. In some instances, the ligaments of the footplate are kept in position proximate the oval window. Following operation **210**, the flow can move to one or both of operation **220** and operation **230**.

[0107] Operation **220** includes placing one or more electrodes **112** of the body **110** proximate the recipient's oval window. This can include placing the body **110** partially or entirely on the oval window of the recipient. In some examples, the body **110** contacts the temporal bone surrounding the oval window. The placing of the electrodes **112** can include placing the electrodes such that they do or do not pierce the oval window. In examples, the electrodes **112** are inserted through the oval window to a depth of 2.5 mm or less, 2 mm or less, 1.5 mm, or less, 1 mm or less, 0.5 mm or less. In some examples, the electrodes **112** are inserted into the oval window to a depth less than a depth to which auditory and vestibular anatomy is damaged by the electrodes **112** during insertion (e.g., damaged in a way to cause loss of hearing or vestibular function, respectively). In some examples, a portion of the body **110** at which the electrodes **112** are disposed is positioned such that the electrodes face the area where the recipient's otolith organs are believed to be disposed.

[0108] Operation **230** includes implanting a body **110** at least partially in contact with an ossicular chain of the recipient. Placing the body **110** in contact with the ossicular chain can include connecting the body **110** to one or more of the bones of the recipient's ossicular chain. This can include connecting the coupling **400** to the bone. In addition, in some recipients, the facial nerve may impinge on the implantation area. In such instances, a material (e.g., foam) can be placed between the implanted body **110** and the impinging facial nerve.

[0109] Following operations **220** and **230**, the flow can move to operation **240**. Operation **240** includes finishing the implantation procedure. Finishing the implantation procedure can include closing one or more incisions made to access the implantation area. Following operation **240**, the flow can move to operation **250**.

[0110] Operation **250** includes calibrating the vestibular stimulation prosthesis **100**. This operation can be performed at various times and can be performed various numbers of times. For instance, the vestibular stimulation prosthesis **100** can be calibrated before or during implantation, such as to confirm appropriate functioning of the vestibular stimulation prosthesis **100** prior to implantation or to confirm appropriate placement of the electrodes **112** prior to operation **240**. The calibration can include performing vestibular response telemetry. Vestibular response telemetry can be used to confirm that one or more of the electrodes **112** are able to provide appropriate stimulation (e.g., to the vestibular tissue, such as nerve tissue). The vestibular response telemetry can include providing stimulation and measuring a response to the stimulation to determine whether placement of the electrodes **112** is appropriate. If the placement is inappropriate, the body **110** can be repositioned. In some examples, the vestibular response telemetry is used to determine which one or more electrodes of the one or more electrodes **112** is

best able to stimulate target anatomy. Those one or more electrodes best able to stimulate the target anatomy can be selected as the electrodes to provide stimulation and the remaining electrodes can be (at least initially) deactivated. In many examples, additional calibration is performed subsequent to the finishing of the implantation procedure.

[0111] In examples, at least one month after implantation, the performance of the vestibular stimulation prosthesis **100** is tested. In an example, the recipient is asked to stand with their legs together and looking forward. Stimulation is provided by the vestibular stimulation system. The stimulation level of the stimulation provided can begin at a relatively low level. The stimulation level of the stimulation provided by the vestibular stimulation prosthesis **100** is then increased while the recipient's posture is poor or exhibits signs of poor balance (e.g., the recipient is swaying or shaking). When the recipient's posture and/or balance improves, the increase to the stimulation is stopped. Further, the recipient's subjective reports of their own perception of balance can used to determine whether to stop increasing stimulation levels. The stimulation level provided by the vestibular stimulation prosthesis **100** that ameliorates the recipient's balance can then be set such that the vestibular stimulation prosthesis **100** provides that level of stimulation going forward. The stimulation level can include a rate of stimulation. In examples, the stimulation rate is within the range of 200 Hz to 1000 Hz. Other levels are also possible. Further, while the electrodes **112** can be configured to provide a same stimulation rate or level, they need not. For instance, one electrode **112** can provide stimulation at a rate of 900 Hz and other electrodes **112** can provide stimulation at a rate of 500 Hz. Following operation **250**, the flow can move to operation **260**.

[0112] Operation **260** includes providing therapeutic stimulation with the vestibular stimulation prosthesis **100**. This operation **260** can include providing therapeutic stimulation to the vestibular system, as well as conducting sound vibrations to the oval window or associated tissue. After calibration, the vestibular stimulation prosthesis **100** can provide therapeutic stimulation to the recipient. This can include the vestibular stimulation prosthesis **100** providing stimulation according to a schedule generated based at least in part on the calibration of the vestibular stimulation prosthesis. Providing the therapeutic stimulation can include providing stimulation continuously to the recipient. Providing the therapeutic stimulation can include providing the stimulation periodically. Providing the stimulation periodically can include providing an amount of stimulation every approximately forty minutes to one hour for a therapeutic amount of time.

[0113] In an example, the operation **260** includes one or more operations described in relation to FIG. **27**, which describes an example process **300** stimulating vestibular tissue of a recipient. In an example, the process **300** begins with operation **310**.

[0114] Operation **310** includes conducting vibrations from an ossicular chain to an inner ear of the recipient. In an example, the body **110** of the vestibular stimulation prosthesis **100** can conduct the vibrations from a bone of the ossicular chain (e.g., incus, malleus, or stapes). A connector **402** of the body can connect to the bone and receive the vibrations. The connector **402** can conduct the vibrations to the base **404**. The base **404** can conduct the vibrations to the portion of the body **110** that contacts the oval window. In some examples, the vibrations are conducted via the one or more electrodes **112** to the oval window. In some examples, the vestibular stimulation prosthesis **100** can attenuate the vibrations received from the ossicular chain. The attenuation can, in some examples, cause a measurable (but not necessarily total) hearing loss in the recipient.

[0115] The method further includes operation **320**. In the illustrated example, operation **320** follows operation **310**, but in most implementations the operations occur without respect to the timing of the other. For example operation **310** can occur passively while the vestibular stimulation prosthesis **100** is implanted and operation **320** can occur according to a schedule.

[0116] Operation **320** includes generating a stimulation signal. In examples, the stimulation signal is generated by the stimulator **156**. The stimulation signal can be, for example, an electrical stimulation signal. The stimulator **156** can generate the stimulation signal based on a schedule or program. In other examples, the stimulator **156** generates the stimulation signal based on input from another component of the stimulator device **150** (e.g., a processor thereof) or based on input from another device of the vestibular stimulation prosthesis **100** (e.g., an external device). Generating the stimulation signal can include generating a stimulation signal selected to treat a vestibular condition of the recipient. Following operation **320**, the flow can move to operation **330**.

[0117] Operation **330** includes transmitting the stimulation signal to the one or more electrodes **112**. The transmitting can include transmitting the stimulation signal through a wired (e.g., via the lead **140**) or wireless connection between the stimulator **156** and the one or more electrodes **112**. In examples, a same stimulation signal can be sent to all of the electrodes **112**. In other examples, different stimulation signals are applied to different electrodes. In some examples, certain of the electrodes can be selectively activated to target stimulation at a particular anatomical location (e.g., to target vestibular anatomy through the oval window). In some examples, the one or more electrodes **112** are selectively activated or deactivated. Following operation **330**, the flow can move to operation **340**.

[0118] Operation **340** includes stimulating vestibular tissue of the recipient. For example, the one or more electrodes **112** can provide the stimulation using the received stimulation signal. In examples the vestibular tissue stimulated includes one or more of the vestibular canals or one or more of the otolith organs (e.g., the utricle and the saccule). In examples, stimulating vestibular tissue includes stimulating one or more nerves associated with the vestibular system, such as the vestibulocochlear nerve. The operation can include providing electrical stimulation through an oval window of the recipient.

Reference Electrodes

[0119] Disclosed examples can also include a reference electrode system **500** for affixing a reference electrode to bony structure of middle ear anatomy. The use of a reference electrode in the middle ear with the vestibular stimulation prostheses **100** described herein can provide advantages. For example, the use of the reference electrode system **500** can facilitate current steering, (e.g., so that stimulation currents can be more precisely applied to their intended targets). Although described herein in the context of a vestibular stimulation system, the reference electrodes described

herein can be used in addition to or instead of the reference electrodes for inner ear stimulation devices described in U.S. 2012/0078337, entitled "Reference electrodes for inner ear stimulation devices", which is hereby incorporated herein by reference for any and all purposes. Reference electrodes for heritage inner ear stimulation devices have commonly been affixed between the skull and the muscle and are not implanted within the middle ear cavity.

[0120] FIG. **29** illustrates a side view of an example reference electrode system **500** affixed to tissue. The illustrated reference electrode system **500** includes a reference electrode **510**, a reference electrode lead **520** coupled to and extending from the reference electrode **510**, and a reference electrode fastener **530** that fastens the reference electrode **510** to tissue. The reference electrode lead **520** can be a cable that electrically connects the reference electrode **510** to another component (e.g., the stimulator device **150**). The tissue can be any of a variety of tissue. In an example the tissue is tissue of the middle ear or inner ear. The tissue can be a bone of the ossicular chain or temporal bone located within the middle ear.

[0121] The reference electrode fastener **530** is a component configured to fasten the reference electrode **510** to tissue. The fastener **530** can take any of a variety of different forms, such as one or more clips, screws, hooks, clamps, fasteners, adhesives, cements (e.g., bone cement), other kinds of couplings, or combinations thereof. In an example, the fastener **530** comprises a metal, such as titanium. In some examples the fastener **530** is conductive to facilitate the performance of the reference electrode **510**. In other examples, the fastener **530** is non-conductive. The reference electrode fastener **530** is a screw that passes through the reference electrode (e.g., through an opening defined by the reference electrode **510**). The shaft of the screw extends primarily on a first tide of the reference electrode **510** (e.g., below the reference electrode **510** in the illustrated configuration) and the head of the screw extends primarily on a second surface of the reference electrode (e.g., above the reference electrode in the illustrated configuration). In examples, the reference electrode fastener **530** can be configured to form a path into tissue (e.g., by having a self-tapping feature or a piercing structure). In examples, the reference electrode fastener **530** is configured to follow a pre-formed hole through tissue (e.g., a path formed via a drill) formed into the target tissue.

[0122] The reference electrode **510** can be an electrode configured to act as a reference electrode for a device or system, such as the vestibular stimulation prosthesis **100**. The reference electrode **510** can take any number of shapes and can be disposed in any of a variety of configurations. Such shapes and configurations can be selected to facilitate contacting particular tissue, such as middle or inner ear anatomy, when the reference electrode system **500** is implanted. The reference electrode **510** can have any of a variety of different shapes or combinations of shapes. The reference electrode **510** can be formed as part of an n-sided polygon or an n-pointed star polygon in shape or in cross-section. The reference electrode **510** can include one or more structural features, such as protrusions, concavities, convexities, tips, other structures, or combinations thereof. For example, the reference electrode **510** can be configured to resist or promote penetrating of tissue, such as by having a blunt shape or a sharp structure, respectively. Example configurations of the reference electrode **510** are shown in FIGS. **30-38**.

[0123] FIG. **30** illustrates a first example top or bottom view of the reference electrode system **500** of FIG. **29** with the tissue and the reference electrode fastener omitted **530**. The illustrated reference electrode **510** defines an opening **512**. The opening **512** can be a region lacking material. The opening **512** can be sized and shaped to be configured to receive the reference electrode fastener **530**. For example, as illustrated, the reference electrode **510** has a washer shape with the opening **512** being an area through which a fastening screw can pass to fasten the reference electrode to tissue. As illustrated, the opening **512** is substantially centered in the reference electrode **510** and is surrounded by the reference electrode **510** on all sides when viewed down an axis of the opening **512**.

[0124] FIG. **31** illustrates a second example top or bottom view of the reference electrode system **500** of FIG. **29** with the tissue and the reference electrode fastener omitted **530**. Like the reference electrode **510** of FIG. **30**, the reference electrode **510** illustrated in FIG. **31** defines an opening **512**. But this opening **512** is not completely surrounded by the reference electrode **510** on all sides when viewed down an axis of the opening. In the illustrated configuration, the reference electrode **510** is U-shaped. This configuration of the electrode **510** can facilitate the reference electrode **510** being slipped onto an existing reference electrode fastener or clipping the reference electrode **510** onto existing anatomy.

[0125] FIG. **32** illustrates an example implementation of reference electrode **510** having a triangular shape. The reference electrode **510** can have a point configured to pierce tissue. The triangular shape can be configured to pierce tissue during implantation of the reference electrode **510** to facilitate affixing the reference electrode **510** in tissue.

[0126] FIG. **33** illustrates an example implementation of reference electrode **510** having an arrowhead-like shape. The reference electrode **510** is triangular in shape. The reference electrode **510** can have a point configured to pierce tissue. The illustrated reference electrode **510** further includes one or more fins **514** at a proximal region of the reference electrode **510**. The fins **514** can be configured to pierce or slice tissue during implantation of the reference electrode **510** to facilitate affixing the reference electrode **510** in tissue.

[0127] FIG. **34** illustrates an example implementation of reference electrode **510** having a harpoon-tip-like shape. The reference electrode **510** is triangular in shape with a point configured to pierce tissue. The illustrated reference electrode **510** further includes one or more barbs **516** extending proximally from a region near a tip of the reference electrode. The one or more barbs **516** can be configured to resist the removal of the reference electrode and thereby facilitate affixing the reference electrode **510** in tissue.

[0128] FIG. **35** illustrates an example implementation of reference electrode **510** having a barbed-arrowhead-like shape. The reference electrode **510** is triangular in shape with a point configured to pierce tissue. The illustrated reference electrode **510** further includes a plurality of rows of barbs **516** extending proximally from a region near a tip of the reference electrode. The one or more barbs **516** can be configured to resist the removal of the reference electrode and thereby facilitate affixing the reference electrode **510** in tissue.

[0129] FIG. **36** illustrates an example implementation of a reference electrode **510** having a reference electrode fastener **530** configured as a clip. For example, the reference electrode fastener **530** can clip the reference electrode **510** to target anatomy. As illustrated, the reference electrode fastener **530** includes a spring **518** that forces apart a proximal portion of the reference electrode fastener **530**, which forces together a distal portion of the fastener **530** at which the reference electrode **510** is disposed. The reference electrode fastener **530** can have a resting closed state. For instance, absent an outside force, the spring **518** causes the distal portion of the fastener **530** to close together. A clinician can force apart the distal portion by pressing the proximal portion of the fastener **530** together.

[0130] FIG. **37** illustrates an example implementation of a reference electrode **510** having a reference electrode fastener **530** configured as a clip. For example, the reference electrode fastener **530** can be clip the reference electrode **510** to target anatomy. As illustrated, the reference electrode fastener **530** includes a spring **518** that forces together a distal portion of the reference electrode fastener **530** at which the reference electrode **510** is disposed, which forces apart a distal portion of the fastener **530**. The reference electrode fastener **530** can have a resting closed state. For instance, absent an outside force, the spring **518** causes the distal portion of the fastener **530** to close together. A clinician can force apart the distal portion by pressing the proximal portion of the fastener **530** together.

[0131] FIG. **38** illustrates an example configuration of the reference electrode system **500** in which the reference electrode system **500** can extend an existing reference electrode **560**. In the illustrated configuration, the distal portion of the reference electrode lead **520** is electrically coupled to the reference electrode **510** and a proximal portion of the reference electrode lead is coupled to a reference electrode connector **550**. The reference electrode connector **550** can be configured to couple with an existing reference electrode **560** to electrically connect the existing reference electrode **560** with the reference electrode **510**. In this manner, the reference electrode system **500** can act as an extension to an existing reference electrode **560** to add additional length or fixation capabilities.

[0132] FIG. **39** illustrates an example sensory prosthesis that can benefit from use of the technologies disclosed herein: a cochlear implant system **610**. The cochlear implant system **610** includes an implantable component **644** typically having an internal receiver/transceiver unit **632**, a stimulator unit **620**, and an elongate lead **618**. The internal receiver/transceiver unit **632** permits the cochlear implant system **610** to receive signals from and/or transmit signals to an external device **650**. The external device **650** can be a button sound processor worn on the head that includes a receiver/transceiver coil **630** and sound processing components. Alternatively, the external device **650** can be just a transmitter/transceiver coil in communication with a behind-the-ear device that includes the sound processing components and microphone.

[0133] The implantable component **644** includes an internal coil **636**, and preferably, a magnet (not shown) fixed relative to the internal coil **636**. The magnet can be embedded in a pliable silicone or other biocompatible encapsulant, along with the internal coil **636**. Signals sent generally correspond to external sound **613**. The internal receiver/transceiver unit **632** and the stimulator unit **620** are hermetically sealed within a biocompatible housing, sometimes collectively referred to as a stimulator/receiver unit. Included magnets (not shown) can facilitate the operational alignment of an external coil **630** and the internal coil **636**, enabling the internal coil **636** to receive power and stimulation data from the external coil **630**. The external coil **630** is contained within an external portion. The elongate lead **618** has a proximal end connected to the stimulator unit **620**, and a distal end **646** implanted in a cochlea **640** of the recipient. The elongate lead **618** extends from stimulator unit **620** to the cochlea **640** through a mastoid bone **619** of the recipient. The elongate lead **618** is used to provide electrical stimulation to the cochlea **640** based on the stimulation data. The stimulation data can be created based on the external sound **613** using the sound processing components and based on the sensory prosthesis settings. As illustrated, the stimulator unit **620** further includes the stimulator **156** configured to deliver stimulation to vestibular tissue of the recipient via electrodes of the body **110** disposed proximate the oval window of the recipient. The lead **140** connects the stimulator **156** to the electrodes of the body **110**.

[0134] In certain examples, the external coil **630** transmits electrical signals (e.g., power and stimulation data) to the internal coil **636** via a radio frequency (RF) link. The internal coil **636** is typically a wire antenna coil having multiple turns of electrically insulated single-strand or multi-strand platinum or gold wire. The electrical insulation of the internal coil **636** can be provided by a flexible silicone molding. Various types of energy transfer, such as infrared (IR), electromagnetic, capacitive and inductive transfer, can be used to transfer the power and/or data from external device to cochlear implant. While the above description has described internal and external coils being formed from insulated wire, in many cases, the internal and/or external coils can be implemented via electrically conductive traces.

[0135] Other sensory prostheses can benefit from technologies described herein. For example, the technology disclosed herein can be implemented with a direct acoustic stimulator prosthesis configured to generate vibrations and conduct the vibrations to move perilymph in scala tympani to activate hair cells to cause hearing percepts. Such a stimulator can include an actuator, a stapes prosthesis and a coupling element connecting the actuator to the stapes prosthesis. In an example, the prosthesis stimulation arrangement can be implanted and/or configured such that a portion of stapes prosthesis abuts a recipient's round or oval window. In examples, the portion of the prosthesis that abuts the oval window can include one or more electrodes **112** described herein for stimulating vestibular anatomy.

[0136] As should be appreciated, while particular uses of the technology have been illustrated and discussed above, the disclosed technology can be used with a variety of devices in accordance with many examples of the technology. The above discussion is not meant to suggest that the disclosed technology is only suitable for implementation within systems akin to that illustrated in the figures. For examples, while certain technologies described herein were primarily described in the context of auditory prostheses (e.g., cochlear implants), technologies disclosed herein are applicable to medical devices generally (e.g., medical devices providing pain management functionality or therapeutic electrical stimulation, such as deep brain stimulation). In general, additional configurations can be used to practice

the processes and systems herein and/or some aspects described can be excluded without departing from the processes and systems disclosed herein. Further, the techniques described herein can be applicable to determining a recipient's response to other stimuli, such as visual stimuli, tactile stimuli, olfactory stimuli, taste stimuli, or another stimuli. Likewise, the devices used herein need not be limited to auditory prostheses and can be other medical devices configured to support a human sense, such as bionic eyes.

[0137] This disclosure described some aspects of the present technology with reference to the accompanying drawings, in which only some of the possible aspects were shown. Other aspects can, however, be embodied in many different forms and should not be construed as limited to the aspects set forth herein. Rather, these aspects were provided so that this disclosure was thorough and complete and fully conveyed the scope of the possible aspects to those skilled in the art.

[0138] As should be appreciated, the various aspects (e.g., portions, components, etc.) described with respect to the figures herein are not intended to limit the systems and processes to the particular aspects described. Accordingly, additional configurations can be used to practice the methods and systems herein and/or some aspects described can be excluded without departing from the methods and systems disclosed herein.

[0139] Similarly, where steps of a process are disclosed, those steps are described for purposes of illustrating the present methods and systems and are not intended to limit the disclosure to a particular sequence of steps. For example, the steps can be performed in differing order, two or more steps can be performed concurrently, additional steps can be performed, and disclosed steps can be excluded without departing from the present disclosure. Further, the disclosed processes can be repeated.

[0140] Although specific aspects were described herein, the scope of the technology is not limited to those specific aspects. One skilled in the art will recognize other aspects or improvements that are within the scope of the present technology. Therefore, the specific structure, acts, or media are disclosed only as illustrative aspects. The scope of the technology is defined by the following claims and any equivalents therein.

What is claimed is:

1. An apparatus comprising:

a flexible body having one or more electrodes;

an implantable housing remote from the flexible body;

a stimulator disposed in the implantable housing and configured to deliver stimulation to vestibular tissue of a recipient through an oval window of the recipient via the one or more electrodes; and

a lead for electrically connecting the one or more electrodes to the stimulator.

2. The apparatus of claim **1**, wherein the one or more electrodes each comprise a respective tip configured to resist penetrating oval window tissue.

3. The apparatus of claim **1**, wherein the one or more electrodes are configured to penetrate the oval window tissue to a depth of 1 mm or less.

4. The apparatus of claim **1**, wherein the apparatus is configured to preserve inner ear anatomy of the recipient.

5. The apparatus of claim **1** wherein the flexible body defines:

a first surface configured to contact oval window tissue; and

a second surface configured to contact a portion of an ossicular chain of the recipient.

6. The apparatus of claim **5**, wherein the flexible body is configured to conduct vibrations from the ossicular chain to the oval window tissue.

7. The apparatus of claim **1**, wherein the stimulator is configured to deliver stimulation to vestibular tissue of the recipient through the oval window via the one or more electrodes without respect to a communication from a source external to the recipient.

8. The apparatus of claim **1**,

wherein the flexible body has an elongate shape and a thickness less than a width;

wherein the flexible body comprises a shape of an n-sided polygon, where n is an integer three or greater;

wherein the flexible body comprises a shape of an n-pointed star polygon, where n is an integer three or greater;

wherein the one or more electrodes comprise a pyramidal shape having an n-sided base, where n is an integer three or greater;

wherein the one or more electrodes comprise three or more electrodes arranged linearly;

wherein the one or more electrodes have a length selected to penetrate the oval window to a depth of depth of 2.5 mm or less, 2 mm or less, 1.5 mm, or less, 0.5 mm or less;

wherein the apparatus further comprises a non-rechargeable battery disposed in the implantable housing for powering the stimulator; or

wherein each respective tip has a blunt shape, thereby being configured to resist penetrating the oval window tissue.

9. A method comprising:

surgically accessing an implantation area in a recipient;

placing one or more electrodes of a flexible body of a vestibular stimulation prosthesis proximate an oval window of the recipient;

implanting the flexible body at least partially in contact with an ossicular chain of the recipient; and

finishing implantation.

10. The method of claim **9**, wherein implanting the flexible body includes placing the flexible body between a stapes of the ossicular chain and the oval window.

11. The method of claim **9**, wherein placing the one or more electrodes of the flexible body proximate the oval window includes:

placing the one or more electrodes in contact with the oval window without the one or more electrodes penetrating the oval window.

12. The method of claim **9**, wherein implanting the flexible body includes:

performing a mastoidectomy;

enlarging a posterior tympanotomy; and

excavating ossicular chain tissue define a location for implanting the flexible body.

13. The method of claim **9**, further comprising:

calibrating the vestibular stimulation prosthesis;

providing therapeutic stimulation with the vestibular stimulation prosthesis.

14. The method of claim **9**,
wherein the method further includes inserting electrodes of the flexible body through the oval window to a depth of 2.5 mm or less, 2 mm or less, 1.5 mm, or less, 1 mm or less, or 0.5 mm or less;
wherein the method further includes positioning a portion of the flexible body at which electrodes are disposed such that the electrodes face an area where otolith organs of the recipient are believed to be disposed;
wherein the method further includes placing a material between the flexible body and a facial nerve of the recipient;
wherein the method further includes connecting the flexible body to one or more bones of the recipient's ossicular chain;
wherein the method further includes removing an incus of the recipient's ossicular chain to make room for the flexible body;
wherein implanting the flexible body includes transtympanically implanting the flexible body;
wherein the method further calibrating the vestibular stimulation prosthesis by performing vestibular response telemetry;
wherein the method further calibrating the vestibular stimulation prosthesis by determining which the one or more electrodes of the flexible body are best able to stimulate target anatomy; or
wherein the method further comprises calibrating the vestibular stimulation prosthesis at least one month after implantation.

15. A method comprising:
via a flexible body disposed in a recipient:
conducting vibrations from an ossicular chain to an inner ear of the recipient; and
electrically stimulating vestibular tissue of the recipient.

16. The method of claim **15**, wherein electrically stimulating the vestibular tissue of the recipient includes:
electrically stimulating the vestibular tissue using one or more electrodes of the flexible body.

17. The method of claim **15**, further comprising:
generating a stimulation signal at a stimulator device remote from the flexible body; and
transmitting the stimulation signal to one or more electrodes of the flexible body via a lead electrically connecting the stimulator device with the one or more electrodes.

18. The method of claim **15**,
wherein electrically stimulating the vestibular tissue of the recipient includes providing electrical stimulation through an oval window of the recipient;
wherein electrically stimulating the vestibular tissue of the recipient includes repeating the stimulating every forty minutes to one hour for an amount of time;
wherein electrically stimulating the vestibular tissue of the recipient includes providing stimulation at a rate within the range of 200 Hz to 1000 Hz, inclusive;
wherein electrically stimulating the vestibular tissue of the recipient includes providing stimulation at a different rate at different electrodes;
wherein electrically stimulating the vestibular tissue of the recipient includes providing stimulation via a first electrode at a rate of 900 Hz and at via a second electrode at a rate of 500 Hz; or
wherein conducting vibrations from a vestibular chain to the inner ear of the recipient includes attenuating the vibrations, thereby resulting in hearing loss for the recipient of at least 5 decibels.

19-25. (canceled)

26. The apparatus of claim **1**, further comprising:
a reference electrode;
a reference electrode lead coupled to the reference electrode for electrically coupling the reference electrode to the implantable housing; and
a reference electrode fastener configured to fasten the reference electrode to middle ear anatomy.

27-29. (canceled)

30. The apparatus of claim **26**,
wherein the reference electrode defines an opening through which the reference electrode fastener can extend;
wherein the reference electrode fastener comprises a spring that forces together a distal portion of the reference electrode fastener;
wherein the reference electrode fastener comprises a spring that forces apart a proximal portion of the reference electrode fastener;
wherein the reference electrode fastener comprises one or more of the following fasteners: clips, screws, hooks, clamps, fasteners, adhesives, or cements;
wherein the reference electrode comprises a triangular shape with a point configured to pierce tissue;
wherein the reference electrode comprises a barb configured to resist removal of the reference electrode and thereby facilitate affixing the reference electrode in tissue;
wherein the reference electrode comprises a plurality of rows of barbs; or
wherein the reference electrode comprises one or more fins configured to pierce or slice tissue during implantation of the reference electrode to facilitate affixing the reference electrode in tissue.

* * * * *

Capítulo 5

Discusión y conclusiones

5.1. Discusión

Demostramos que las respuestas ECAP vestibulares se obtienen después de la estimulación eléctrica del órgano otolito utilizando un paradigma de estimulación similar al de los implantes cocleares. La respuesta de VRT, que se ha registrado en el órgano terminal vestibular humano, muestra muchas de las características del potencial de acción compuesto registrado en la cóclea. La capacidad de registrar respuestas neuronales en el 83,3 % de los electrodos probados respalda la validez del sistema VRT para medir las ECAP de origen vestíbulo en sujetos adultos. Ya habíamos demostrado que era posible generar una respuesta VRT correlacionada con las respuestas eoVEMPs a través de un electrodo colocado en los órganos del otolito. La ubicación ideal del electrodo se determinó controlando el VRT realizado en lugares ligeramente diferentes durante la inserción. Observamos que un desplazamiento mínimo del electrodo resultó en cambios drásticos en la amplitud de las respuestas, por lo que es necesaria la estabilización de la matriz de electrodos para obtener buenas respuestas. Esto también indica que la presencia de ECAP obtenida de VRT y la correlación con las respuestas de eoVEMPs, cuando el estímulo se entrega en el órgano otolítico y no cuando el electrodo está colocado incorrectamente, se debe a que es una ECAP vestibular y no una respuesta auditiva. Asimismo, es importante mencionar que los eoVEMPs no se obtuvieron cuando se realizó la telemetría de respuesta neuronal auditiva del implante coclear. Los mejores parámetros de configuración de la prueba son una tasa de estimulación de 90 Hz, una ganancia del amplificador de 40 dB, 140 barridos, un nivel de enmascaramiento fijo igual a la sonda +10 CL, un avance de enmascaramiento de 400 us y un retardo de 120 us, y esto proporciona los resultados más rápidos y confiables en los adultos evaluados. También se observó que es posible correlacionar la respuesta de ECAP vestibular con las respuestas de oVEMPs eléctricamente a través de un electrodo colocado en los órganos

otolíticos. La ubicación ideal del electrodo se determinó controlando el ECAP vestibular en lugares ligeramente diferentes durante la inserción. Observamos que un desplazamiento mínimo del electrodo resultó en cambios drásticos en la amplitud de las respuestas, por lo que la estabilización de la matriz de electrodos es necesaria para obtener buenas respuestas. Esto también indica que la presencia de ECAP vestibular se correlaciona con respuestas de eoVEMPs eléctricamente, y podría usarse como un signo de estimulación vestibular [**?**] En cuanto a la estimulación, aunque no se sabe bien cómo el estímulo en el órgano vestibular puede proporcionar una respuesta eficaz en el nervio vestibular aferente, se han presentado muchos estudios con diferentes investigaciones sobre este tema. Recientemente se ha realizado un modelo del laberinto de primates a partir de imágenes de reconstrucción 3-D para estudiar la propagación de la corriente protésica en el oído interno y facilitar el diseño de conjuntos de electrodos y protocolos de estimulación para un sistema VI, que ofrece datos importantes de la propagación y el efecto de la estimulación [Hedjoudje et al., 2019]. El papel de los otolitos en humanos (utrículo y sáculo) en la función global de la función vestibular no ha sido ampliamente estudiado y es difícil de determinar [**?**] El nistagmo puede verse afectado por las posiciones de la mirada. Sin embargo, aún quedan dudas por resolver, como el papel que juega el estímulo otolítico en la restauración del VOR, ya que una cierta modulación en los resultados del video test de impulso craneal y en el nistagmo espontáneo en uno de nuestros pacientes fue observado. Con respecto a la relación con el VOR, un estudio reciente que examina el papel de los otolitos en la adaptación del VOR en un modelo animal muestra que los otolitos no contribuyen a la adaptación del VOR angular normal, como se ha demostrado durante la activación. en nuestros pacientes. Sin embargo, los otolitos proporcionan la pista principal para la adaptación de VOR específica al contexto de la gravedad, y también pueden tener algún efecto en el nistagmo espontáneo, que también se ha observado en nuestro estudio [**?**].

5.2. Conclusiones

El sistema otolítico debe establecerse como primer órgano a estimular en aquellos pacientes con disfunción vestibular bilateral. Esto se fundamenta en base a la superioridad sobre los canales semicircular estal como se observa desde un punto de vista de la evolución, la evidencia clínica y los principios físicos.

La telemetría de respuesta vestibular proporciona un método para evaluar la función neural periférica, y la técnica de grabación es análoga a las grabaciones ECAP que se utilizan ampliamente en la investigación y la práctica clínica de implantes cocleares. La técnica VRT es eficaz para registrar las respuestas neurales en la región de la mácula y nos proporciona una herramienta conveniente para determinar si los electrodos implantados están generando una respuesta neural y, por lo tanto, para brindar información que ayude a identificar la coloca-

ción óptima de los electrodos durante la cirugía VI. La debilidad de este estudio es el pequeño tamaño de la muestra, que se debe a las condiciones del comité ético ya la baja prevalencia de la enfermedad. Se ha establecido un conjunto de parámetros de prueba predeterminados para proporcionar un método relativamente rápido de medir la ECAP vestibular en nuestros sujetos. Hasta donde sabemos, este es el primer estudio que demuestra la respuesta evocada eléctricamente del órgano otolítico estimulado directamente en humanos.

La implantación protésica del órgano otolítico en humanos es técnicamente factible. La estimulación eléctrica puede tener efectos potenciales sobre el equilibrio y este es estable después de un año de seguimiento. Esta investigación brinda nuevas posibilidades para el desarrollo de implantes vestibulares para mejorar la sensación de aceleración gravito-inercial, en este caso, por la estimulación de los otolitos.

5.3. Trabajo futuro

- Estudio multicentrico: Repetir el estudio en haciendo uso de un nuevo implantes cocleo-vestibular en 4 centros (Las Palmas de Gran Canaria (España), Pamplona(España), Antwerpt (Belgica), Roma (Italia) para evaluar si replicamos los resultados obtenidos en esta tesis 4.3.

- Diseñar abordaje quirurgico para pacientes con restos auditivos. El objetivo es ser capaces de realizar una implantación vestibular sin afectar a la via auditiva. Este estudio hace frente a una mayor población de posibles candidatos al tratamiento.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