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Research paper

Considering optogenetic stimulation for cochlear implants

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ABSTRACT

Electrical cochlear implants are by far the most successful neuroprostheses and have been implanted in over 300,000 people worldwide. Cochlear implants enable open speech comprehension in most patients but are limited in providing music appreciation and speech understanding in noisy environments. This is generally considered to be due to low frequency resolution as a consequence of wide current spread from stimulation contacts. Accordingly, the number of independently usable stimulation channels is limited to less than a dozen. As light can be conveniently focused, optical stimulation might provide an alternative approach to cochlear implants with increased number of independent stimulation channels. Here, we focus on summarizing recent work on optogenetic stimulation as one way to develop optical cochlear implants. We conclude that proof of principle has been presented for optogenetic stimulation of the cochlea and central auditory neurons in rodents as well as for the technical realization of flexible μLED-based multichannel cochlear implants. Still, much remains to be done in order to advance the technique for auditory research and even more for eventual clinical translation.

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1. Introduction – why look for alternatives to electrical stimulation?

Most cochlear implant (CI) patients achieve open speech comprehension in quiet and to some degree in noise but music appreciation is generally reduced (Kohlberg et al., 2014). Given current cochlear implant technology the discrimination thresholds for pitch are still 3 times higher in CI patients vs. normal hearing listeners (3 vs. 1 semitone) and they are still much less able to recognize familiar melodies and instruments (25% vs. 88% and 45% vs. 94%, respectively, Kang et al., 2009). Even though some CI musicians can still perform music and are able to tune an instrument very accurately (<0.5 Hz deviation from wanted pitch; Lu et al., 2014) this is achieved by listening to beats rather than discriminating pitch. Electrode pitch to cochlear frequency mapping is also not as predicted but rather found to be shifted towards lower values by about 1–2 octaves and compressed, which limits pitch/frequency discriminability (Boëx et al., 2006; Dorman et al., 2007; Zeng et al., 2014). In fact, some state that poor electric pitch discriminability is the main factor limiting contemporary cochlear implant performance (e.g. Zeng et al., 2014). Pitch is not only encoded by the place of excitation in the cochlea but also by the temporal structure of responses of spiral ganglion neurons phase locked to the periodicity of sound (Plack et al., 2005). During natural listening the pitch of impinging sounds is dominated by lower-numbered, resolved harmonics, which indicates that information about pitch is normally combined across frequencies and thus cochlear location (Carlyon et al., 2008). Due to the aforementioned low spectral resolution, CI users typically have to rely on temporal

Abbreviations: AAV, adeno-associated virus; ABI, auditory brainstem implant; ChR2, channelrhodopsin 2; CI, cochlear implant; dB, decibel; Hz, Hertz; IC, inferior colliculus; mV, milli Volt; mW/mm^2, milli Watt per square millimeter; nm, nanometer; SGN, spiral ganglion neuron; SI, synchronization index; Thy1, thymocyte 1; VCSEL, vertical cavity surface emitting laser; μA, micro Ampere; μJ, micro Joule; μLED, micro light emitting diodes

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envelope cues to track pitch (Green et al., 2004). Temporal cues have been demonstrated to provide pitch up to around 300 Hz in CI users whereas normal hearing listeners can discern differences in pitch up to around 4 kHz (Oxenham, 2012; Zeng, 2002). Further psychophysical experiments suggest that timing information does not allow to extract pitch independent of the place of excitation in the cochlea (Oxenham et al., 2004). Together, these data suggest that pitch might be represented by a spatio-temporal code (Cedolin and Delgutte, 2010) which current CI coding strategies only partially fulfill. Current steering to create virtual stimulation channels has been investigated as a means to improve spectral resolution, word recognition and music appreciation with mixed, usually small effects (Berenstein et al., 2008; Landsberger and Srinivasan, 2009; Srinivasan et al., 2013). In either case, current steering significantly increases the current necessary to elicit a percept (Landsberger and Srinivasan, 2009).

In addition to the low frequency resolution of electrical coding, coding with a cochlear implant is also limited by relatively poor encoding of sound intensity. The output dynamic range of cochlear implant electrodes is restricted to a small range of electric currents, typically below 10 dB (Zeng et al., 2008) such that major compression and limitation of the dynamic range of incoming auditory signals is required. Given this compression several studies have shown linear correspondence between acoustic amplitude in dB and current amplitude in μA (Zeng and Shannon, 1992, 1994). When stimulus intensity is appropriately matched, just noticeable differences can be comparable between acoustic and electric stimulation (Donaldson and Viemeister, 2000; Wojtczak et al., 2003; Wojtczak and Viemeister, 1999). While reducing the dynamic range of electrical stimulation amplitudes when mapping acoustic signals to CIs has minor effects on phoneme recognition in quiet, it may significantly reduce speech perception in noisy environments (Zeng and Galvin, 1999). Additionally, reducing the intensity dynamic range of acoustic signals which are mapped to electrical stimulation amplitudes also reduces phoneme recognition in noise (Zeng et al., 2002). Thus, to provide cochlear implant users with a dynamic range of acoustic signals comparable to normal-hearing listeners (100–120 dB; see e.g. Hudspeth, 2014) while maintaining comparable intensity discrimination between acoustic and CI hearing likely require to increase the intensity resolution of CI coding.

In summary, there is still significant room for improvement in auditory prosthetics, even for the cochlear implant. Here, we review novel approaches aiming to improve cochlear implants via optical stimulation. Future optical cochlear implants promise lower spread of excitation in the cochlea (Fig. 1). Via the increased number of independent stimulation channels optical stimulation is expected to enhance spatial resolution of frequency and intensity coding. This, in turn might improve speech recognition in noise, music appreciation, prosody detection, and tonal language perception. Last but not least, optical stimulation might support a richer listening experience.

2. Light-tissue interactions

Is it possible to stimulate neural elements by light? Probably one of the first successful attempts at neural stimulation with light was reported by (Fork, 1971). In his experiments with *Aplysia californica* blue light was able to stimulate any tested cell to fire action potentials. This seminal observation makes optical stimulation an attractive target for basic research as well as to devise prosthetic devices including cochlear implants.

Light interacts with tissue in various ways due to absorption, scattering and changes in refractive indices (for a review see Jacques, 2013). These optical properties differ between different

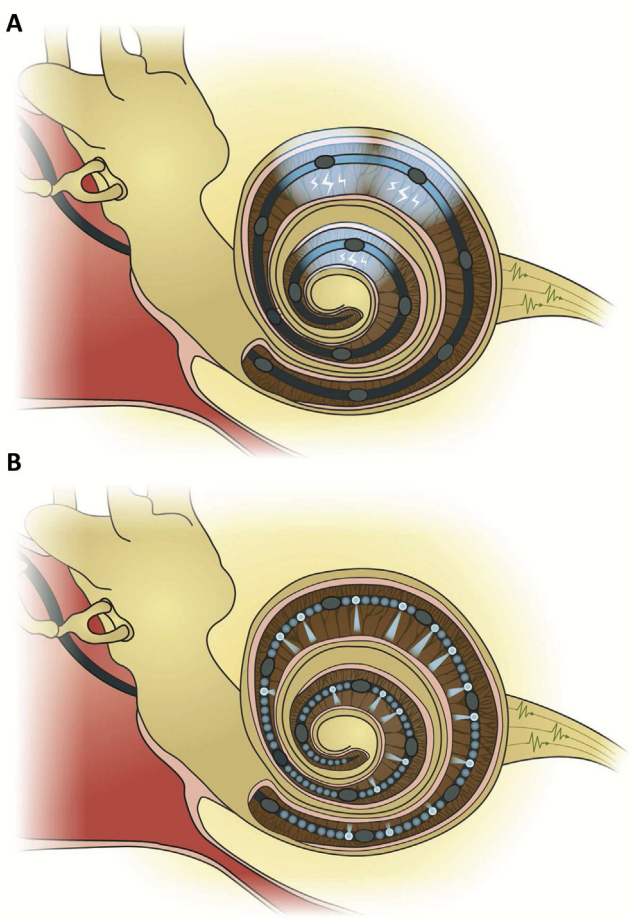

Fig. 1. Schematic overview of the 'promise' of the concept of optical cochlear implants. Current cochlear implants use around 10 to 20 stimulation channels spread out along the cochlea (A). Broad spread of activation caused by electrical pulses, which leads to channel crosstalk. Focused optical stimulation (B) promises to increase the number of effective stimulation channels and thus to make better use of the fine grained frequency resolution available in the cochlea.

tissues and are wavelength dependent (Yi and Backman, 2012). Scattering of light diverts the light from a straight path without significantly changing the energy of the light. Thereby, scattering limits the spatial resolution of optical stimulation. Scattering in the tissue can be understood as light traveling through cellular and extracellular components of various sizes with a refractive index different from the aqueous medium they immerse in. Absorption is usually dominated by water at infrared wavelengths and by hemoglobin in the visible spectrum. The amount of absorption by tissues determines the penetration depth of light. Together, the absorption spectra of hemoglobin and water exhibit a dip around 800 nm (Jacques, 2013). Hence, light with wavelengths around 800 nm travels farthest in tissue. Upon absorbing a photon a molecule is excited and might relax in principle in 2 different ways: radiative and non-radiative. Radiative relaxation results in emission of a photon (this effect is used in fluorescence imaging) while non-radiative relaxation includes collisions with other molecules (thus the tissue heats up).

Both, scattering and absorption reduce the density of light available for optical stimulation and consequently are related to the power requirement of an optical prosthetic device. Thus to understand the path of light during optical stimulation detailed modelling of cochlear tissue is required (Hernandez et al., 2014; Thompson et al., 2012). In an attempt to simulate optical

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