CORTICAL AUDITORY EVOKED POTENTIALS:

IS THE ACOUSTIC CHANGE COMPLEX A TRANSIENT ONSET RESPONSE IN DISGUISE?

by

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Abstract

Cortical auditory evoked potentials (CAEPs) are believed to reflect the neural discrimination and encoding of sound. These responses include obligatory evoked potentials including the P1-N1-P2 complex. The P1-N1-P2 response that occurs at the beginning of the stimulus presentation is called the onset response, while the P1-N1-P2 response that occurs at the re-introduction of sound, such as after a silent interval (gap) in noise stimulus, is called the auditory change complex (ACC). Though the onset and the ACC responses are evoked by the same auditory stimulus, the matter of whether they are mediated by the same physiological mechanisms is met with inconsistency in the cortical auditory evoked response literature. The current trend is to refer to the responses as different events, indicating a possible belief that the source generators are also different. This retrospective study of 35 participants' datasets tested the null hypothesis that both the onset and ACC responses are generated from the same neural location. Dipole source modelling was conducted on existing CAEP gap-detection data to determine each response's source generators. Results showed dipoles for the ACC were significantly located more posteriorly (0.4±1 mm) than dipoles for onset P1-N1-P2 response, thus rejecting the null hypothesis. These unexpected results provide evidence that the transient onset and ACC responses are likely undergoing differing underlying neural processes in response to acoustic changes in the environment. These findings allow researchers to more confidently refer to both the onset and ACC responses as different events,

thereby diminishing confusion and increasing accuracy of future discussions about and clinical applications with CAEPs.

Lay Summary

Certain brain waves that are elicited by sound are called cortical auditory evoked potentials (CAEPs). When a noise stimulus begins, the resulting CAEPs are called the onset response. A silent interval, or gap, embedded in the noise stimulus, produces similar CAEPs that mimic the onset called the acoustic change complex (ACC). There is a lack of consistency in the CAEP literature, referring to the onset and ACC as either the same or completely separate responses. To clarify this confusion and further existing knowledge of CAEPs, this thesis analyzed gap-detection data to determine the areas of the brain where the onset and ACC responses occur. Findings show that the responses occur in different parts of the brain. Researchers can now confidently refer to the responses as different events and apply this knowledge in further studies as well as in any clinical applications of CAEPs.

Preface

This master's thesis is the original work of S. Cheema, completed under the guidance and mentorship of A. T. Herdman. Usage of data collected by R. Angel and A. T. Herdman at the University of British Columbia's BRANE Lab as part of a master's thesis is described in Section 2: Methods, subsections 2.1 to 2.7. The methods used to acquire the data received approval from the Behavioural Research Ethics Board of the University of British Columbia (certificate #H14-00441). Analyses of the data for the current thesis were conducted by S. Cheema and A. T. Herdman. Publications may be derived from this material at a later date.

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List of Abbreviations

ACC	Acoustic Change Complex
ANSD	Auditory Neuropathy Spectrum Disorder
BESA	Brain Electrical Source Analysis
CAEP	Cortical Auditory Evoked Potential
CAPD	Central Auditory Processing Disorder
CMS	Common-Mode Signal
DRL	Driven-Right Leg
EEG	Electroencephalography
EOG	Electrooculography
ERP	Event-Related Potential
HEOG	Horizontal Electrooculogram
MATLAB	Matrix Laboratory
MEG	Magnetoencephalography
SES	Socio-Economic Status
SNR	Signal-to-Noise-Ratio
UBC	University of British Columbia
VEOG	Vertical Electrooculogram
WEIRD	Western, Educated, Industrialized, Rich, and Democratic

Acknowledgements

A big thank you to my thesis supervisor, Anthony T. Herdman, for teaching me that if it walks like a duck and talks like a duck, it's probably a duck; and for reminding me that when it turns out not to be a duck, that's okay too. I am thankful for and inspired by his unrelentingly positive guidance and perpetual enthusiasm for the neural workings of the brain. I am also grateful to my thesis committee, Alexis K. Black and Todd C. Handy, for taking the time to support this work.

A special thank you to Rebecca Angel for her impressive work and data collection, that continues to further research conducted by members of UBC's BRANE Lab.

A fond thank you to my friend and future colleague, Heidi Schaefer, for her constant encouragement with this thesis.

Thank you also to my former classmates and fellow audiologists for their continued support.

Dedication

To my family, in deep gratitude for your support throughout this thesis, I could not have done this without you:

Mama, thank you always for your unconditional love. You are magnificent.

Pam, thank you for being the absolute best sister and friend I could have ever asked for. No coal for you this Christmas!

Fareedah, Bobby, and Keanu, thank you for Saturday night DnD, pancake/crepe/waffle breakfasts, and campouts in the dinosaur jungle.

Yumi, Darcey, and Emily, thank you for puzzle nights, pj parties, cathartic laughs, and fancy teas with those amazing éclairs.

And finally, to Kristin and Daniel: MMABOOYAH!!!

…and because dedications feel special

almost like wishes…

To COVID-19 and the resulting world-wide pandemic, I bid you away now.

1 Introduction

1.1 Cortical Auditory Evoked Potentials

Cortical auditory evoked potentials (CAEPs) are responses arising in the auditory cortex, elicited by acoustic stimuli (Davis & Onishi, 1969). They are believed to reflect electrical neural activity responsible for the encoding of sound (Abeles & Goldstein, 1972).

Literature has expounded on the viable clinical uses of CAEPs, which include objective measurements of auditory threshold in both older children and adults (Davis, 1965; Lightfoot, 2016), assessing the improvements in speech processing through auditory training, (Alain et al., 2015; Martin et al., 2008; Menning et al., 2000), measuring cortical plasticity and auditory encoding in hearing impaired individuals (Billings et al., 2012), and identifying disorders such as auditory neuropathy spectrum disorder (ANSD) and central auditory processing disorder (CAPD) (Michaelewski et al., 2004; Picton, 2013).

These CAEP responses include the obligatory transient evoked potentials consisting of three components: a small, positively deflected peak (P1), followed by a negative trough (N1), and a second more prominent positive peak (P2)

(Davis, 1965; Davis & Onishi, 1969). The transient responses have fittingly been termed the P1-N1-P2 complex.

1.2 Onset Response

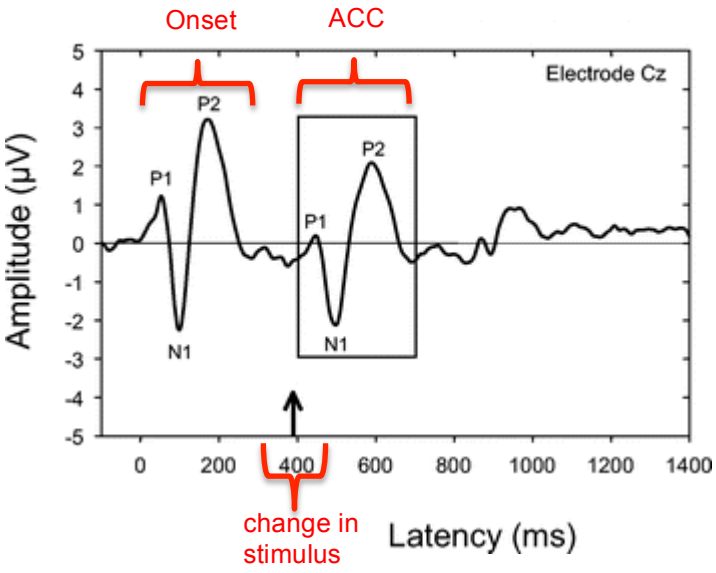
An elicitation of the transient P1-N1-P2 response complex that occurs at the start of a stimulus has traditionally been termed the onset response (Davis & Onishi, 1969; Hillyard & Picton, 1978; Näätänen & Picton, 1987; Pantev et al., 1996). Each component's peak occurs at specific timings between 50 to 200 ms from stimulus (Davis, 1965).

1.3 ACC Response

An acoustic change within a stimulus also elicits a transient-like P1-N1-P2 evoked potential, which has been labeled the acoustic change complex (ACC) (Martin & Boothroyd, 1999). An ACC can be evoked by a perceptible change in any of the acoustic properties of an ongoing stimulus, such as intensity, frequency, and phase. Most relevant to this thesis, is that an ACC can be evoked by a silent period (i.e., gap) in a stimulus, which is a rapid decrease and increase in intensity.

Figure 1.1

Onset and ACC Responses



Note. Adapted from "Speech Evoked Potentials: From the Laboratory to the Clinic", by B.A. Martin, K.L. Tremblay, and P. Korczak, 2008, *Ear & Hearing*, *29*(3), 285–313. Copyright 2008 by Lippincott Williams & Wilkins, Inc.

As shown in Figure 1.1, the ACC response has similar waveform morphology and timing as compared to the transient onset responses (Billings et al., 2009; Martin & Boothroyd, 2000; Martin et al., 2008). This leads to the impression that the onset and ACC are possibly the same responses. After all, the onset response can be considered an ACC response to a sudden increase in intensity.

An aim of this thesis was to investigate this possibility through source modelling analyses.

In recent years, the ACC has been increasingly studied due to its potential practical benefits in clinical assessment of auditory functions, specifically in terms of speech discrimination (Martin & Boothroyd, 1999). The ACC amplitude has been found to change proportionately to the magnitude of the acoustic change, such that the larger a change in stimulus frequency, the larger the change in ACC amplitude and morphology; just as what happens with the onset P1-N1-P2 complex. In their study, Kaukoranta et al. (1987) proved that the ACC could be elicited in an ongoing speech stimulus when a consonant transitioned to a vowel. To further demonstrate this, Martin & Boothroyd (2000) used a change in synthetic vowels, from /u/ to /i/, in an ongoing stimulus to study the elicited ACC. They found a shift in ACC amplitude after the spectral change in stimuli, specifically the shift in frequency modification that occurred in the second formant. Similarly, Ostroff et al. (1998), used the word “say” (/sei/) as their stimulus to determine if CAEP changes would be evoked in reflection of the acoustic shifts that arise during the transition of the fricative consonant /s/ to the voiced vowel /ei/. The authors also found spectral and amplitude changes to the ACC, and concluded that these shifts do indeed mirror acoustic changes in speech. Ostroff et al. (1998) as well as Martin & Boothroyd (2000) argued that the precision of discrimination produced by the ACC that were elicited by minute

spectral changes in speech stimuli bode well for the clinical use of ACC responses.

Additionally, the ACC shows acceptable agreement with behavioural measures (Martin & Boothroyd, 2000), and has good test-retest reliability among individuals with normal hearing as well as hearing aid and cochlear implant users (Friesen & Tremblay, 2006; Tremblay et al., 2003, 2006). Furthermore, evoking the ACC is a simple procedure, which yields good results even when listeners are passively exposed to sound stimuli. In addition, adequate signal-to-noise ratio can be achieved with relatively few presentations of stimuli (Kim, 2015; Martin et al., 2008). Researchers have thus concluded that the ACC shows promise as a tool for objective clinical application of auditory discrimination and speech perception capacity (Kim, 2015; Martin & Boothroyd, 2000; Martin et al., 2008; Ostroff et al., 1998).

1.4 Onset = ACC?

The similarity of the ACC to the onset response, however, raises the question: is the ACC simply a transient onset response in disguise, occurring during a change in a stimulus? If this is found to be true, it follows that the reverse must also be true: the transient onset P1-N1-P2 response is essentially an ACC response to a “change” from low-level acoustic noise to a higher intensity sound.

To answer the question of whether or not the onset and ACC responses are in fact the same neurological events in the brain, this thesis proposes to investigate and compare the neural sources of these two response complexes.

Though the onset and ACC responses are evoked by similar changes in the acoustic stimulus, the matter of whether or not they are mediated by the same physiological mechanisms is met with inconsistency in the CAEP literature. The prevailing position is to refer to the responses as different events, indicating a possible belief that the source generators are also different (Kim, 2015; Lightfoot, 2016; Martin et al., 2010; Martin & Boothroyd, 1999; Mathew et al., 2017; Presacco & Middlebrooks, 2018).

Although the ACC is being increasingly explored for clinical use, research devoted to the ACC's underlying physiological mechanisms is limited. Most studies determining the source generators of CAEPs mainly focus on onset and offset responses (Hillyard & Picton, 1978; Pantev et al., 1996; Picton, 2010; Takahashi et al., 2004). The literature is still mostly sparse with respect to investigating the neural sources of the ACC responses and whether or not they differ from the onset responses.

In their paper, Martin et al. (2008) noted the lack of clarity between the onset and ACC responses but added that this differentiation may not affect the previously

outlined proposed clinical uses of the ACC response. However, it can be argued that clarifying the differences, if any, of the onset and ACC responses may provide further understanding of the function of CAEPs as well as add to our existing knowledge of auditory processing, which can perhaps lead to more efficient and accurate clinical usage of CAEPs.

1.4.1 Source Localization

Source localization using electroencephalography (EEG) has been used for more than 80 years as a non-invasive technique to study the function of the brain. CAEP responses are recorded from electrodes located on the scalp (Davis, 1965); these voltage potential measurements can be used to determine neural sources underlying the responses (Grech et al., 2008; Hämäläinen, 1992). Dipole modelling has proven to provide accurate results (Ponton et al., 2002; Scherg, 1990; Scherg & Von Cramon, 1986) and studies have successfully used source localization to compare onset and offset CAEPs in animal and human cortices (Abeles & Goldstein, 1972; Pantev et al., 1996).

1.4.2 Gap-in-Noise Testing

CAEP gap-detection can be used to evaluate temporal resolution acuity. This refers to the ability of the auditory system to detect changes (eg. frequency, duration, phase) in stimuli over time. The central auditory nervous system relies heavily on temporal resolution in terms of detecting and discriminating sound.

Research, including previous results from UBC's BRANE Lab, has shown that ACC responses occur to gaps (silent intervals) embedded in noise bursts (Angel, 2016; Lister et al., 2007; Martin & Boothroyd, 1999). Using gaps embedded within a stimulus, effectively changes the auditory signal by means of silence and results in another P1-N1-P2 response, the ACC. Furthermore, because gaps in noise do not present any other acoustical change in stimulus properties (e.g. frequency) that might add to generating extra perceptually or cognitively evoked potentials, gaps can be effective in generating ACCs that might mimic the onset responses.

Additionally, it can be thought that presenting a stimulus immediately following a gap is akin to presenting a stimulus after a longer interval between stimuli. In other words, a gap is just a very short inter-stimulus interval, thus, it is reasonable to posit that the ACC to the gap might simply be the onset response to the start of the next stimulus following the gap.

1.5 Purpose

This thesis proposes to test the null hypothesis that these differently labeled CAEPs – onset and ACC responses – are generated from the same neural location. The resulting evidence, whether the responses are the same event or truly different phenomena, will supply useful data in clarifying CAEPS (in particular, the ACC) in all future discussions, furthering the understanding of

central auditory processing functions, and the application of clinical evaluations of such functions.

2 Methods

2.1 Data Collection

Using the retrospective design, this study acquired existing CAEP gap-detection data collected within the BRANE Lab at UBC. The data was collected for a previous study whose methods were approved by the Behavioural Research Ethics Board at the University of British Columbia (Angel, 2016).

2.2 Participants

All 47 participants (31 female, 16 males; ages 18 to 40 years) who engaged in the original study granted informed consent and reported a history of normal hearing, clear of otitis media. They reported no cognitive, neurological, learning, communication, or perceptual problems. No injuries to the head nor ototoxic drugs were reported. All procedures were conducted at UBC's BRANE Lab. Participants were given an honorarium for their involvement.

The original study's data consisted of 47 sets of EEG information in two conditions, active (behavioural) and passive (objective). The resulting active condition data was comprised of 36 complete sets of EEG information, while passive condition data was collected from all 47 participants. Of the 47 passive datasets initially included in this thesis, 11 were excluded because three datasets

were collected as pilot recordings and eight datasets contained elevated levels of blink artefacts and EEG noise (see methods section 2.8 below). The current study included 35 participants' passive-condition datasets.

2.3 Procedure

As explained in Angel (2016), procedures consisted of audiometric testing to confirm normal auditory function, behavioural gap-detection trials to obtain active response data for the purposes of the original study, and objective gap-detection trials where passive response CAEP information was recorded. The following sections describe each procedure in greater detail.

2.4 Audiometric Testing

A hearing screening was performed on every participant. Normal hearing status was screened for using pure-tone air conduction via E-A-RTONE 3A insert earphones in a soundproof room and determined by a criterion of equal to or less than 20 dB hearing sensitivity at 500 to 4000 Hz in both ears. Tests for middle-ear function included otoscopy and immittance testing, using the typical tympanometric probe tone of 226 Hz. All participants were found to have typical hearing sensitivity and middle-ear function.

2.5 Behavioural (Active) Gap Detection Trials

Angel (2016) used behavioural gap-detection testing to confirm participants' temporal integration was within normal limits; normal was defined as < 20 ms for gap-in-noise tests. This data was used in the present study only to confirm typical temporal resolution of the participants' hearing sensitivity. .

2.6 EEG Recording

Every participant's EEG data was recorded via BioSemi's ActiView2 system and included their CAEP information from each trial. A sampling rate of 1024 Hz was used on the EEG signal and a band-pass filter was applied, with a minimum of 0.16 Hz and a maximum set at 208 Hz. The raw data was saved in BioSemi data format (.bdf) on UBC's BRANE Lab computer system.

Testing took place in a sound booth where participants wore a BioSemi electrode cap with a 64-channel expanded 10/20 layout with the addition of two electrodes placed on the mastoids. A cap was selected to match each individual's head size using measurements based on their Fz, Pz, T8, T9, as well as nasion and ion positions. Two common electrodes, called the common-mode signal (CMS) and driven-right leg (DRL) that were located close to CP2 and CPz, served as a reference for each of the 64 channels. Horizontal and vertical electrooculography (EOG) were collected to capture eye blinks and movements. The EOG

electrodes were placed close to the outer canthi of both eyes, as well as on the supraorbital and infraorbital margins of the left eye.

2.7 Stimuli

A custom Matrix Laboratory (MATLAB) program, developed by the Mathworks Corporation, generated stimuli, which had a complete duration of 1000 ms, with a broadband noise burst occurring for the first 500 ms. A silent gap was presented at 500 ms post-stimulus onset, with a duration of either 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 ms. Each gap duration was presented a total of 100 times per participant in a randomized order to prevent bias. The gap was always followed by a broadband noise burst lasting until the 1000 ms post-stimulus onset mark. Thus, the trailing noise was shorter in duration as the gap duration increased. This ensured consistency of stimulation duration in each trial and did not provide a duration cue for participants when they performed the active task of detecting gaps in noise (data not used in this thesis). The stimulus onset asynchrony was also randomized to be between 1850 and 2150 ms in order to reduce slow steady state responses such as the contingent negative variation (Picton, 2010).

The stimuli were sent via an Interacoustics audiometer and calibrated using a sound level meter, SoundPro™ to a 60 dB SPL baseline to peak. Stimuli were delivered to a participant's left ear through E-A-RTONE 3A insert earphone, while a foam plug occluded the right ear to minimize air-conducted sound crossover.

While sound crossover to the right ear might have still occurred via bone conduction, it would be at very low levels considering most adults have 0-15 dB interaural attenuation via bone conduction (Katz et al., 2015; Nolan & Lyon, 1981; Stenfelt, 2012). Participants were specifically instructed to ignore the stimuli as they remained awake, watching a muted movie with subtitles.

2.8 CAEP Data Analysis

To test this study's hypothesis, the raw EEG data was loaded in the Brain Electrical Source Analysis (BESA®) software program (BESA GmbH company). Preprocessing steps were performed for the following: artefact correction, rejection, filtering, and averaging. These are described below.

2.8.1 EEG Preprocessing

Artefact correction was applied to the entire EEG information of each participant's data to remove EOG noise interference due to participant eye blinks, eye movements, muscle artefacts, and unwanted high amplitude EEG changes that might result from intermittent electrode impedance changes. Horizontal Electrooculogram (HEOG) artefact limit was set at 150 μV while Vertical Electrooculogram (VEOG) artefact limit was set at 250 μV for the program to find, isolate, and correct eye blink artefacts. After a visual scan of each dataset to ensure the majority of eye blinks were removed and observations were logged, the data was prepared to be parsed into trials for averaging.

Within BESA's paradigm viewer, artefact rejection was run with a band-pass filter of 0.10 Hz with a slope of 6 dB per octave to 30 Hz with a slope of 24 dB per octave to remove artefacts in waveforms caused by equipment and patient fatigue, in addition to eye blinks. The artefact rejection amplitude method was used and set at a criterion of ±100 μV, meaning any event-related potential (ERP) trial with an amplitude over 100 μV from -200 to 1000 ms were rejected. An ERP trial was defined as an epoch of -500 to 1500 ms time locked to the onset of each stimulus noise burst.

Conditions with gaps < 10 ms had varying morphologies across participants as the gap duration got closer to their behavioural gap-detection thresholds. ERPs for conditions with 10 to 20 ms gap durations had remarkably similar morphologies because they were suprathreshold with respect to the participant's gap-detection threshold. To improve signal-to-noise ratio (SNR), ERPs to gaps of 10 to 20 ms were averaged together. An a priori SNR criterion was set at ≥ 4. An additional criterion was set such that the total number of trials had to be greater than 40 trials per condition. This was set as a lower limit for obtaining an adequate SNR for CAEPs (Billings et al., 2009; Picton, 2010). BESA's paradigm automatically counted and displayed the number of trials. Only one dataset was found to have a total number below the criterion of 40 trials and was excluded from analysis. The mean number of trials included in each of the remaining 35

participants' averaged ERP waveforms was 437±91 trials. The ERP data were then averaged across trials to generate averaged evoked responses where CAEPs can be observed. ERP trials were band-pass filtered between 1.6 Hz (6dB per octave) and 20 Hz (24dB per octave) for each dataset and baselined between -250 to 0 ms. As the N1, P2 responses have a frequency around 4 to 6 Hz, a minimum of -250 ms is required to visualize the pre-stimulus interval and determine whether or not a waveform has been influenced by accompanying noise. The pre-event epoch was set at 250 ms and the post-event epoch was set at 1500 ms to ensure both the onset and ACC responses were visible for source analysis.

2.9 Dipole Source Analysis

Dipole source modelling was performed, independently, for the onset and ACC responses within the same dataset. This process was carried out for each of the 35 datasets as follows.

Before dipoles were placed and fitted, a fit interval of 175 ms was selected a priori to encompass the onset and ACC responses based on the typical P1-N1-P2 latencies (Martin & Boothroyd, 2000; Näätänen & Picton, 1987; Picton, 2010; Picton et al., 1992). The P1 peak response typically occurs at 70 ms after the stimulus onset, while the N1 and P2 peak responses occur around 100 and 200 ms, respectively, post-stimulus onset (Davis, 1965; Davis & Onishi, 1969). As

such, the onset fit interval was set from 50 to 225 ms for the onset responses and between 550 to 725 ms for the ACC fit interval because the gaps consistently occurred at 500 ms after stimulus onset.

Dipole modelling was performed by first placing two vector dipoles at the eye locations in order to fit any residual eye-movement related artefacts that might have been subthreshold and missed during artefact rejection. Following this, dipoles were manually placed, one in each hemisphere, in the approximate location of auditory cortices on the supratemporal plane using BESA's 2D source imaging head model. According to the literature, the N1 response is generated within in the auditory cortex, specifically in Heschl's gyrus, while P2 likely occurs within the posterior planum temporale (Crowley & Colrain, 2004; Lightfoot, 2016; Martin et al., 2008; Näätänen & Picton, 1987). For this study, the entire P1-N1-P2 complex was fitted to capture global location differences between onset and ACC generators.

Because the data consisted of monotic (left ear) stimulation only and CAEPs tend to have a contralateral bias (Ross et al., 2005; Wolpaw & Penry, 1977), symmetrically constrained dipoles across hemispheres were used rather than unconstrained dipoles. Generally, there are more contralateral fibres than ipsilateral in the human auditory cortex, thus we would expect to see more contralateral cortical activity. However, individuals may have developed more

ipsilateral fibres and therefore lack strong contralateral auditory activity. The use of non-symmetrical dipoles would fail to account for this and skew the dipole locations or obscure the overall results.

Vector dipoles were used in analysis as, unlike scalar dipoles that collect information from one direction in the cortex, vector dipoles include activation information from horizontal and vertical locations in the auditory cortex, including the curved sulcus within Heschl's gyrus, a likely secondary source location of the N1 cortical response. Using vector dipole modelling of CAEP responses is a well-documented procedure and provides accurate results (Ponton et al., 2002; Scherg, 1990; Scherg & Von Cramon, 1986).

The vector dipole location information was extracted from BESA representing the left and right hemispheres in X, Y, Z coordinates, referring to each of the three spatial locations. The direction represented by X is medial-lateral, Y is anterior-posterior, and Z is inferior-superior. Henceforth, a dipole is referred to as a single location, one representing the left hemisphere, the other the right hemisphere. Analysis was conducted on one hemisphere (the right side) because the dipoles were symmetrical.

Once the dipoles were manually placed within the auditory cortices, the BESA spatiotemporal modelling was run to automatically fit the source dipoles within

the chosen 175 ms fit window. After checking BESA's 3D MRI display, the resulting solution was accepted only if the final dipole placement remained within or nearby (within 25 mm) the auditory cortex and the solution's residual variance (RV) met the specified a priori criterion of < 5%. The RV is the total error percentage of the source fitted solution, which is the variance between the recorded scalp ERP data and the forward-projected source modelled ERP data. Thus, the forward projected ERP data from the fitted dipoles should account for at least 95% of recorded ERP data at the scalp electrodes.

The dipole solutions of each condition were saved as .bsa files after source localization was successfully completed. The data was also saved as a montage (.mtg) file signal-space projected into this montage to generate the source waveforms. These source waveforms were then exported as a multiplexed (.mul) formatted file to be uploaded and read by a custom MATLAB program for visualization. The source waveforms were not analyzed in this thesis but they were visually evaluated to confirm that the source modelling procedures resulted in generating expected source waveform morphologies consistent with P1-N1-P2 ERP components.

2.10 Statistical Analysis

The dipole location and source waveform data were imported into MATLAB from BESA using a custom-developed program. MATLAB was used to amalgamate

and analyze the information into a grand average of both onset and ACC response conditions. Because the dipoles were symmetric across hemispheres, only the right hemispheric dipole locations were compared between the two conditions. To test the null hypothesis that the generators of the onset and ACC responses are the same, a paired *t*-test was conducted using the MATLAB "ttest.m" function. An a priori alpha criterion was set at $\alpha = .05$ for significance.

3 Results

3.1 Statistical Results

As depicted in Table 3.1, the results of the *t*-test showed a significant difference in the dipoles' Y locations between the onset and ACC responses (M = 0.4, SD = 1.0), $t(34) = 2.3$, $p = .027$). The ACC response dipoles are more posteriorly located as compared to the onset response dipoles. Therefore, the null hypothesis that stated that the onset and ACC CAEPs are generated from the same location was rejected.

Table 3.1

Results of t*-test and Descriptive Statistics*

Dipole Directions	Onset			ACC			Onset v. ACC			*t*	*df*	*p*
	M[a]	SD	n	M[a]	SD	n	M[a]	SD	n			
X	5.0	0.9	35	4.9	0.9	35	0.1	0.8	35	0.96	34	.343
Y	0.2	0.9	35	-0.2	1.0	35	0.4	1.0	35	2.31	34	.027*
Z	1.4	0.9	35	1.2	0.7	35	0.5	0.7	35	1.24	34	.225

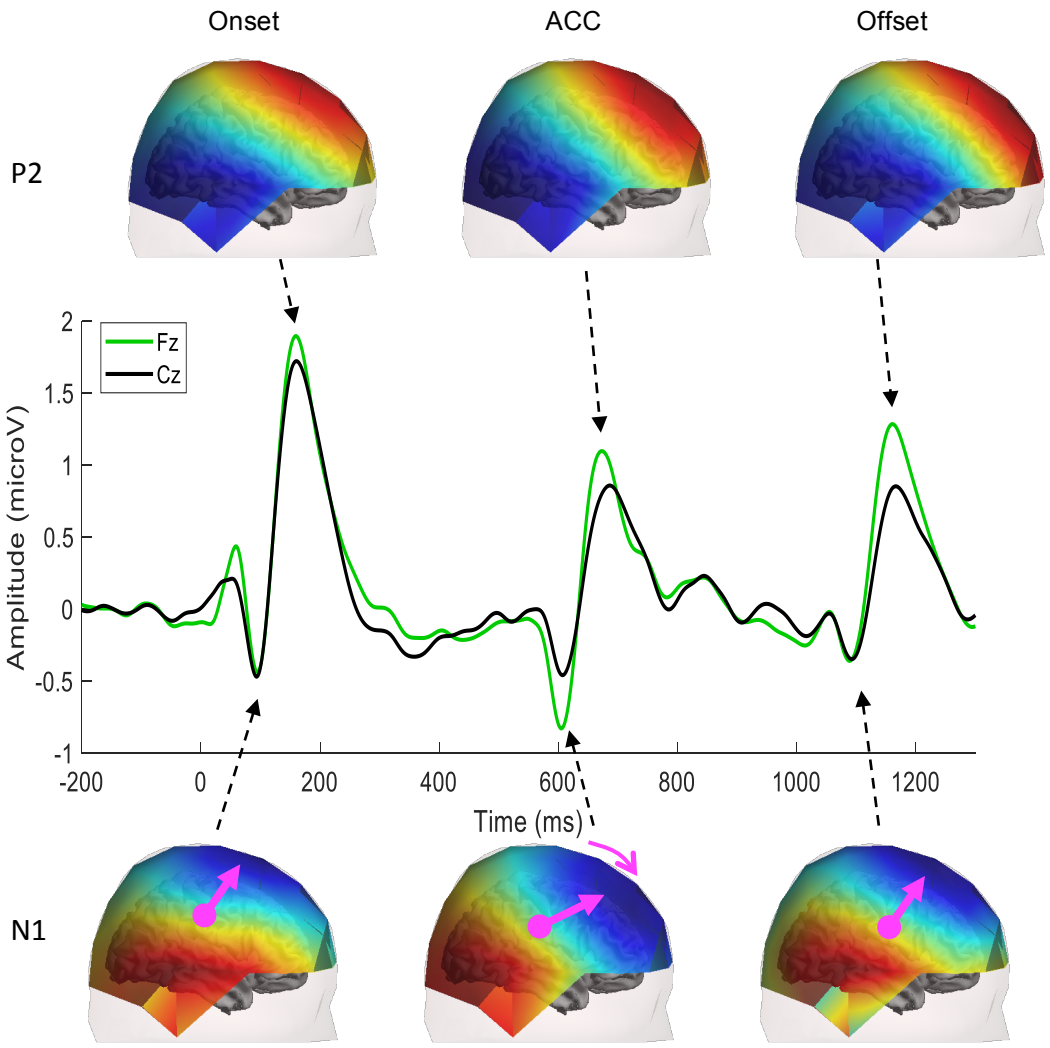
Note. Results are for grand average onset and ACC response dipole locations.

[a] Mean (M) is measured in millimeters (mm).

* $p < .05$.

Figure 3.1

Grand Average Waveform Morphology with Topographies



Note. Grand average sensor waveforms (Cz and Fz) and topographies (P2, N1) for onset, ACC, and offset responses are depicted. Pink arrows were manually placed on the figure to graphically illustrate the posterior-to-anterior tilt in the topography and they do not represent the true dipole locations and orientations.

The topography in Figure 3.1 shows the grand average onset, ACC, and offset responses. Similar polarization patterns are depicted for all three N1 and P2 responses. The original grand average sensor waveforms also show similar morphology between the onset and ACC CAEP responses. However, the peak of the ACC N1 response appears to have shifted frontally, as visually depicted by the pink arrows. The offset response was included here to demonstrate the tilt back to the original (onset) dipole orientation. This frontal tilt, found only in the ACC N1 generators, may be due to another, additional neural source, perhaps located in a gyrus that is positioned more posterior in reference to the onset N1 generators. Additionally, this ACC N1 source may be located in a gyrus in the planum temporale, which has a more anterior-posterior tilt as compared to the onset N1, which is typically found to be located on top of Heschl's gyrus and tilts in a more vertical direction.

Similarly, comparing Cz and Fz waveform morphology, a difference can be seen in the peak-to-peak amplitude of the ACC N1-P2 waveform but not in the peak-to-peak amplitude of the onset N1-P2 (Fig. 3.1). The ACC N1 response has a larger Fz deflection than its corresponding Cz waveform, unlike the onset N1 response, which shows nearly identical Fz and Cz waveform morphology. This provides a further illustration of the difference between the onset and ACC responses.

Figure 3.2

Grand Average Source Generator Locations

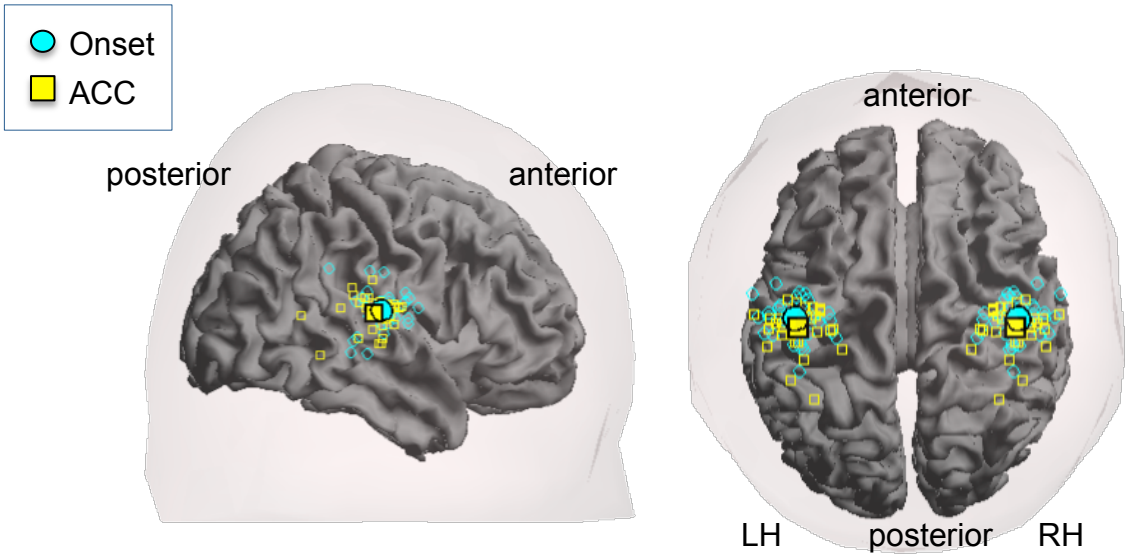


Figure 3.2 visually depicts the source locations, revealing the posteriorly located ACC response dipoles (squares) as compared to the onset (circles) response dipoles. The small open circles and squares are the dipole locations for each participant. The filled larger circles and squares with a black outline are the grand-averaged source locations.

3.2 Effect Size

To confirm reliability of significant findings, the effect size was also calculated in MATLAB for both eta-squared (η_p^2) and Cohen's *d* (*d*) values.

Table 3.2

Effect Size Benchmarks

Description of Effect Size	*d*	η_p^2
Small	$d < 0.2$	$\eta_p^2 < 0.01$
Moderate	$0.2 < d < 0.8$	$0.01 < \eta_p^2 < 0.14$
Large	$d > 0.8$	$\eta_p^2 > 0.14$

Note. Adapted from *The 7 Steps of Data Analysis*, by W.M. Bannon, 2013, p. 58. Copyright 2013 by Stats Whisperer.

As shown in Table 3.2, a moderate effect size was found ($\eta_p^2 = 0.136$, $d = 0.391$), meaning that there is moderate evidence to support the claim that the onset and ACC CAEPs are generated from significantly different locations within the brain.

3.3 Signal-to-Noise-Ratio

Literature has repeatedly shown that CAEP morphology is sensitive to SNR (Billings et al., 2009; Kaplan-Neeman et al., 2006; Whiting et al., 1998) making the SNR a good indicator of the reliability of EEG recordings (Picton, 2010). The grand average SNR was calculated using MATLAB and a custom-developed

program. SNR to baseline results were found to range between 4 to 19, averaging 10±3.42, which is well above this study's a priori criterion of ≥ 4, signifying a high SNR and thus reliable CAEP interpretations and findings.

4 Discussion

4.1 Results Interpretation

The purpose of this study was to test the null hypothesis that the onset and ACC P1-N1-P2 complex responses were generated by the same neural dipoles. The resulting evidence, however, rejected the null hypothesis. The ACC dipoles were found to be located significantly posterior to the onset generator locations.

4.1.1 Evidence for a Posterior ACC Source Generator

One plausible explanation for the current study's difference finding would be that there are different neural sources for the onset and ACC dipoles that reflect different auditory processing functions. For example, Jones et al. (1998) studied the sensor waveforms of onset and ACC CAEP components obtained via complex tone stimuli. They found that changes in stimuli evoked ACC N1 activity that was distributed across the scalp posterior to the onset N1 response scalp distribution. The authors attributed this difference to cortical spectral change analyses that are conducted in the supratemporal plane, posterior to tone onset spectral analyses. They speculate that the change in stimulus elicits cortical activation in addition to those elicited by, and located posterior to, the onset response.

Though the literature on ACC source generators is limited, other researchers have also speculated that the function of the ACC may differ from the onset response (Martin & Boothroyd, 1999; Ostroff et al., 1998). Martin & Boothroyd (2000) also concluded that the ACC responses elicited by spectral changes in stimuli likely indicate that frequency coding is occurring within the cortex, which may be different in function from the onset response.

As found in this study, the ACC and onset dipole locations differ significantly. Although a dipole orientation analysis was not conducted for this thesis, the anterior shift in the N1 response topographies is suggestive of an anterior tilt in the ACC N1 dipole orientation. Further differences found in sensor waveform morphology between Cz and Fz locations for the ACC N1 response that were absent in the onset N1 response, suggest the likelihood of differing neurological events occurring after an acoustic change, such as a gap. This evidence indicates the two responses, onset and ACC, are different with respect to their underlying neural origins.

4.1.2 Anterior ACC Source Generator

If the results from this study had shown that the ACC dipoles were anteriorly located in reference to the onset dipoles, then this would have been consistent with some previous literature. A plausible explanation for an anterior ACC generator could have been due to the blending of the ACC with a preceding

offset P1-N1-P2 complex. For example, in their study, Ross & Tremblay (2009) compared CAEP component source generators of onset responses. They confirmed that the underlying P2 source generator is located anteriorly to the N1 CAEP generator.

Furthermore, Pantev et al. (1996) compared the source locations of each CAEP component of the onset and offset responses. They found that the P2 source generators for both onset and offset were indistinguishable, and positioned anteriorly to the N1 onset and offset source generators, which were also indistinguishable from one another.

Additionally, it has been shown that the amplitude of the P1 response, that precedes the N1 response, though prominent amongst children, is often smaller in adults due to cortical maturation (Martin et al., 2008; Shafer et al., 2015). As such, researchers have sometimes found the elicitation of a P1 response at onset and often a smaller amplitude or absent P1 response for the ACC and offset (Jones et al., 1998; Martin & Boothroyd, 1999; Pantev et al., 1996). Additionally, in their study, Pantev et al. (1996) found that the P1 component had been elicited in nearly all of their participants only at onset, but not at offset, and their source locations were indistinguishable from the N1 onset and offset responses.

Because a gap in a stimulus can be considered as two onset stimuli with a very short inter-stimulus interval, P1-N1-P2 responses to gaps may simply be an offset P1-N1-P2 response to the first stimulus overlapped by the succeeding onset P1-N1-P2 response to the second stimulus. There may also be an ACC component within this complex. Thus, a stimulus with an embedded gap will have five components: 1) an onset response to the start of the first stimulus, 2) an offset response to the stop of the first stimulus, 3) an ACC to a change detection, 4) an onset response to the start of the second stimulus, and 5) another offset response at the stop of the second stimulus. Because the ACC complex may occur directly after the first offset response (herein referred to as $offset_1$), source generators of both complexes are likely overlapping. Evidence for a true intervening ACC component comes from Jones et al. (1998), who found larger P2 amplitudes in the ACC as compared to the onset P2 amplitudes in gap-detection stimuli with gap durations of less than 200 ms. A significant increase in ACC P2 amplitude was found with gap durations lasting 40 ms or less, which the authors attributed to the overlap of $offset_1$ potentials with the ACC.

Applying this information to the current study, it could be argued that the ACC dipole locations, elicited at gap durations between 10 to 20 ms, overlap with the $offset_1$ response generators. As such, the combined ACC P1 will be a weaker response than the combined ACC P2 component (located anterior to P1) as compared to the onset P1 and P2 dipoles. This could result in the appearance of

the collective ACC P1-N1-P2 complex to have generators located anterior to the onset CAEP complex generators. However, evidence from this thesis found the opposite, whereby ACC generators were more posteriorly located than the onset responses.

While this reasoning may have merit, analysis of the $offset_1$ response was not conducted for this study, though it would be prudent to pursue further studies comparing the ACC and $offset_1$ response source locations to further clarify differences and similarities in generators, as well as any overlap that may be occurring.

Another conceivable explanation as to why the ACC CAEP source locations would more likely be found significantly in the anterior direction relative to the onset CAEP sources would be attentional effects. Attention, especially directed towards changes in stimuli, has been shown to activate a central source within the anterior-singulate cortex (Nieuwenhuis et al., 2003). Cozzi (2017) also found that an N2b response, activated in the anterior-singulate cortex, is elicited by attention to and expectation of a change in stimulus. As such, the ACC responses, elicited by changes in an ongoing stimulus, would likely be affected more than the onset response dipoles (Martin et al., 1999).

Simultaneous activation of an additional source anterior to the presumed generators of the ACC P1-N1-P2 complex, absent during onset response, could essentially pull the ACC dipoles forward in relation to the onset dipoles, resulting in a significant difference finding in the anterior direction.

However, as only passive-task data was used for this study, attentional effects cannot be factored into these results. Furthermore, the previously discussed $offset_1$ P2 component locations and amplitudes as well as attentional effects cannot explain this study's posterior location finding of the ACC P1-N1-P2 complex generators.

4.2 Clinical Implications

Literature has treated the onset and ACC CAEP responses as either interchangeable or separate. In the present study's case of a rejected null hypothesis, researchers may more confidently interpret ACC responses as being different than the onset P1-N1-P2 responses or as having supplementary neural processing. The current study's findings add to the collective knowledge of CAEPs, especially in terms of the ACC response. This addition can potentially bolster reliability and accuracy in the future clinical use of this type of electrophysiological testing. Such testing includes the objective measurements of auditory thresholds (Davis, 1965; Lightfoot, 2016), identifying impairments in temporal processing disorder (Picton, 2010, 2013), and assessing and regulating

treatment of speech processing in hearing aid and cochlear implant users (Martin et al., 2008; Menning et al., 2000; Tremblay et al., 2009). Although, the findings from this study indicate that the ACC is different from the onset CAEP responses, it doesn't identify "what" this difference is. Future research is warranted to investigate "what" is the additional activity or shifting neural resource for ACC responses.

4.3 Limitations and Future Research

There are a few limitations to this study, which if addressed in future studies may lead to a better understanding of the underlying mechanisms involved in more posteriorly located ACC dipole generators. The following sections expand on these areas.

4.3.1 Component Comparisons

The present study compared the generator locations of the onset and ACC P1-N1-P2 complexes as a combined whole. Because each component within the complex has been found to be generated from slightly different cortical locations along the superior temporal gyrus, it would be prudent to repeat the comparative source analysis for each individual component. This would aid in determining more precisely which component of the onset and ACC responses is responsible for such a localization difference.

4.3.2 Ill-Posed Problem

Dipole source modelling has an inherent ill-posed problem, a mathematics term referring to the availability of multiple solutions for a given problem. In other words, the pattern created by the original EEG data, meant to represent overall electrical activity of cortical neurons, may have multiple dipole arrangements, or solutions (Grech et al., 2008). Albeit, dipole source modelling has been able to accurately localize CAEPs. For example, Pantev et al. (1996) used dipole modelling strategies, similar to those used in this study, to successfully locate generators of the onset, offset, and sustained responses in human brains. Furthermore, Verkindt et al. (1995) used several dipole source modelling approaches in their study of tonotopic arrangements in the cortex. They concluded that source modelling is an efficient way to detect CAEP generators. However, to overcome the associated ill-posed problem, they suggested applying a priori knowledge of auditory cortical physiology as well as a rough understanding of targeted generator functions, as was carried out for this thesis.

4.3.3 Magnetoencephalography

While EEG reveals the sum of neuronal electric energy at the scalp, magnetoencephalography (MEG) obtains the resulting magnetic energy produced by the same electrical currents. Because EEG is measured on the scalp, distortion can occur via reduced conductivity from brain tissue, cortical fluid, or the skull itself, whereas magnetic fields recorded in MEG are largely

unimpeded (Godey et al, 2001; Wikswo et al., 1993). It may be reasonable to suggest MEG recordings, with comparatively improved SNR, may provide better localization than EEG. For example, in his review of auditory temporal facets measured using CAEPs, Picton (2013) included studies using MEG recordings. The author noted that MEG measures of auditory cortical activity are more accurate than EEG recordings.

Furthermore, Godey et al. (2001) used both MEG and EEG measures on the same patients to localize P2 generators. They found that both measures localized P2 in the planum temporale while MEG was able to further locate an additional generator in Area 22 that EEG recordings had missed.

However, it is important to note that EEG offers valuable information in source localization. While both measurements excel at detecting tangentially oriented dipoles, EEG recordings were found to be better than MEG at detecting radially oriented dipoles (Hämäläinen, 1992; Shahin et al., 2007). As some auditory processes activate the lateral superior temporal gyrus as well as the superior temporal sulcus, modelling with radial as well as tangential sources is necessary (Picton et al., 1999; Virtanen et al., 1998). Additionally, one study even found minor differences between EEG and MEG measurements, in terms of source localization (D. Cohen et al., 1990).

Because of the benefits of both types of recordings, authors have often recommended combining EEG and MEG recordings to obtain further information about CAEP components (Crowley & Colrain, 2003; Hämäläinen, 1992; Neukirch et al., 2002; Shahin et al., 2007; ; Wikswo et al., 1993). Applying the same suggestion here, it would be worthwhile to conduct this study again, this time employing MEG measurements to obtain further information and clarification of the posterior location of the ACC responses in relation to the onset responses.

4.3.4 WEIRD Sample

In their comprehensive analysis, Henrich et al. (2010) found that humans vary in considerable ways including perception, memory, cognitive reasoning, beliefs in fairness, understanding of cooperation, and genetic intelligence. They further found that a person's upbringing, language, socio-economic status, cultural background, and country of residence, among other things, greatly contribute to these factors.

The authors recommended that researchers avoid past mistakes in which the participants were mainly (or, in many cases, only) from Western, educated, industrialized, rich, and democratic (WEIRD) countries. They found that people from WEIRD societies are the least representative of human beings and that using solely WEIRD samples will thus diminish external validity.

Though the authors emphasized behavioural differences in their review, they showed evidence of cognitive differences as well, which can lead to the assumption that cortical pathways and activity may also be different between WEIRD and non-WEIRD participants. This has also been demonstrated by D'Angiulli et al. (2008), who studied brain ERP differences in children with lower- versus higher socio-economic status (SES). The authors found evidence of differing neural mechanisms employed in children from lower-SES as compared to children from higher-SES. Their findings support the claim that factors like SES can affect developing neural processes.

Because the data for the present study was acquired without accompanying identifying sample features, these potentially crucial factors remain unknown. It is, however, presumed that the participants are members of a WEIRD society as they were recruited in British Columbia for testing that took place on the campus of the University of British Columbia. Because of this, external validity of this study's findings is limited and future studies should avoid this shortcoming by ensuring the sample is representative of the world's population.

4.4 Conclusion

Literature includes investigations of each separate CAEP component source locations and comparisons of the onset and offset response generators, while the ACC response generators have largely been ignored. The hypothesis of this

study was that the generator locations for the onset and ACC CAEPs were the same. This null hypothesis was rejected based on the obtained results, thus the neural generators for the onset and ACC CAEPs are different. The resulting significant difference between the two response locations moves us one step closer to understanding the neural computational resources involved in auditory perception of transient changes in acoustic signals.

References

Abeles, M., & Goldstein, M. H. (1972). Responses of single units in the primary auditory cortex of the cat to tones and to tone pairs. *Brain Research*, *42*(2), 337–352. https://doi.org/10.1016/0006-8993(72)90535-5

Alain, C., Zhu, K. D., He, Y., & Ross, B. (2015). Sleep-dependent neuroplastic changes during auditory perceptual learning. *Neurobiology of Learning and Memory*, *118*, 133–142. https://doi.org/10.1016/j.nlm.2014.12.001

Albrecht, R., Suchodoletz, W., & Uwer, R. (2000). The development of auditory evoked dipole source activity from childhood to adulthood. *Clinical Neurophysiology*, *111*(12), 2268–2276. https://doi.org/10.1016/s1388-2457(00)00464-8

Angel, R. (2016). *Cortical Auditory Evoked Potentials to Estimate Gap-Detection Thresholds in Adults* (Master's Thesis). cIRcle: UBC's Digital Repository: Electronic Theses and Dissertations (ETDs) 2008+. https://circle.ubc.ca

Bannon, W. M. (2013). *The 7 Steps of Data Analysis*. Stats Whisperer.

Billings, C. J., Papesh, M. A., Penman, T. M., Baltzell, L. S., & Gallun, F. J. (2012). Clinical Use of Aided Cortical Auditory Evoked Potentials as a Measure of Physiological Detection or Physiological Discrimination. *International Journal of Otolaryngology*, *2012*, 1–14. https://doi.org/10.1155/2012/365752

Billings, C. J., Tremblay, K. L., Stecker, G. C., & Tolin, W. M. (2009). Human evoked cortical activity to signal-to-noise ratio and absolute signal level. *Hearing Research*, *254*(1–2), 15–24. https://doi.org/10.1016/j.heares.2009.04.002

Cohen, D., Cuffin, B. N., Yunokuchi, K., Maniewski, R., Purcell, C., Cosgrove, G. R., Ives, J., Kennedy, J. G., & Schomer, D. L. (1990). MEG versus EEG localization test using implanted sources in the human brain. *Annals of Neurology*, *28*(6), 811–817. https://doi.org/10.1002/ana.410280613

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Routledge.

Cowan, N. (1984). On short and long auditory stores. *Psychological Bulletin*, *96*(2), 341–370. https://doi.org/10.1037/0033-2909.96.2.341

Cozzi, J. (2017). *Effects of Attention on Cortical Auditory Evoked Potentials during a Gap Detection Task* (Master's Thesis). clRcle: UBC's Digital Repository: Electronic Theses and Dissertations (ETDs) 2008+. https://circle.ubc.ca

Crease, R. (1991). Images of conflict: MEG vs. EEG. *Science*, *253*(5018), 374–375. https://doi.org/10.1126/science.1862336

Crowley, K. E., & Colrain, I. M. (2003). A review of the evidence for P2 being an independent component process: age, sleep and modality. *Clinical Neurophysiology*, *115*(4), 732–744. https://doi.org/10.1016/j.clinph.2003.11.021

D'Angiulli, A., Herdman, A., Stapells, D., & Hertzman, C. (2008). Children's event-related potentials of auditory selective attention vary with their socioeconomic status. *Neuropsychology*, *22*(3), 293–300. https://doi.org/10.1037/0894-4105.22.3.293

Davis, H. (1965). Slow Cortical Responses Evoked by Acoustic Stimuli. *Acta Oto-Laryngologica*, *59*(2–6), 179–185. https://doi.org/10.3109/00016486509124551

Davis, H., & Onishi, S. (1969). Maturation of Auditory Evoked Potentials. *International Audiology*, *8*(1), 24–33. https://doi.org/10.3109/05384916909070186

Friesen, L. M., & Tremblay, K. L. (2006). Acoustic Change Complexes Recorded in Adult Cochlear Implant Listeners. *Ear and Hearing*, *27*(6), 678–685. https://doi.org/10.1097/01.aud.0000240620.63453.c3

Godey, B., Schwartz, D., de Graaf, J., Chauvel, P., & Liégeois-Chauvel, C. (2001). Neuromagnetic source localization of auditory evoked fields and intracerebral evoked potentials: a comparison of data in the same patients. *Clinical Neurophysiology*, *112*(10), 1850–1859. https://doi.org/10.1016/s1388-2457(01)00636-8

Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., Xanthopoulos, P., Sakkalis, V., & Vanrumste, B. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of NeuroEngineering and Rehabilitation*, *5*(1), 25. https://doi.org/10.1186/1743-0003-5-25

Hämäläinen, M. S. (1992). Magnetoencephalography: A tool for functional brain imaging. *Brain Topography*, *5*(2), 95–102. https://doi.org/10.1007/bf01129036

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The Weirdest People in the World? *SSRN Electronic Journal*. Published. https://doi.org/10.2139/ssrn.1601785

Hillyard, S. A., & Picton, T. W. (1978). ON and OFF components in the auditory evoked potential. *Perception & Psychophysics*, *24*(5), 391–398. https://doi.org/10.3758/bf03199736

Hirata, K., & Lehmann, D. (1990). N1 and P2 of frequent and rare event-related potentials show effects and after-effects of the attended target in the oddball-paradigm. *International Journal of Psychophysiology*, *9*(3), 293–301. https://doi.org/10.1016/0167-8760(90)90061-h

Jones, S., Longe, O., & Vaz Pato, M. (1998). Auditory evoked potentials to abrupt pitch and timbre change of complex tones: electrophysiological evidence of `streaming'? *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(2), 131–142. https://doi.org/10.1016/s0168-5597(97)00077-4

Kaplan-Neeman, R., Kishon-Rabin, L., Henkin, Y., & Muchnik, C. (2006). Identification of syllables in noise: Electrophysiological and behavioral correlates. *The Journal of the Acoustical Society of America*, *120*(2), 926–933. https://doi.org/10.1121/1.2217567

Katz, J., Chasin, M., English, K., Hood, L. J., & Tillery, K. L. (2015). *Handbook of Clinical Audiology* (Seventh ed.). Wolters Kluwer Health.

Kaukoranta, E., Hari, R., & Lounasmaa, O. (1987). Responses of the human auditory cortex to vowel onset after fricative consonants. *Experimental Brain Research*, *69*(1). https://doi.org/10.1007/bf00247025

Kim, J. R. (2015). Acoustic Change Complex: Clinical Implications. *Journal of Audiology and Otology*, *19*(3), 120–124. https://doi.org/10.7874/jao.2015.19.3.120

Liegeois-Chauvel, C., Musolino, A., & Chauvel, P. (1991). Localization of the Primary Auditory Area in Man. *Brain : A Journal of Neurology*, *114A*(1), 139–151. https://doi.org/10.1093/oxfordjournals.brain.a101854

Lightfoot, G. (2016). Summary of the N1-P2 Cortical Auditory Evoked Potential to Estimate the Auditory Threshold in Adults. *Seminars in Hearing*, *37*(01), 001–008. https://doi.org/10.1055/s-0035-1570334

Lister, J. J., Maxfield, N. D., & Pitt, G. J. (2007). Cortical Evoked Response to Gaps in Noise: Within-Channel and Across-Channel Conditions. *Ear & Hearing*, *28*(6), 862–878. https://doi.org/10.1097/aud.0b013e3181576cba

Martin, B. A., & Boothroyd, A. (1999). Cortical, Auditory, Event-Related Potentials in Response to Periodic and Aperiodic Stimuli with the Same Spectral Envelope. *Ear and Hearing*, *20*(1), 33–44. https://doi.org/10.1097/00003446-199902000-00004

Martin, B. A., & Boothroyd, A. (2000). Cortical, auditory, evoked potentials in response to changes of spectrum and amplitude. *The Journal of the Acoustical Society of America*, *107*(4), 2155–2161. https://doi.org/10.1121/1.428556

Martin, B. A., Boothroyd, A., Ali, D., & Leach-Berth, T. (2010). Stimulus Presentation Strategies for Eliciting the Acoustic Change Complex: Increasing Efficiency. *Ear & Hearing*, *31*(3), 356–366. https://doi.org/10.1097/aud.0b013e3181ce6355

Martin, B. A., Tremblay, K. L., & Korczak, P. (2008). Speech Evoked Potentials: From the Laboratory to the Clinic. *Ear & Hearing*, *29*(3), 285–313. https://doi.org/10.1097/aud.0b013e3181662c0e

Mathew, R., Undurraga, J., Li, G., Meerton, L., Boyle, P., Shaida, A., Selvadurai, D., Jiang, D., & Vickers, D. (2017). Objective assessment of electrode discrimination with the auditory change complex in adult cochlear implant users. *Hearing Research*, *354*, 86–101. https://doi.org/10.1016/j.heares.2017.07.008

Menning, H., Roberts, L. E., & Pantev, C. (2000). Plastic changes in the auditory cortex induced by intensive frequency discrimination training. *NeuroReport*, *11*(4), 817–822. https://doi.org/10.1097/00001756-200003200-00032

Michalewski, H. J., Starr, A., Nguyen, T. T., Kong, Y. Y., & Zeng, F. G. (2004). Auditory temporal processes in normal-hearing individuals and in patients with auditory neuropathy. *Clinical Neurophysiology*, *116*(3), 669–680. https://doi.org/10.1016/j.clinph.2004.09.027

Näätänen, R. (2020). *Attention and Brain Function (Psychology Library Editions: Neuropsychology)* (1st ed.). Routledge.

Näätänen, R., & Picton, T. (1987). The N1 Wave of the Human Electric and Magnetic Response to Sound: A Review and an Analysis of the Component Structure. *Psychophysiology*, *24*(4), 375–425. https://doi.org/10.1111/j.1469-8986.1987.tb00311.x

Neukirch, M., Hegerl, U., Kötitz, R., Dorn, H., Gallinat, U., & Herrmann, W. (2002). Comparison of the Amplitude/Intensity Function of the Auditory Evoked N1m and N1 Components. *Neuropsychobiology*, *45*(1), 41–48. https://doi.org/10.1159/000048672

Nieuwenhuis, S., Yeung, N., van den Wildenberg, W., & Ridderinkhof, K. R. (2003). Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cognitive, Affective, & Behavioral Neuroscience*, *3*(1), 17–26. https://doi.org/10.3758/cabn.3.1.17

Nolan, M., & Lyon, D. J. (1981). Transcranial attenuation in bone conduction audiometry. *The Journal of Laryngology & Otology*, *95*(6), 597–608. https://doi.org/10.1017/s0022215100091155

Ostroff, J. M., Martin, B. A., & Boothroyd, A. (1998). Cortical Evoked Response To Acoustic Change Within A Syllable. *Ear and Hearing*, *19*(4), 290–297. https://doi.org/10.1097/00003446-199808000-00004

Pantev, C., Eulitz, C., Hampson, S., Ross, B., & Roberts, L. E. (1996). The Auditory Evoked “Off” Response: Sources and Comparison with the “On” and the “Sustained” Responses. *Ear and Hearing*, *17*(3), 255–265. https://doi.org/10.1097/00003446-199606000-00008

Picton, T. W. (2010). *Human Auditory Evoked Potentials* (1st ed.). Plural Publishing, Inc.

Picton, T. (2013). Hearing in Time. *Ear & Hearing*, *34*(4), 385–401. https://doi.org/10.1097/aud.0b013e31827ada02

Picton, T., Alain, C., Woods, D., John, M., Scherg, M., Valdes-Sosa, P., Bosch-Bayard, J., & Trujillo, N. (1999). Intracerebral Sources of Human Auditory-Evoked Potentials. *Audiology and Neuro-Otology*, *4*(2), 64–79. https://doi.org/10.1159/000013823

Picton, T. W., Champagne, S. C., & Kellett, A. J. (1992). Human auditory evoked potentials recorded using maximum length sequences. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *84*(1), 90–100. https://doi.org/10.1016/0168-5597(92)90071-i

Ponton, C., Eggermont, J. J., Khosla, D., Kwong, B., & Don, M. (2002). Maturation of human central auditory system activity: separating auditory evoked potentials by dipole source modelling. *Clinical Neurophysiology*, *113*(3), 407–420. https://doi.org/10.1016/s1388-2457(01)00733-7

Presacco, A., & Middlebrooks, J. C. (2018). Tone-Evoked Acoustic Change Complex (ACC) Recorded in a Sedated Animal Model. *Journal of the Association for Research in Otolaryngology*, *19*(4), 451–466. https://doi.org/10.1007/s10162-018-0673-9

Ross, B., Herdman, A., & Pantev, C. (2005). Right Hemispheric Laterality of Human 40 Hz Auditory Steady-state Responses. *Cerebral Cortex*, *15*(12), 2029–2039. https://doi.org/10.1093/cercor/bhi078

Ross, B., & Tremblay, K. (2009). Stimulus experience modifies auditory neuromagnetic responses in young and older listeners. *Hearing Research*, *248*(1–2), 48–59. https://doi.org/10.1016/j.heares.2008.11.012

Scherg, M. (1990). Fundamentals of dipole source analysis. In M. Hoke, G. L. Romani, & F. Grandori (Eds.), *Auditory Evoked Magnetic Fields and Electric Potentials (Advances in Audiology)* (1st ed., Vol. 6, pp. 40–69). S. Karger.

Scherg, M., & Von Cramon, D. (1986). Evoked dipole source potentials of the human auditory cortex. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *65*(5), 344–360. https://doi.org/10.1016/0168-5597(86)90014-6

Shafer, V. L., Yu, Y. H., & Wagner, M. (2015). Maturation of cortical auditory evoked potentials (CAEPs) to speech recorded from frontocentral and temporal sites: Three months to eight years of age. *International Journal of Psychophysiology*, *95*(2), 77–93. https://doi.org/10.1016/j.ijpsycho.2014.08.1390

Shahin, A. J., Roberts, L. E., Miller, L. M., McDonald, K. L., & Alain, C. (2007). Sensitivity of EEG and MEG to the N1 and P2 Auditory Evoked Responses Modulated by Spectral Complexity of Sounds. *Brain Topography*, *20*(2), 55–61. https://doi.org/10.1007/s10548-007-0031-4

Stenfelt, S. (2012). Transcranial Attenuation of Bone-Conducted Sound When Stimulation Is at the Mastoid and at the Bone Conduction Hearing Aid Position. *Otology & Neurotology*, *33*(2), 105–114. https://doi.org/10.1097/mao.0b013e31823e28ab

Takahashi, H., Nakao, M., & Kaga, K. (2004). Cortical mapping of auditory-evoked offset responses in rats. *NeuroReport*, *15*(10), 1565–1569. https://doi.org/10.1097/01.wnr.0000134848.63755.5c

Tremblay, K. L., Billings, C. J., Friesen, L. M., & Souza, P. E. (2006). Neural Representation of Amplified Speech Sounds. *Ear and Hearing*, *27*(2), 93–103. https://doi.org/10.1097/01.aud.0000202288.21315.bd

Tremblay, K. L., Friesen, L., Martin, B. A., & Wright, R. (2003). Test-Retest Reliability of Cortical Evoked Potentials Using Naturally Produced Speech Sounds. *Ear and Hearing*, *24*(3), 225–232. https://doi.org/10.1097/01.aud.0000069229.84883.03

Tremblay, K. L., Shahin, A. J., Picton, T., & Ross, B. (2009). Auditory training alters the physiological detection of stimulus-specific cues in humans. *Clinical Neurophysiology*, *120*(1), 128–135. https://doi.org/10.1016/j.clinph.2008.10.005

Verkindt, C., Bertrand, O., Perrin, F., Echallier, J. F., & Pernier, J. (1995). Tonotopic organization of the human auditory cortex: N100 topography and multiple dipole model analysis. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *96*(2), 143–156. https://doi.org/10.1016/0168-5597(94)00242-7

Virtanen, J., Ahveninen, J., Ilmoniemi, R., Näätänen, R., & Pekkonen, E. (1998). Replicability of MEG and EEG measures of the auditory N1/N1m-response. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(3), 291–298. https://doi.org/10.1016/s0168-5597(98)00006-9

Whiting, K. A., Martin, B. A., & Stapells, D. R. (1998). The Effects of Broadband Noise Masking on Cortical Event-Related Potentials to Speech Sounds /ba/ and /da/. *Ear and Hearing*, *19*(3), 218–231. https://doi.org/10.1097/00003446-199806000-00005

Wikswo, J. P., Gevins, A., & Williamson, S. J. (1993). The future of the EEG and MEG. *Electroencephalography and Clinical Neurophysiology*, *87*(1), 1–9. https://doi.org/10.1016/0013-4694(93)90169-v

Wolpaw, J., & Penry, J. (1977). Hemispheric differences in the auditory evoked response. *Electroencephalography and Clinical Neurophysiology*, *47*(4), 514. https://doi.org/10.1016/0013-4694(79)90176-7