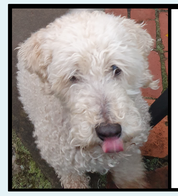
MRC Cognition and Brain Sciences Unit

UNIVERSITY OF CAMBRIDGE

Cambridge Hearing Group



ALFIES stands for ALternating-Frequency Interleaved Electrical Stimulation. By pure coincidence, it also happens to be the name of Bob Carlyon's dog.

ALFIES unwrapped: recording cortical responses to sustained high-rate stimulation in cochlear implant users

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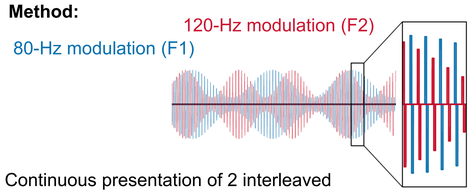
ALFIES Introduction

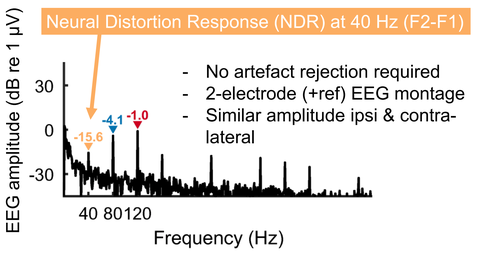
We recently developed a method called ALFIES that exploits neural nonlinearity to measure the sustained cortical neural responses to electrical stimulation, uncontaminated by electrical artefacts, using a hyper-rate (262 kHz) electroencephalography (EEG) system [1,2].

Method:



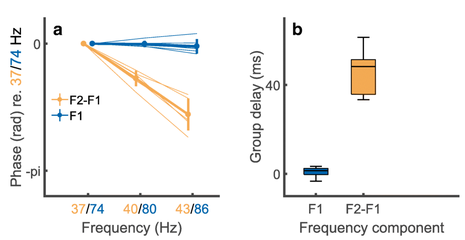
Continuous presentation of 2 interleaved amplitude-modulated pulse trains with high-rate carriers

Example result from one participant:



Group Delay:

The group delay across participants (2 AB & 5 Cochlear) suggested that the NDR is coming from the thalamus / cortex whereas F1 & F2 contain artefact:



Figures in this panel are from Carlyon *et al* 2021 [1]

Research Questions

Where is the neural distortion generated?

For there to be a response at F2-F1 Hz, there needs to be temporal smoothing (undoing the interleaving) *followed* by a nonlinearity.

Neural pathway

If temporal smoothing happens at the cortex, changing the inter-pulse interval between the two carriers from 8 µs to 1ms should not matter. If it happens at the auditory nerve, there should be a significant reduction after a few hundred µs. We have shown that this reduction occurs after 200-400 us, suggesting that smoothing happens as early as the auditory nerve [2].

Stimulation/Recording pathway

Stimulating/recording with equipment should not create significant amounts of distortion, unless it also introduces significant smoothing (enough to "undo" interleaving) followed by nonlinearities [1].

Further Questions

- ☐ Is the neural distortion response recorded with ALFIES quadratic or cubic? In previous experiments the two were confounded. If they are both present, they must be in phase with each other to allow for the strongest measurable response:
  - ☐ Quadratic (QDR): F2 – F1 = 120 – 80 = 40 Hz
  - ☐ Cubic (CDR): 2*F1 – F2 = 160 – 120 = 40 Hz
- ☐ Recent studies tried to record objective measures of auditory responses from the brainstem and thalamus using the CI reverse telemetry systems (instead of EEG) [4-8]. Is the CI telemetry system sufficiently linear to capture a neural distortion response with ALFIES?

Can it be used for clinical applications?

To be used as an aid for clinical programming, it should:

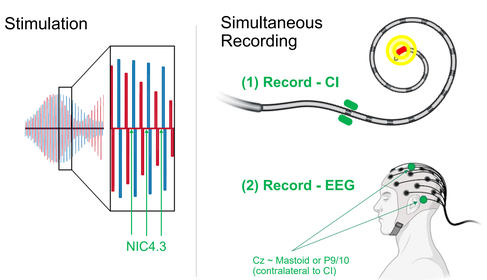
- ☑ be measurable in several makes of implants (Cochlear & AB implants have been evaluated [2])
- ☑ not require specialist equipment ([1,2] only used 262-kHz custom-made EEG, whereas [3] showed the method works with a standard 2 kHz system as well).
- ☑ have a strong relationship with loudness, as shown in [2]
- ☑ be measurable in real-time (simple fft processing can detect strong responses in 2-3 instead of 5 minutes) [1,2]

Methods

Recruited 10 users of Cochlear devices

- Recorded with an 8-channel 262-kHz BioSemi EEG
- Separated the QDR and CDR by shifting F1 from 80 Hz to 82 Hz:
  - Quadratic (QDR): 120 – 82 = 38 Hz
  - Cubic (CDR): 2*82 – 120 = 44 Hz
- Stimulated with two interleaved amplitude-modulated pulse trains (in sine phase = 0) with stimulus onset asynchrony of 200 µs and on adjacent electrodes, with a 4*F2 carrier rate for 5 min.
- Leveraged the **NIC4.3 telemetry** libraries in python v3.9 to record the voltage between stimulation pulses

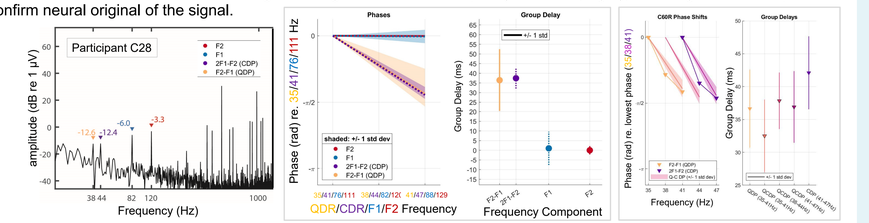
Stimulation Paradigm



Schematic of ALFIES recording using NIC4.3 recording telemetry & EEG

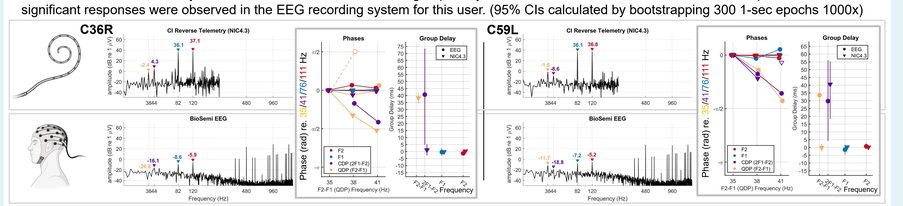
(1) Results: Quadratic vs Cubic Distortions

We observed significant QDRs in 8 of 10 CI users, and CDRs in 6 of 10 (see example participant C28, left). Across participants, primary amplitude modulation frequency components were dominated by electrical artefact, showing group delays of -2.2 – 2.2ms (F2) and -7.6 – 9.6ms (F1). Both QDR (F2-F1) and CDR (2*F1-F2) components showed group delays consistent with thalamo-cortical neural generators, between 32.1 – 42.8ms (CDR) and 20.4 – 52.5ms (QDR) (see below, middle box). Within participants, the two distortion products showed group delays weren't significantly different from each other (t(4)=0.79, p = 0.48), but showed significantly different amplitudes at the same frequency (41Hz: t(3) = 3.97, p = 0.028, QDR > CDR), and a consistent phase difference (41Hz: QDP-CDP phase ≈ -3π/2). Adjusting for the constant phase shift between the QDR and CDR and assuming that they originate from the same generators, group delays could be obtained within ≈ 5-minutes of recording at a single stimulation rate-pair (see C60R, right), reducing the time required to confirm neural original of the signal.



(2) Results: ALFIES 'Roaming Free'

Using the telemetry system of the CIs via the NIC4.3 research interface, we observed significant distortion responses with non-zero group delays that suggest a neural component in 3 of 10 CI users. However, these responses were inconsistent with the simultaneously-recorded EEG measurements. For CI user C36R (left), while a significant component was observed at the CDR, the group delay was indistinguishable from 0 ms (indicating it was dominated by electrical artefact), but the QDR showed a group delay of 38.3 ± 4.0 ms, consistent with a cortical neural generator. However, no significant component was observed at the QDR frequencies in the EEG recordings, and the CDR showed a non-zero group delay of 40.6 ± 34.3 ms, confirming a neural generator with the signal too close to the noise floor to distinguish whether it was cortical or subcortical. For C59L (right) we see a different pattern: a QDR dominated by electrical artefact and a CDR with a group delay of 37.0 ± 17.0 ms, consistent with a cortical generator. These EEG recordings showed QDRs and CDRs of 29.8 ± 25.9 and 33.6 ± 11.3 ms, respectively. Here, the two recording systems could be detecting the same neural signal from the CDR component, but not the QDR. A third user (C44R, not shown) showed a QDR dominated by electrical artefact and a CDR with a group delay of 22.9 ± 6.2 ms, consistent with a cortical response. However, no significant responses were observed in the EEG recording system for this user. (95% CIs calculated by bootstrapping 300 1-sec epochs 1000x)



Discussion

ALFIES allows for measuring the cortical neural response to high-rate, amplitude-modulated, sustained electrical stimulation, and could be leveraged clinically as an objective cortical measure of auditory perception in cochlear implant users in response to stimulation similar to that employed in clinical coding strategies. These results show that ALFIES distortion products measured with an EEG system represent a combination of quadratic and cubic components with consistent phase relationships, the former showing larger amplitudes. Further work is underway to optimise recording parameters (i.e. F1 vs F2 phase relationships) to maximize the observable response for clinical application. The results also demonstrate that it is possible in a few cases to observe cortical ALFIES responses using the reverse telemetry system of a CI itself, although these measurements are inconsistent with EEG recordings. For a reverse-telemetry system to work more consistently across patients for recording cortical responses, an additional electrode near the vertex is likely needed to capture a similar dipole as an EEG system.

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References: [1] Carlyon RP, et al (2021) JARO 22:141-159. [2] Guérit F, et al (2023) JARO 24:253-264. [3] Guérit, F, et al, Poster, 'ALFIES.' ARO M.W.M. Feb (2023). [4] McLaughlin M, et al, (2012) IEEE 20:443-454. [5] Attias J, et al (2022) Ear & Hear 43:1426-1436. [6] Sommers B, et al, (2023) Sci. Rep. 11:5383. [7] Beynon AJ, et al, (2021) Audiol. Res. 11:691-705. [8] Bell-Souder D. et al (2024) SciRep 14: 28366