Microcontroller-Based Low Latency Audio System to Study Cortical Auditory Evoked Potentials: Applications with Intraoperative Language Mapping

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***Abstract*—Language processing in the brain comprises complex neurophysiology involving multiple regions and multimodal functions like cognition, memory, speech, etc. Recent studies show language processing is not restricted within anatomically established cortical language regions, and there is considerable inter-person variability. Clinically intraoperative functional language mapping is critical for studying patient-specific language processing and identifying the eloquent cortex to retain language functionalities during resection surgeries. Cortical auditory evoked potential (CAEP) induced by different auditory stimuli can provide a profound understanding of language processing. In this study, we present a low-cost, low-latency microcontroller-based audio system to induce and analyze CAEP. The system is established using off the shelf components; a 32bit Teensy (3.2) microcontroller, Teensy (3) audio shield etc. which makes it easily replicable. The Teensy can generate digital trigger locked to auditory stimulus onset to interface the system with biosignal amplifiers to record and study neural data simultaneously. The presented hardware tools enable the analysis of neural signals aligned with the audio stimuli with sub-millisecond temporal precision. Implementation of the system can provide a flexible platform to observe and analyze real-time cortical CAEP in the clinical settings. The system also provides great customization opportunities to study not only CAEP but also complex language processing tasks.**

Keywords—Cortical auditory evoked potential (CAEP), Electrocorticography (ECoG), Language processing, Functional brain mapping

I. INTRODUCTION

Human language functions are complex processes involving multiple brain regions and often involve additional functions like memory, cognition, motor, etc. Anatomically frontal and temporal cortical regions are known to be language areas [1]. But studies show that different cortical regions can be activated depending on the modality of language function, and there is significant inter-personal variability. Pathological conditions such as epilepsy and tumor can alter functional connectivity and/or induce reorganization [2]. In clinical practice, when a tumor is near functional brain regions and requires resection surgery, the eloquent cortex needs to be localized to achieve a safe maximal tumor resection to retain functionalities. This is done routinely with somatosensory evoked potential (SSEP) to map the sensorimotor cortex and delineate the central sulcus [3].

Currently, cortical mapping with direct electrical stimulation (DES) remains the gold standard for defining language areas [4,5]. But DES frequently induces seizures from prolonged usage and cannot provide information about functional brain activity, which is important to understand language processing and generation. Moreover, cortical language areas identified by DES might not be able to predict post-surgical outcomes properly [6]. Intraoperatively electrocorticogram (ECoG) data recorded while patients are engaged with different cognitive-linguistic tasks have been used to study language processing [7,8]. Recent studies show differences in active language areas identified using neural recording and DES [9,10].

Cortical auditory evoked potential (CAEP) has been studied mainly in epileptic patients from electroencephalogram (EEG) and magnetoencephalogram (MEG) data using click, tone, or burst stimuli [1,11,12]. Properties of N1, first negative peak of AEP signals around 100ms, and P2, positive peak after N1, are mostly studied in different experiments [13,14]. CAEP recordings in these studies were performed using various commercially available amplifiers including TDT RZ2 processor, Bio-logic Navigator Pro System (Bio-logic Systems Corporation, Natus Medical Inc., Mundelein, IL), Madsen OB-822 Audiometer, GSI 61 clinical audiometer, etc. These systems include offline analysis of recorded data and use expensive audio systems that require sophisticated operations. Moreover, it is important to understand the propagation of cortical activities due to different auditory stimuli to understand the complex language functions.

This study proposes a low-cost, low-latency microcontroller-based audio system, built using off the shelf components to provide controlled auditory stimuli with sub-millisecond temporal resolution and stimulus onset information. The system is designed to deliver auditory stimuli in the form of meaningful words/speech or tone in a controlled fashion and record neural data simultaneously while the patients categorize between types of stimuli. The system can be customized to provide different auditory stimuli; click, tone burst, phrase, sentence etc. to study different language functions. Using this system, we have collected ECoG from three patients intraoperatively using

This work was supported by the National Science Foundation (Award Number 2124705).

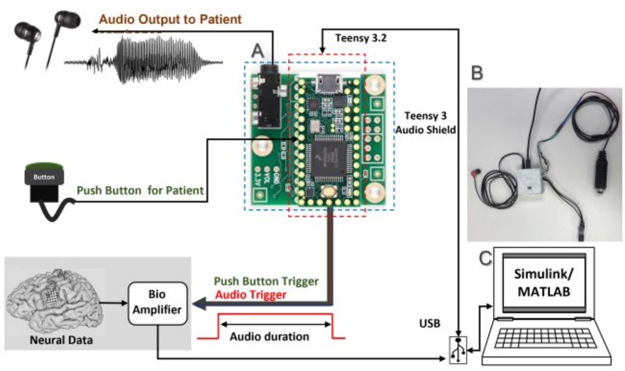

Fig. 1. Audio system setup. (A) Internal structure consisting of 32-bit Teensy 3.2 microcontroller (red dotted box) embedded on Teensy 3 audio shield board (blue dotted box) which houses the SD card (B) 3D printed box containing the audio system, with earphone, digital trigger output, button input (C) Computer Interface with Simulink/MATLAB for synchronized recording and visualization of neural and trigger data.

beep, word, and tone auditory stimuli. Automatic synchronization of the neural data with the auditory stimuli using the established setup enables real-time mapping of elicited evoked responses over the electrode grid placed on the cortical surface.

II. Materials and Methods

A. Hardware Components

The audio system has two main hardware components, the Teensy 3.2 microcontroller which includes a 32-bit 72MHz ARM Cortex-M4 processor as shown in Fig.1 and the Teensy 3 audio shield [15]. The hardware components are compatible with the Arduino programming integrated development environment (IDE) and many Arduino Libraries [16].

The audio shield converts digital audio to analog stereo output and allows working with 16-bit, 44.1 kHz sample rate audio with Teensy [17]. A secure digital (SD) card is used to store the audio files in WAV format, which is connected to the serial peripheral interface (SPI) of the Arduino board. Earphones are connected to the audio shield with audio jack, which provides auditory stimulus to patients. Digital I/O pins of Teensy are used to read the push button input to register the response of a subject. Digital I/O pins are also used to provide digital trigger output at 3.3V, which can be connected to the digital input of the bioamplifier to synchronize auditory stimulus onset with neural data for better interpretation of electrophysiological activities. The trigger output is a 3-bit digital signal that encodes the type of auditory stimulus and button state (Table I).

TABLE I. AUDITORY STIMULUS SUMMARY

Stimulus Type	*Description*	*Duration (ms)*	*Trigger Level*
Short beep	5 sine waves tapered at both ends with frequencies 750, 1000, 1250, 2000, 3000 Hz	30	2
Long beep	5 sine waves tapered at both ends with frequencies 750, 1000, 1250, 1500, 1750 Hz	300	
Word	14 nouns (apple, bite, car, cat, cry, doctor, dog, jump, move, phone, radio, run, sing, swallow)	400~600	2
Tone	7 piano tones, 7 sine waves (500, 600, 700, 800, 900, 1000, 1500Hz)	500	3

To quantify the latency and jitter between the auditory stimulus and digital trigger output, a USB based data acquisition card (USB-1208FS, Measurement Computing Corporation), and DAQami v4.2.1 software was used to acquire auditory and digital trigger signals at 25kHz sampling rate.

B. Audio

The system is designed to deliver custom auditory stimuli with different duration. Using Audacity software version 3.2.1, the WAV files can be modified to have desired amplitude (up to 60dB), duration, etc. In our study, we created 3 types of stimuli: beep, word, and tone (Table I). The words were recorded in-house with a microphone by a native US English speaker, using ABLETON-LIVE software. For the word and tone categorization task, fourteen words and fourteen tones, each having a specific ID, are organized randomly. The words consist of object and action names chosen from the studies of the most frequently used words in Written and Spoken English [18]. The words were chosen to ensure ease of understandability by patients. The system generated a digital trigger for each category.

C. Software Modules

The audio system is connected to a computer where communication between these is established with CNELBehv, an in-house built C software running in Windows MS OS [19]. It is a general-purpose software module that implements a buffered User Datagram Protocol (UDP) server utilizing MS Windows Socket API [20]. It uses Windows OS Multimedia Timers to run periodic tasks at 10ms resolution. The Teensy of the audio system also runs at 10ms resolution (100Hz) to match the rate. In addition to generating digital triggers, the audio system sends the ID of the audio being played over the serial port of the microcontroller at the rate of 115200 bits per second. CNELBehv receives these USB packets and forwards them to Simulink/MATLAB over UDP. A customized MATLAB Graphical User Interface (GUI) controls the audio delivery.

D. Intraoperative Recording Setup

Three subjects (2 male and 1 female) aged 56 to 64 years with intact language functionalities were operated on for temporal lobe glioma resection (Table II). Intra-operatively, ECoG mapping using the audio system was performed while the subjects engaged in cognitive-linguistic tasks. The Institutional Review Board (IRB) of the University of Houston and UT MD Anderson Cancer Center, Houston, TX, USA, reviewed and approved the study protocol.

One or two days before the surgery, patients were trained with the audio system to verify their hearing capabilities. During the surgery, patients were anesthetized to perform the craniotomy. Then 32 channel (4×8) subdural grid electrodes (Ad-Tech, Michigan, MI) of 4.0mm diameter platinum contacts with 2.3mm contact exposure and 10mm contact

TABLE II. AUDIO SYSTEM BASED TASK SUMMARY

Patient ID	*Ear*	*CAEP Task*	*Word/Tone Categorization Task*
P1	Ipsilateral	Short beep (1, 2Hz)	Button press and verbal response
P2	Contralateral	Short beep (2Hz)	Button press and verbal response
P3	Contralateral	Long beep (0.5Hz)	Verbal response

spacing were placed above the cortical region invaded by the tumor. FDA cleared 256 channel biosignal amplifier g.HIamp (g.Tec, Graz, Austria) was used to record ECoG data and trigger signals provided by the audio system with a sampling rate of 2.4kHz and 24bit A/D resolution. In Simulink/MATLAB, data recorded from the amplifier and CNELBehv were synchronized and visualized using gHisys Simulink Highspeed library (v3.16.01, gTec, Graz, Austria).

After the grid placement, beep stimuli were delivered at different frequencies when the patients were anesthetized (Table II). Then, patients were awakened from anesthetized state by discontinuing anesthetic agents. When they were hemodynamically stable, patients were asked to pay attention while beep stimuli were provided again. Afterward, word and tone stimuli were delivered at a 3s time interval. In separate sessions, they were asked to respond by pressing a push button or verbally if they heard either word or tone. Using this feedback we ensured that the patients were paying attention to the task.

Intraoperatively the average real-time CAEP was visualized within a time window of 100ms pre-onset, 300ms post-onset for the beep stimuli. The onset time was identified using the positive edge of the trigger obtained from the audio system using the amplifier. The CAEP amplitudes were also projected as a 2D heatmap using a MATLAB GUI. During the word and tone categorization task, average CAEP activities were visualized within a time window of 500ms pre-onset and 750ms post-onset. A similar 2D heatmap was also projected.

III. Results

A. Audio System Latency

To assess the latency of the audio system, the word 'radio' was played 50 times at 3s intervals, while both the auditory output and digital trigger generated by Teensy were recorded at 25kHz using a USB DAQ board. Sample raw audio and digital trigger codes generated by the system are visualized in Fig 2A. As shown in Fig. 2C and D, with respect to trigger output, we observed an average audio output latency of 2.6ms with a jitter of 80µs. The sub-millisecond jitter (80µs) is expected to improve the estimation of the phase locked CAEP.

B. CAEP Analysis

The CAEP activities are analyzed separately for beep stimuli in the anesthetized and awake state. In P1 and P2 short beep stimuli did not produce significant CAEP. In P3, long beep stimuli generated evoked activity as early as 75ms post-onset in the anesthetized state (Fig. 3). The ECoG signals were high pass filtered with a cutoff frequency of 5Hz using second-order Butterworth IIR filter (slope +40dB/ decade) on MATLAB. A time-locked dipole of evoked potentials was observed around the sylvian fissure. At 120ms post-onset, we observed phase reversal of evoked potential dipole around the sylvian fissure. In the awake state, a similar dipole of evoked potentials was observed at the same cortical regions, much earlier at 60ms post-onset, where the phase reversal occurred at 100ms. The amplitudes of evoked potentials were higher in the awake state compared to the anesthetized state.

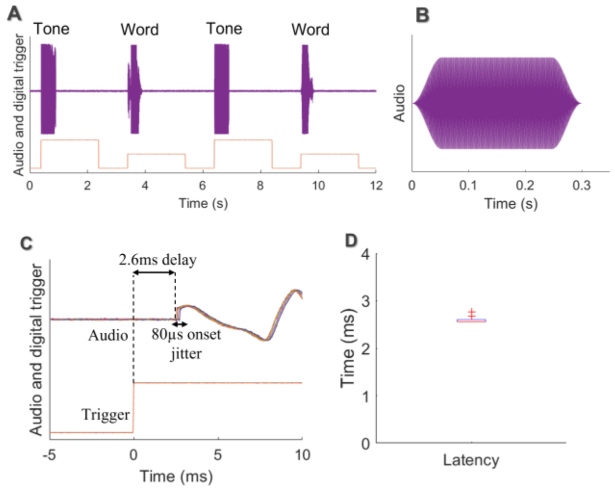

Fig. 2. Latency test between audio output and trigger from audio system (A) Analog audio output (purple) and digital trigger (orange) played at 3s time interval (B) Sample long beep (750Hz) audio used for CAEP task, (C) Overlap plot of audio and trigger output for latency test (D) Latency box plot. Audio output is 2.6ms delayed on average with a standard deviation of 80µs.

C. Word/Tone Categorization Task

ECoG signals (>5Hz) from word/tone categorization tasks were analyzed for CAEP activities separately for word and tone. In P3, CAEP induced by both word and tone generated a dipole, T1 around sylvian fissure at 55ms (Fig. 3). At 100ms phase reversal of the dipole, T2 was observed. In P1 and P2 similar CAEP dipoles, T1 around sylvian fissure were observed at 60ms and 50ms respectively, for both word and

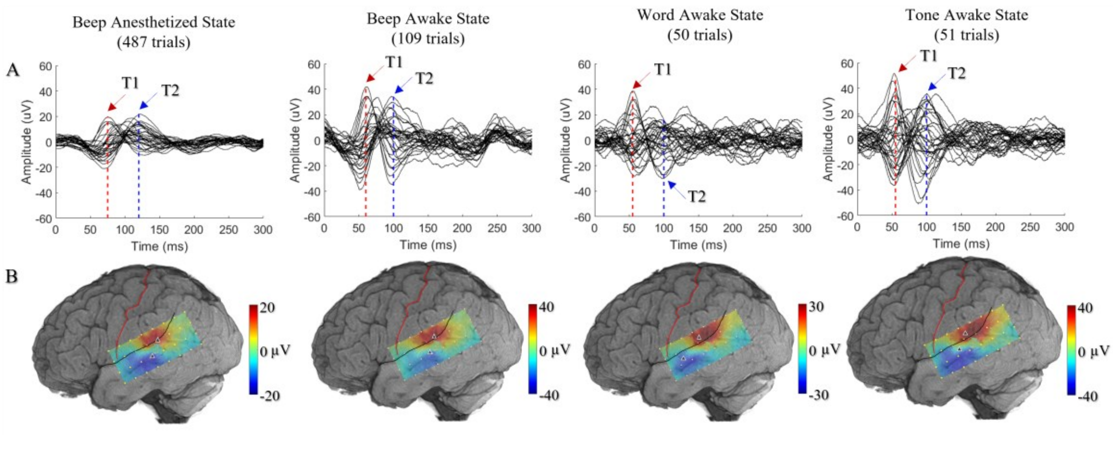

Fig. 3. CAEP in P3. (A) Average CAEP signals at different electrodes induced by different auditory stimuli, T1 indicates first dipole time, T2 indicates dipole phase reversal time. (B) CAEP amplitude heatmaps on 3D brain mesh generated from patient MRI, with marked sylvian fissure (black line), central sulcus (red line), and peak amplitude electrodes (gray triangle) at T1 time point. Positive peaks were consistently observed superior to the sylvian fissure.

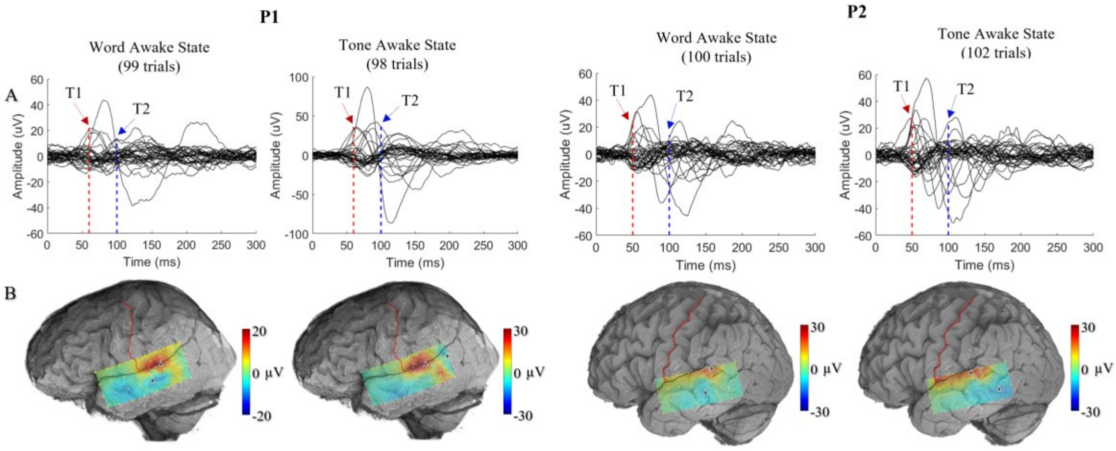

Fig. 4. CAEP in P1, P2. (A) Average CAEP signals induced by different auditory stimuli, first and second dipole time points are indicated as T1 and T2. (B) CAEP amplitude heatmaps on 3D brain meshes generated from patient MRI at T1 time point. Sylvian fissure (black line), central sulcus (red line), and peak amplitude electrodes (gray triangle) are marked.

tone stimuli (Fig. 4). In P2, the electrode grid was placed more inferior-posterior than in P1, P3.

We observed that regardless of the type of provided auditory stimulus (beep, word, tone), all stimuli induced evoked potentials that formed dipoles T1 and T2 around the sylvian fissure at 58.12±8ms and 102.5±7ms respectively. The dipole phase reversal from T1 to T2 was similar to the dipole phase reversal observed in SSEP (N20/P30) in the sensorimotor cortex [3].

IV. Conclusion

In this study, we described and used a low-cost and low-latency audio system. The system is built with off the shelf components and is easily replicable. It presents a platform to study neural activities induced by auditory stimuli with sub-millisecond temporal precision. To observe and analyze cortical CAEP in real-time, utilizing the established hardware tools can provide a unique opportunity to use the audio system in clinical settings. The proposed microcontroller-based system provides the capability to use customized auditory stimuli to design different linguistic tasks, so that it can be implemented to study different modalities of cortical language processing other than CAEP as well. The source code of our system, and the used audio files are provided on GitHub (https://github.com/InceLab/Audio_System).

V. Acknowledgment

We thank audio engineer Antonio Gonzales for recording the auditory stimuli.

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