MRC Cognition and Brain Sciences Unit

UNIVERSITY OF CAMBRIDGE

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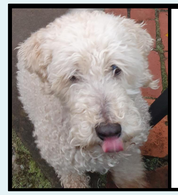

ALFIES stands for ALternating-Frequency Interleaved Electrical Stimulation. By pure coincidence, it also happens to be the name of Bob Carlyon's dog.

Towards using cochlear implant electrodes to record cortical responses to sustained high-rate stimulation

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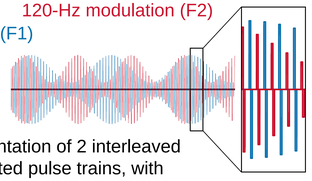
ALFIES Introduction

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) electroencephalogram (EEG) system [1,2].

Method:

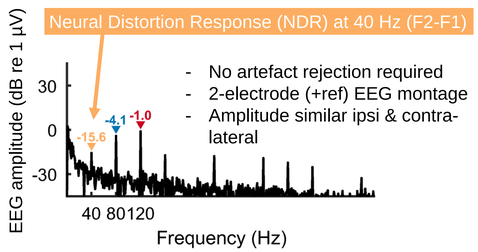
120-Hz modulation (F2)

80-Hz modulation (F1)



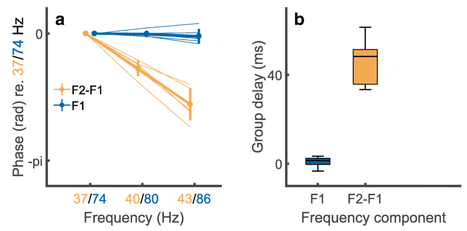
Continuous presentation of 2 interleaved amplitude modulated pulse trains, with either 2160 or 480 pps carriers

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 are artefact:



Research Questions

Where is the neural distortion generated?

For there to be a neural response, there needs to be smoothing (undoing the interleaving) *followed* by a nonlinearity.

Neural pathway

Smoothing/Temporal dependencies → Nonlinearities

F1 F2 F1 F2 F1 → F1 F2 F1 F2 F1 → F2 – F1

If 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

Nonlinearities (stimulation) → Smoothing/Filtering (EEG)

F1 F2 F1 F2 F1 → F1* F2* F1* F2* F1* → F1* F2* F1* F2* F1*

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

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 (can do in 3-6 minutes; method not shown here) [1,2]

Further Questions

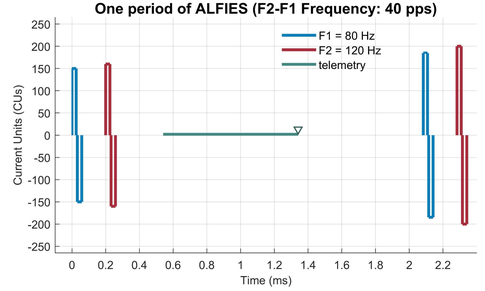
- ☐ Is the neural distortion response recorded with ALFIES quadratic or cubic? In previous experiments:
  - ☐ Quadratic (QDR): F2 – F1 = 120 – 80 = 40 Hz
  - ☐ Cubic (CDR): 2*F1 – F2 = 160 – 120 = 40 Hz
- ☐ Recent studies tried to record objective measures of auditory responses more central than ECAP responses that originate from the auditory nerve [4-7]. Is it possible to record a neural distortion response with ALFIES using only the electrodes currently in a cochlear implant?

Methods

Recruited users of Cochlear devices

- Used 8-channel 262-kHz or 2-kHz BioSemi EEG
- In most conditions, 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 2 interleaved amplitude-modulated pulse trains with stimulus onset asynchrony of 200 µs and on adjacent apical electrodes, with a 4*F2 carrier rate (either 444, 480, or 516 pps) for 5 minutes
- Leveraged the **NIC4.3 telemetry** libraries in python v3.9 to record the voltage between stimulation pulses

Stimulation Paradigm

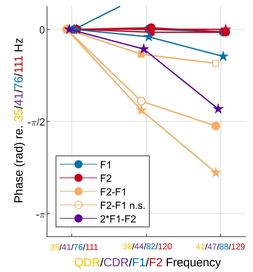


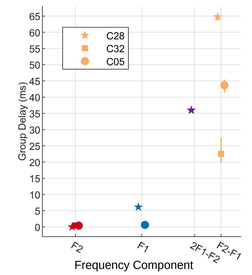
Schematic of 1 stimulation period of ALFIES using NIC4.3 recording telemetry

Preliminary Results: Quadratic vs Cubic Distortions

We expect that the neural distortion response seen in previous ALFIES studies is largely quadratic (F2-F1). However, it's possible that there is also another (cubic, 2*F1-F2) component that contributes to these responses. Therefore, 4 Cochlear users were stimulated in Monopolar mode using two adjacent electrodes at the apex with F1 shifted up 2 Hz to separate the quadratic and cubic distortion products.

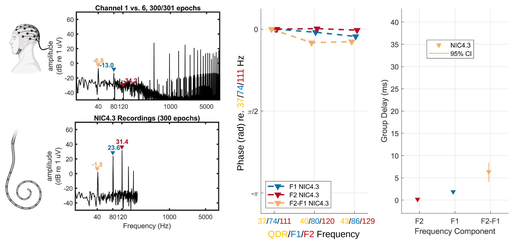
One user did not show significant responses at either distortion frequency. Two users (C05 and C32) showed significant power at the QDR but not at the CDR. The third (C28) showed significant power at both the QDR and the CDR. All group delays suggest neural responses from the thalamus / cortex. For C28, the CDR (35-37 ms) responses showed shorted group delays than the QDR (63-66 ms). Fig error bars are 95% confidence intervals:





Preliminary Results: ALFIES 'Off the Lead'

Preliminary data from one participant stimulated using adjacent apical electrodes in a bipolar (BP-3) configuration is shown on the right. Distortion products are observed at 40 Hz both with the EEG recordings using a contralateral montage of Cz vs P9 (top left), and the implant recordings collected using a basal electrode with reference to the extra-cochlear Case electrode (bottom left). The group delay is 41.6 ± 0.8 ms for the EEG recording, consistent with cortical responses. The group delay calculated from the NIC4.3 recording is 6.3 ± 2.1 ms, consistent with brainstem responses. 95% confidence intervals were calculated by bootstrapping the 300 one-second epochs 10,000 times.



However, these delays should be interpreted with caution for a few reasons. The lack of linearity in the phases as the distortion frequency is changed suggests that the measured response at the distortion frequency may be a combination of neural response and electrical artefact, or of multiple neural generators. This means that the assumptions made to determine the neural generator of a response using the group delay may be flawed, as it assumes a single neural generator. We also conducted saline bath experiments with a CI522 cochlear implant, allowing us to characterize the electrical artefact without any neural response present. Often these recordings showed no power at the distortion frequency, but when they did they sometimes showed group delays with lower 95% confidence intervals at 0.5-1 ms.

Discussion

ALFIES allows for measuring the cortical neural response to high-rate, sustained electrical stimulation. Preliminary results suggest that ALFIES distortion products measured with an EEG system are likely to be primarily quadratic, but may also be a mixture of quadratic and cubic. Preliminary results also suggest that it *may* be possible to record neural responses to the ALFIES stimulus using the telemetry system of the Cochlear device, but these responses may not be cortical, may be a mixture of artefact and neural response, or a mixture of multiple neural generators. More data is needed to confirm.

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References: [1] Carlyon RP, Guérit F, Deeks JM, et al (2021) JARO 22:141-159. [2] Guérit F, Deeks JM, Arzounian, D, et al (2023) JARO 24:253-264. [3] Guérit, F, et al, Poster, 'ALFIES.' ARO M.W.M. Feb (2023). [4] McLaughlin M, Lu T, Dimitrijevic A, Zeng FG (2012) IEEE 20:443-454. [5] Attias J, HabibAllah S, Tarigoppula, VSV, et al (2022) Ear & Hear 43:1426-1436. [6] Sommers B, Long CJ, Francart T (2023) Sci. Rep. 11:5383. [7] Beynon AJ, Luijten BM, Mylanus EAM (2021) Audiol. Res. 11:691-705