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NEURAL PLASTICITY FOR SPEECH SOUND PROCESSING IN ADULTS: THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION

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by

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ABSTRACT

NEURAL PLASTICITY FOR SPEECH SOUND PROCESSING IN ADULTS: THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION

Garrett Sweitzer

We examined the possible modulatory effect of tDCS on the automatic processing of speech sounds by evaluating the components of two ERP waveforms (P1-N1-P2 and T-Complex. The P1-N1-P2 components were measured at frontocentral sites F3, F4, C3, C4, Cz, and Fz while the T-Complex components were measured at temporal cortices T7 and T8. A 64-channel sensor cap from Electrical Geodesics, Inc was placed on each of the participants' scalp. The 17 young adults (12 females, 5 males) sat comfortably during the EEG measurements within an electrically shielded and sound-attenuated booth while watching a silenced movie with subtitles delivered through a handheld tablet computer. The two auditory stimulus conditions were presented to each participant across two time periods (pre and post tDCS) using over-the-ear headphones at a comfortable listening volume. A total of 1000 standard trials were delivered for both Step 3 (/I/) Step 9 (/Ɛ/) at a rate of 650 ms (interstimulus interval of 450 ms). The auditory stimuli were delivered using E-prime 2 software (version 270 2.0.10.356). The EEG data were acquired and digitized via Netstation software version 5.4. Each participant received 1.0 mA (milliampere) of electrical current for a total of 10 continuous minutes. The anodes were placed at F3, F4, T7, and T8 and the cathode was placed at Cz. Our results suggested that tDCS modules the automatic processing of speech sounds, but with asymmetrical

responses across different brain structures. The relatively small effects or lack of effects of tDCS on some P1-N1-P2 and T-Complex components could be attributable to experimental parameters such as the intensity, duration, frequency, and location of the tDCS across the scalp. It is crucial to understand the relationship between tDCS and speech sound processing and performance given that the current environment is considering tDCS as both a treatment for a wide-range of disorders and deficits as well as a tool for enhancing learning.

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Introduction

The obligatory P1-N1-P2 and T-Complex auditory evoked potentials provide a useful index to evaluate neural plasticity in the primary and secondary auditory cortex in response to auditory stimulation. Functionally, the P1-N1-P2 waveforms represent the cortical indices of the physical characteristics of the speech signal in the auditory cortex. Earlier studies have not only provided evidence for experience and maturation-dependent plasticities in the obligatory P1-N1-P2 waveforms, but also showed that the neural activity underlying these waveform changes occurred unevenly across the scalp (Courchesne, 1978; Ponton et al., 1996; Ponton et al., 1996 ; Putter-Katz et al., 2005 ; Sharma et al., 1997).

Similarly, the T-Complex may serve as a neural marker to represent processing of the frequency and duration characteristics of the speech signal in the secondary auditory cortex. The T-complex component is independent from the N1-P2 responses, and the notion that the T-complex components an inversion of activity emanating from the same cortical sources as the N1-P2 waveforms is outdated (Wolpaw & Perry, 1975). It is useful to examine both the P1-N1-P2 and T-Complex waveforms in the same individual in order to better understand deficits in auditory processing and identify the area of the cortex that might be responsible for auditory processing deficits such as along the lateral superior temporal gyrus or within the superior temporal plane (Wagner et al., 2016). The few studies examining the T-complex responses in children revealed that there were important amplitude differences between children who were typically-developing and children with developmental language disorders when presented with both speech and non-speech stimuli (Bishop et al., 2012; Shafer et al., 2011). The smaller T-complex

waveforms found in children with developmental language disorders suggest that poor auditory processing contributes, at least in part, to deficient language skills.

It is difficult to make therapeutic decisions based upon these observations considering the lack of complete understanding of the developmental trajectories of the underlying neural generators as well as the fact that at least two parallel neural pathways appear to be activated in response to auditory stimulation (Ponton et al., 2000; Ponton et al., 2002). Furthermore, Rinker et. al. (2017) suggested that differences in T-complex waveforms might reflect differences in phonological processing that are indicative of language-experience rather than indicative of a phonological processing disorder. In this study, bilingual students exhibited a smaller Ta amplitude compared to monolingual peers. This suggests that language experience, rather than simply maturational factors, also has an influence over the neural activity at the lateral temporal cortex that responds to the speech signal. Thus, if language experience can modulate the size of the Ta component, then it stands to reason that another form of stimulation, such as electrical currents, delivered near or at the temporal cortex might also alter the T-complex responses.

Recently, researchers have increasingly employed transcranial direct current stimulation (tDCS) as a form of non-invasive cortical stimulation in order to examine its potential for influencing cortical activity. Compared to other brain stimulation techniques such as transcranial electrical stimulation (TES) or transcranial magnetic stimulation (TMS), tDCS does not directly invoke a spontaneous action potential at the neuronal synapses, but rather exerts its influence by adjusting the probability of an action potential at the neuronal synapses based upon the direction (anodal or cathodal) of the electrical

current (Nitsche et al., 2008). Electrical current from the underlying cortical area flows into the anode whereas it flows out of the cathode into the underlying cortical area (De Rojas et al., 2012). In general, anodal stimulation depolarizes the underlying cortical membranes whereas cathodal stimulation hyperpolarizes the underlying cortical membranes. These factors, in addition to the cortical layer(s) upon which the electrical currents exert an influence over, have been suggested as possible explanations for anodal stimulation's role in hyperpolarizing the cellular membrane whereas cathodal stimulation's role in depolarizing the cellular membrane (Antal et al., 2004; Creutzfeld et al., 1962; Manola et al., 2007; Radman et. al., 2005).

Moreover, the size and duration of the electrical current also interact to influence the modulatory effects of tDCS. Studies involving human and animal subjects have revealed that larger direct current inputs, such as 2 mA comparing to 1.0 or lower when applied over a longer time horizon such as 20 minutes (comparing to 5 minutes or shorter), induce the greatest and most durable modulations in spontaneous neuronal firing patterns (Nitsche & Paulus, 2000; Iyer, Mattu, Grafman et al., 2005) by influencing a handful of different ionic and molecular events which continue to unfold after the stimulation has been removed. (Ardolino et. al., 2005; Chesler, 2003; Gartside, 1968; Hayashi et al., 1990; Islam et al., 1995; Liebetanz et al., 2002; Nitsche & Paulus, 2001; Zaghi et al., 2009; Zaehle et al., 2011).

Other studies have elaborated on the specific ionic activities that might dictate the effect of tDCS on the neuronal membrane and thus influence synaptic transmission. The administration of carbamazepine, a sodium channel blocker, and flunarizine, a calcium channel blocker, dampened motor cortex excitability with the introduction of

anodal tDCS. Furthermore, antagonizing the N-methyl-D-aspartate (NMDA) (glutamate) receptors with the administration of dextromethorphane prevented the release of glutamate which plays a critical role in learning and the development of new, and more neural connections (neuroplasticity) at the motor cortex (Nitsche et al., 2003). Thus, blocking the opening of the sodium and calcium channels seemed to diminish the excitatory effects of anodal tDCS on synaptic transmission.

The tDCS likely affects activity at the neuronal synapses, whether by hyperpolarizing or depolarizing the cellular membrane, in much the same manner that activating NMDA-receptors increases both the spontaneous firing patterns as well as reorganizes/expands cortical networks (Artola & Singer, 1987;Iriki et al., 1989; Kirkwood & Bear, 1993). For example, studies have shown a relationship between the activation of NMDA receptors and long-term potentiation at the sensorimotor cortex while blocking the activation of NMDA receptors has led to a deterioration in synaptic connections, a necessary condition for neuroplastic changes (Kano & Ilino, 1991; Garraghty & Muja, 1996; Ziemann et al., 1998). Thus, by combining auditory with electrical stimulation, there exists the potential for modifying the processing of the speech signal through the expansion and strengthening of new and existing cortical networks (Hebb, 1949).

The theory of neural recovery cycle or refractory period argues that one might expect to see a decrease in the amplitude and/or a longer latency in the processing of the speech signal following a period of stimulation (Budd et al., 1998). Though this theory in ERP research is based upon the functioning of a single nerve cell, there is reason to believe that the physicochemical processes governing the functioning of the cortical

systems generating the P1-N1-P2 and T-Complex either partially or fully prevents the firing of another action potential after a period of stimulation. Thus, it is possible that the P1-N1-P2 and/or T-Complex waveforms might be smaller in size and/or longer in latency following tDCS due to the existence of a refractory period within the underlying cortical networks (Callaway, 1973; Wastell, 1980).

Recent improvements in tDCS have brought about a reduction in the size of the electrodes to allow for more focal stimulation within the cortical tissue underlying the electrode. Previous studies using conventional tDCS have sometimes shown the greatest increases in cerebral blood flow and EEG signaling activity at cortical sites distant from the conventional tDCS electrodes (Ardolino et al., 2005; Keeser et al., 2011; Marshall et al., 2004). The newer high definition (HD tDCS) offers the ability to draw stronger conclusions as to the areas of the cortex receiving the stimulation due to a more spatially-restricted electrical field by reducing the amount of electrical current leaking outside the 4 x 1 circular configuration (Chesters et al., 2013).

Clinically, relatively few studies have addressed the possibility of using tDCS to influence the processing of the speech signal in the auditory cortex and surrounding areas. Furthermore, these studies have produced inconsistent results as to the role of anodal and cathodal stimulation in modulating the underlying cortical activity that serves as an index of speech signal processing. Anodal stimulation has at times improved auditory processing of higher frequency speech signals when the electrodes are positioned closer to the posterior portion of the temporal cortex (Ladeira et. al., 2011). Talavage et al. (2004) pointed to functional neuroimaging studies which suggested that the human auditory cortex contains multiple tonotopic maps that each respond differently

depending on the frequency of the speech signal. On the other hand, anodal stimulation paradigms have also led to a smaller MMN response within the context of low frequency sounds. The reduced ability to discriminate between different low frequency sounds might be due to anodal interference with processing the durational quality of some lower frequency sounds (Tang & Hammond, 2013).

Furthermore, research is beginning to examine the effects of tDCS and its potential for manipulating the mismatch negativity, a neural index of the preconscious shift in attention from a standard to a novel, sensory stimulus that is typically seen 150-250 ms after the presentation of a deviant stimulus (Chen et al., 2014). The production of the mismatch negativity is believed to be partially related to the excitatory effects associated with the release of glutamate and its binding to NMDA receptors (Stagg et al., 2009). Considering anodal stimulation is believed to exert its excitatory influence on neuronal firing patterns partially by increasing the release of glutamate, it was surprising to see a reduction in the height of the mismatch negativity waveform after anodal stimulation (Chen et al., 2014). However, the difference in the frequency of the speech signal from the standard to the deviant condition, in conjunction with anodal stimulation, may have led to this unexpected reduction in the negative deflection due to different neuronal networks responding to the frequency rather than the durational aspect of the speech signal. (Rinne et al., 2005).

A reduction in the negative deflection, signaling a shift in attention as a result of a change in sensory information, has been observed in people with language disorders such as dyslexia (Baldewag et al., 1999) as well as in people with generalized learning disorders (Mowszowski et al., 2012). This might be due to bottom-up processing deficits

which in turn impair the ability to form predictions about sensory information and thus respond to unexpected changes in the sensory information (Friston 2003;Friston, 2005). The reduction in the amplitude of the MMN in response to a change in the frequency of the speech signal, coupled with anodal stimulation, suggests the anodal stimulation might at times place a limit on neuronal activity by interfering with the binding of glutamate to the NMDA receptors (Javitt et al., 1996; Umbricht et al., 2002).

Furthermore, the reduction in the amplitude of MMN in response to anodal tDCS lends support to the possibility of a reduction in activity within superficial pyramidal cells, associated with the ability to form predictions based upon sensory information, that might be due to anodal stimulation's role in restoring, rather than destabilizing, cellular homeostasis (Friston, 2005). Similarly, other studies (Accornero et al., 2006; Heimrath et al., 2012) have pointed to a paradoxically depressing, rather than enhancing, effect on cellular activity with the introduction of anodal tDCS.

Given the relatively few studies conducted using tDCS in relation to the processing of the speech signal in the auditory cortex, the purpose of this study is to explore whether and how a single-session of high-definition tDCS modulates neurological activity related to speech signal processing as seen through the P1-N1-P2 and T-complex waveforms.

Methods

Participants

The EEG recordings were obtained from 17 individuals (5 men, 12 women). All participants passed a standard hearing screening in the laboratory and reported no history of hearing, speech-language, neurological, or developmental impairment. All 17 participants were native English speakers, though 10 had Spanish language exposure through either familial relationships and/or language courses completed while attending school. Nonetheless, all 17 participants reported English as their dominant language. The study was approved by the human subject research institutional review board at St. John's University, New York, and was conducted in compliance with the Declaration of Helsinki.

Speech Stimuli

Two English vowels, /ɪ/ (as in the word bit) and /ɛ/ (as in the word bet), were used as auditory stimuli. To create the vowels, a natural token of a neutral vowel /ʌ/ was produced by a female with an F0 of approximately 190 Hz. This vowel was resynthesized and edited using target formant frequencies based on natural productions of /ɪ/ and /ɛ/ from the same speaker using Analysis by Synthesis Lab, version 3.2 (see Shafer et al., 2010, 2011 for details). A nine-equal-step continuum was created using equal steps for the first formant (F1) and second formant (F2). The two tokens for this study were Step 3 and Step 9 based upon the fact that both tokens are equidistant from the boundary. The stimuli had the following mean center frequencies: for Step 3, F1 = 500, F2 = 2160; for

Step 9 F1 = 650 Hz, F2 = 1980 Hz. The two stimuli had an identical duration of 250 ms and identical third (F3= 2174) and fourth (F4 = 2174) formants. Step 3 was identified as /ɪ/ and Step 9 as /ɛ/, respectively, by monolingual English-speaking children and adults in previous studies (i.e, Datta et al., 2010; Yu et al., 2019).

Data Acquisition and Pre-Processing

A 64-channel sensor cap from Electrical Geodesics, Inc was placed on each participant's scalp. The participants sat comfortably during the EEG measurement within an electrically shielded and sound-attenuated booth while watching a silenced movie with subtitles delivered through a handheld tablet computer. The two stimulus conditions were presented to each participant across two time periods (pre-tDCS and post-tDCS) using over-the-ear headphones at a comfortable listening volume. A total of 1000 standard trials were delivered for both Step 3 and Step 9 at the rate of 650 ms (interstimulus interval of 450 ms).

A Soterix 1 x 1 tDCS low intensity stimulator in combination with a 1X4 high-definition divider was used to deliver the tDCS. The tDCS was conducted immediately between the two ERP sessions. Each participant received 10 minutes of 1.0 mA stimulation with the cathodes centered at Cz and the anodes centered at F3, F4, T7, and T8.

The auditory stimuli were delivered using E-prime 2 Professional software (version 270 2.0.10.356) (Psychology Software Tools). The EEG data were acquired and digitized via Netstation software version 5.4. The impedances of the electrodes were kept at or below 50 kΩ. The EEG was recorded using a bandpass filter of 0.1-100 Hz and

sampling rate of 500 Hz with Cz as the reference electrode. The continuous EEG waveforms were processed offline using a bandpass filter of 0.3-30 Hz in Netstation version 5.4. The EEG responses were divided into time-locked epochs of 200 ms pre-stimulus and 800 ms post-stimulus.

The EEG data were processed with BESA Research 6.0 278 (BESA GmbH, 2014) using an automatic artifact correction set according to a HEOG threshold of 150 μV and a VEOG threshold of 250 μV for eye movement noise. Thresholds for noisy channels were set at 120 μV for amplitude (gradient of 75). All participants have at least 75% of trials after artifact rejection. The data were re-referenced using average reference.

Data Analysis

Permutation analyses was used to control for the multiple comparison problems that commonly arise in parametric statistical procedures (e.g., multiple t-tests, analysis of variance) when these involve many statistical comparisons across multiple correlated sensor sites and correlated time points (Maris & Oostenveld, 2007). This approach reduces the rate of false positives (Type I error) in ERP data analyses (Lage-Castellanos et al., 2010). Permutation tests also have the advantage of making no assumptions about the distribution of the data. The test was performed in Rstudio using the RVAideMemoire package. These analyses were performed at electrode sites F3, Fz, F4, C3, Cz and C4 for the P1-N1-P2 complex, and at electrode sites T7 and T8 for the T-complex including Na, Ta and Tb. Latencies and amplitudes of the P1-N1-P2 complex and the T-complex were compared before and after the tDCS session. Results were considered significant at the level of $p \leq .05$.

Results

The tDCS effect on the amplitudes of the P1-N1-P2 complex

Appendix B shows the amplitudes of the P1-N1-P2 complex pre- and post-tDCS. Appendix E shows the ERP waveforms of the P1-N1-P2 complex pre- and post-tDCS on the two vowel standard stimuli at six sites.

Amplitude of P1

Permutation results suggested that for the amplitude of P1, the effect of tDCS is significant at C3 ($F = 4.27$, $p = 0.04$) with larger P1 amplitude before tDCS than after tDCS. No other relevant significant interactions or main effects.

Amplitude of N1

No significant main effects or interactions involving tDCS were observed.

Amplitude of P2

The effect of tDCS for the amplitude of P2 at site C3 was significant ($F = 8.615$, $p < 0.01$) with smaller P2 responses after tDCS.

The tDCS effect on the latencies of the P1-N1-P2 complex

Appendix A shows the latency of P1-N1-P2. Permutation results showed that the latency of P1 at C3 is shorter after tDCS than before tDCS ($F = 4.63$, $p = 0.03$).

Latency of P1

Permutation results suggested that for the latency of P1, the effect of tDCS is approaching significance at F3 ($F = 3.07$, $p = 0.08$). No other significant interactions or main effects.

Latency of N1

No significant main effects or interactions involving tDCS were observed.

Latency of P2

The effect of tDCS for the latency of P2 at site C3 was approaching significance ($F = 3.16$, $p = 0.07$) with earlier P2 responses after tDCS.

The tDCS effect on the latencies and amplitudes of the T-complex

Appendix C shows the latencies and Appendix D shows the amplitudes of the T-complex pre- and post-tDCS. Appendix F shows the ERP waveforms of the T-complex pre- and post-tDCS on the two standard stimuli at T7 and T8. Permutation results suggested that there is no main effect of t-DCS or interaction that involves the factor of tDCS. The effect of tDCS on the latency of Na is approaching significance ($p = 0.08$). The appearance of Ta is earlier post-tDCS than pre-tDCS ($p = 0.02$).

Discussion

Based upon the widely-accepted theory of neural plasticity, the ability for cortical networks to reorganize themselves in response to stimulation, deprivation, and/or the passage of time, (Mueller et al., 2008) we had reason to believe that the application of weak direct currents over a short time period might invoke alterations in the P1-N1-P2 and T-Complex waveforms. Though it is generally acknowledged that anodal tDCS depolarizes the neuronal membrane while cathodal tDCS hyperpolarizes the neuronal membrane (Nitsche & Paulus, 2001;Nitsche et al., 2003), our study complicates this assumption underlying the interaction between tDCS and synaptic activity.

At the C3 electrode, we saw an earlier appearance of the P1 and P2 waveforms, yet the neurons fired with less synchronization at both of these earlier appearances. This early component, P1, has been associated with the earliest detection of the speech signal in the primary auditory cortex with less frequent neural activity as one advances toward the lateral surface of the cortex (Liégeois-Chauvel et al., 2001). The P2 response appears to be generated by activity within the mesencephalic reticular activating system, beginning in the auditory brainstem, but likely gaining contributions from neural activity in the planum temporale and auditory association cortex, Brodmann Area 22 (Eggermont, 1988; Hari et al., 1997; Ponton et al., 2006b Rifi et al., 1991). The P2 component appears to increase in amplitude across the lifespan, though notable increases have appeared in sleep/less conscious conditions while notable decreases have appeared in situations demanding more attention (Crowley et al., 2004).

While anodal stimulation reduced the size of neural activity as measured by the frontal C3 electrode, the temporal electrodes (T7 and T8) registered an earlier appearance of the Ta after anodal stimulation. The Ta component of the T-complex is believed to

represent neural activity signaling the detection of an auditory stimulus (Naatanen & Picton, 1987) as a result of synaptic activity emanating from the superior temporal gyrus (Hackley et al., 1990; Perrault & Picton, 1984). Our data suggests a lateralization effect of tDCS on the left hemisphere within the neural networks contributing to the earlier Ta appearance at T7.

While our data did not indicate a significant effect as a result of stimulation on either the amplitude or latency of the Tb deflection, nonetheless, the Tb deflection is believed to reflect the activity underlying the ability to discriminate between two different sounds. The Tb deflection likely arises from multiple sources that are responding sequentially, but also overlapping at certain time period, within both the primary and secondary auditory cortex (Naatanen & Picton, 1987; Scherg & Von Cramon, 1985; Scherg & Von Cramon, 1986; Wood & Wolpaw, 1982). Bruneau et al. (1999) found that children with autism displayed a Tb deflection that was smaller in amplitude and later in appearance than the control group. The lack of tDCS effect in Tb may suggest that a single short session of tDCS is not enough to modulate the neural activities indexed by Tb responses.

Though researchers are beginning to better understand the relationship between the different stimulation directions (anodal and cathodal) and synaptic transmission, there remains a host of unanswered questions. Whereas small, direct electric currents that were applied parallel to the somato-dendritic axis induced excitatory effects in various cortical layers of pyramidal cells, large, direct electric currents produced both short and long term changes in synaptic activity and neural network functioning (Bikson et al., 2004; Kabakov et al., 2012). Furthermore, researchers must also consider not only the shape of

the neurons beneath the electrodes, but also the relationship between the different stimulation directions and their effects on the concentration levels of crucial neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate (Clark et al., 2011; Radman et al., 2009; Stagg et al., 2009). Clearly, much remains to be explored in regards to the relationship between direct electric stimulation and the detection and processing of speech in the auditory cortex.

Despite the fact that researchers broadly accept anodal stimulation as increasing cortical excitability by reducing the cortical levels of GABA while recognizing that cathodal stimulation often reduces cortical excitability by lowering the levels of glutamate, the precise mechanisms whereby the two different stimulation directions influence the concentration levels of these and other neurochemicals is still largely unknown. Animal and human studies have shown that glutamate found in pyramidal cells within the fifth layer of the cortex are especially sensitive to transcranial electrical stimulation. The release of glutamate in these pyramidal cells has a subsequent effect on the release of GABA further downstream at the interneurons between synapses (Radman et al., 2009). Though, a study conducted by Molaee-Ardekani et al., 2013 found the relationship between the release of glutamate from pyramidal cells and the subsequent release of GABA at the intraneuronal region to be less than straightforward. It is likely that different types of interneurons react differently to glutamate.

Clinically, studies have shown a relationship between delays in the development of reading ability and the ratio of GABA to glutamate in the auditory cortex. It is suggested that an imbalance in the GABA to glutamate levels in the auditory cortex interfere with the continual adjustments in inhibitory and excitatory synaptic activity that

is required to read and develop other linguistic skills (Tan, A. Y., et al., 2004; Wehr, M. & Zador, A. M, 2003). Thus, an external stimulator such as tDCS that likely affects the concentration levels of both GABA and glutamate in the auditory cortices has the potential to improve reading ability and general auditory processing by restoring the proper balance of GABA and glutamate in the auditory cortex (Dorrn, A.L. et al., 2010; Kadosh, R, 2013; Pugh, K.R. et al., 2014).

From a methodological perspective, though HD tDCS provides a more spatially-restricted electrical field, it is important to remain cognizant of the limitations in interpreting EEG data. Though the C3, C4, T7 and T8 electrodes were placed over specific parts of the cerebral cortex, nonetheless, these electrodes gather information from the extracellular space that encircles thousands of neurons. Thus, the P1-N1-P2 and T Complex waveforms should be interpreted as an estimate of the underlying neural activity collected at 8 electrodes as representative of thousands of neurons within a general cortical location (Crowley & Colrain, 2004).

Not only do the electrodes represent the collective activity of thousands of neurons, but the auditory cortex contains at least 4, though possibly as many as 6 tonotopically arranged maps (Miranda et al., 2006; Talavage et al., 2004 ; Uy, 2003 ; Wagner et al., 2007). The speech signal not only interacts with multiple tonotopic maps, with any number of associated disruptions involved in that process, but the second stimulation in our experimental design, the electrical currents, meet different neural pathways with various shapes and points of interaction with the electrical currents. Coupled with likely differences in the baseline concentration levels of neurotransmitters such as GABA and glutamate, it is exceedingly difficult to draw firm conclusions about

the use of tDCS for the remediation of auditory processing disorders. Nonetheless, future studies should continue to adjust the intensity and duration of the two electrical stimulation directions as well as include a control group which receives sham stimulation.

Appendix A

The latencies of P1-N1-P2 complex at six frontocentral sites.

			P1					
PrePost	Stimuli	Order	F3	Fz	F4	C3	Cz	C4
pre	i	eeei	59.89	59.00	58.56	45.44	52.00	53.78
		SD	*14.04*	*13.48*	*18.18*	*16.30*	*15.51*	*15.80*
post	i	eeei	58.89	61.78	64.22	49.44	53.11	52.67
		SD	*13.63*	*15.90*	*14.92*	*14.40*	*10.94*	*14.40*
pre	i	iiie	61.25	67.38	66.38	52.75	53.25	56.63
		SD	*8.91*	*8.64*	*18.67*	*14.30*	*10.15*	*11.50*
post	i	iiie	53.50	63.88	65.63	49.00	57.25	56.63
		SD	*8.37*	*8.19*	*9.22*	*9.60*	*6.89*	*14.40*
pre	e	eeei	64.22	61.56	56.56	51.78	53.56	53.89
		SD	*10.27*	*9.33*	*13.98*	*16.60*	*16.47*	*16.00*
post	e	eeei	64.33	64.56	52.56	56.78	63.89	51.89
		SD	*8.31*	*6.91*	*18.59*	*18.30*	*17.48*	*15.30*
pre	e	iiie	60.00	68.50	65.50	63.75	60.00	60.13
		SD	*8.15*	*14.39*	*10.11*	*12.50*	*12.08*	*12.00*
post	e	iiie	50.75	67.63	62.88	51.50	62.25	59.38
		SD	*9.35*	*11.96*	*3.72*	*8.15*	*9.07*	*11.30*

N1

PrePost	Stimuli	Order	F3	Fz	F4	C3	Cz	C4
pre	i	eeei	91.89	93.89	94.00	79.33	89.78	91.89
		SD	*15.60*	*9.80*	*9.87*	*20.70*	*15.34*	*21.00*
post	i	eeei	89.78	100.33	97.56	93.67	88.00	94.67
		SD	*22.40*	*20.39*	*25.50*	*21.20*	*13.73*	*9.25*
pre	i	iiie	99.63	92.88	98.75	89.25	89.75	89.63
		SD	*19.20*	*12.19*	*20.50*	*14.80*	*10.20*	*23.00*
post	i	iiie	91.25	93.25	89.88	93.63	97.50	92.00
		SD	*16.80*	*14.49*	*14.80*	*16.30*	*17.06*	*9.25*
pre	e	eeei	104.40	104.56	91.00	90.11	93.78	94.89
		SD	*30.90*	*23.54*	*9.72*	*15.00*	*12.62*	*13.40*
post	e	eeei	98.11	96.78	107.00	87.78	91.44	87.78
		SD	*16.70*	*15.43*	*14.50*	*10.80*	*13.17*	*19.40*
pre	e	iiie	93.75	100.13	87.00	93.50	94.88	92.75
		SD	*21.20*	*24.18*	*11.70*	*13.00*	*10.18*	*5.47*
post	e	iiie	79.13	94.00	90.38	85.50	95.63	93.00
		SD	*16.10*	*14.06*	*12.20*	*14.60*	*16.82*	*12.60*

P2

PrePost	Stimuli	Order	F3	Fz	F4	C3	Cz	C4
pre	i	eeei	153.20	144.78	151.40	152.70	153.56	152.20
		SD	*41.40*	*39.70*	*39.40*	*21.20*	*29.21*	*32.70*
post	i	eeei	133.60	144.22	136.40	135.40	141.89	148.30
		SD	*19.40*	*17.75*	*21.50*	*23.40*	*16.05*	*21.30*

pre	i	iiie	135.80	147.88	130.10	144.30	144.13	146.30
		SD	*20.70*	*24.41*	*28.20*	*8.51*	*16.14*	*27.50*
post	i	iiie	138.80	141.13	129.30	135.80	145.50	131.80
		SD	*19.70*	*17.24*	*18.60*	*17.30*	*12.48*	*26.80*
pre	e	eeei	145.90	148.11	143.30	141.70	140.56	147.10
		SD	*28.90*	*34.52*	*21.00*	*11.60*	*15.49*	*21.00*
post	e	eeei	139.80	144.33	135.10	145.20	143.33	144.10
		SD	*21.70*	*13.30*	*16.80*	*24.30*	*14.96*	*18.00*
pre	e	iiie	118.10	138.75	127.50	140.00	140.75	140.40
		SD	*42.60*	*24.07*	*23.70*	*12.60*	*14.87*	*15.80*
post	e	iiie	126.00	134.75	128.90	130.40	140.00	135.10
		SD	*31.10*	*17.61*	*20.30*	*23.80*	*18.31*	*16.80*

Appendix B

The amplitudes of P1-N1-P2 complex at six frontocentral sites.

			P1					
PrePost	Stimuli	Order	F3	Fz	F4	C3	Cz	C4
pre	i	eeei	1.20	1.01	0.93	0.89	1.05	0.82
		SD	*0.86*	*0.65*	*0.65*	*0.57*	*0.57*	*0.65*
post	i	eeei	0.82	0.61	0.91	0.51	0.99	0.87
		SD	*0.40*	*0.39*	*0.41*	*0.32*	*0.47*	*0.34*
pre	i	iiie	0.64	0.68	0.65	0.66	0.56	0.51
		SD	*0.22*	*0.45*	*0.27*	*0.38*	*0.44*	*0.44*
post	i	iiie	0.70	0.74	0.71	0.75	0.84	0.61
		SD	*0.41*	*0.33*	*0.30*	*0.48*	*0.26*	*0.33*
pre	e	eeei	0.80	0.83	0.73	0.70	0.85	0.76
		SD	*0.52*	*0.59*	*0.45*	*0.31*	*0.39*	*0.31*
post	e	eeei	0.79	0.79	0.75	0.51	0.94	0.73
		SD	*0.28*	*0.50*	*0.55*	*0.32*	*0.56*	*0.36*
pre	e	iiie	0.70	0.70	0.68	0.89	0.96	0.76

		SD	*0.31*	*0.26*	*0.25*	*0.31*	*0.41*	*0.31*
post	e	iiie	0.73	1.05	1.08	0.63	0.86	0.72
		SD	*0.45*	*0.72*	*0.47*	*0.33*	*0.36*	*0.44*

N1

PrePost	Stimuli	Order	F3	Fz	F4	C3	Cz	C4
pre	i	eeei	0.41	0.28	0.18	-0.09	0.29	0.11
		SD	*0.72*	*0.66*	*0.62*	*0.45*	*0.74*	*0.62*
post	i	eeei	0.10	0.14	0.33	-0.08	0.10	-0.02
		SD	*0.37*	*0.45*	*0.45*	*0.42*	*0.53*	*0.44*
pre	i	iiie	0.01	0.15	0.17	0.04	-0.06	-0.19
		SD	*0.36*	*0.52*	*0.32*	*0.32*	*0.50*	*0.34*
post	i	iiie	0.05	0.19	0.27	-0.14	-0.03	0.07
		SD	*0.53*	*0.51*	*0.43*	*0.48*	*0.38*	*0.39*
pre	e	eeei	-0.08	-0.09	0.22	-0.24	-0.13	-0.05
		SD	*0.52*	*0.53*	*0.50*	*0.52*	*0.64*	*0.41*
post	e	eeei	-0.10	0.01	0.12	-0.14	-0.06	-0.12
		SD	*0.33*	*0.34*	*0.46*	*0.49*	*0.61*	*0.44*

pre	e	iiie	0.28	0.18	0.27	0.16	0.11	0.10
		SD	*0.41*	*0.43*	*0.34*	*0.30*	*0.56*	*0.33*
post	e	iiie	0.27	0.49	0.57	-0.02	0.21	0.20
		SD	*0.56*	*0.96*	*0.67*	*0.51*	*0.48*	*0.43*

P2

PrePost	Stimuli	Order	F3	Fz	F4	C3	Cz	C4
pre	i	eeei	1.14	1.12	1.17	1.02	1.30	1.09
		SD	*0.60*	*0.92*	*0.67*	*0.57*	*0.86*	*0.66*
post	i	eeei	0.85	0.81	1.00	0.88	1.72	1.19
		SD	*0.63*	*0.69*	*0.71*	*0.51*	*0.67*	*0.56*
pre	i	iiie	0.57	0.56	0.67	0.84	1.06	0.53
		SD	*0.32*	*0.39*	*0.28*	*0.44*	*0.59*	*0.52*
post	i	iiie	0.65	0.84	0.72	0.52	1.30	0.65
		SD	*0.52*	*0.53*	*0.44*	*0.60*	*0.57*	*0.36*
pre	e	eeei	0.65	0.66	0.80	1.04	1.60	1.25
		SD	*0.66*	*0.95*	*0.95*	*0.68*	*0.93*	*0.82*
post	e	eeei	0.66	0.65	1.10	0.53	1.59	1.03

		SD	*0.50*	*0.62*	*0.63*	*0.32*	*0.68*	*0.70*
pre	e	iiie	0.90	0.84	0.85	1.08	1.57	1.07
		SD	*0.71*	*1.04*	*0.63*	*0.53*	*0.79*	*0.46*
post	e	iiie	0.79	1.12	1.25	0.68	1.53	1.01
		SD	*0.65*	*0.81*	*0.62*	*0.52*	*0.67*	*0.16*

Appendix C

The latencies of T-complex at T7 and T8

			T7 Latency			T8 latency		
PrePost	Stimuli	Order	Na	Ta	Tb	Na	Ta	Tb
pre	i	eeei	66.33	104.33	146.89	61.78	96.67	160.11
		SD	*13.17*	*21.18*	*18.16*	*11.60*	*13.51*	*51.62*
post	i	eeei	62.67	93.67	138.11	60.11	93.89	142.00
		SD	*6.75*	*15.17*	*18.37*	*16.31*	*16.36*	*15.47*
pre	i	iiie	63.88	91.38	129.25	63.50	95.88	133.00
		SD	*6.64*	*6.85*	*17.89*	*8.35*	*12.55*	*17.87*
post	i	iiie	63.13	92.00	135.75	62.75	92.50	137.38
		SD	*5.49*	*7.48*	*16.61*	*5.78*	*10.65*	*15.64*
pre	e	eeei	64.89	106.44	145.67	80.67	109.56	150.00
		SD	*11.87*	*21.62*	*25.37*	*29.15*	*27.30*	*19.60*
post	e	eeei	65.56	101.56	140.33	65.33	91.89	149.11
		SD	*14.64*	*21.24*	*22.34*	*12.88*	*13.68*	*14.79*
pre	e	iiie	63.00	93.88	129.25	62.38	93.38	140.13
		SD	*6.30*	*13.91*	*21.98*	*6.46*	*10.17*	*17.78*
post	e	iiie	62.88	95.88	138.38	63.25	100.50	148.13
		SD	*7.10*	*9.84*	*17.49*	*9.19*	*16.48*	*18.29*

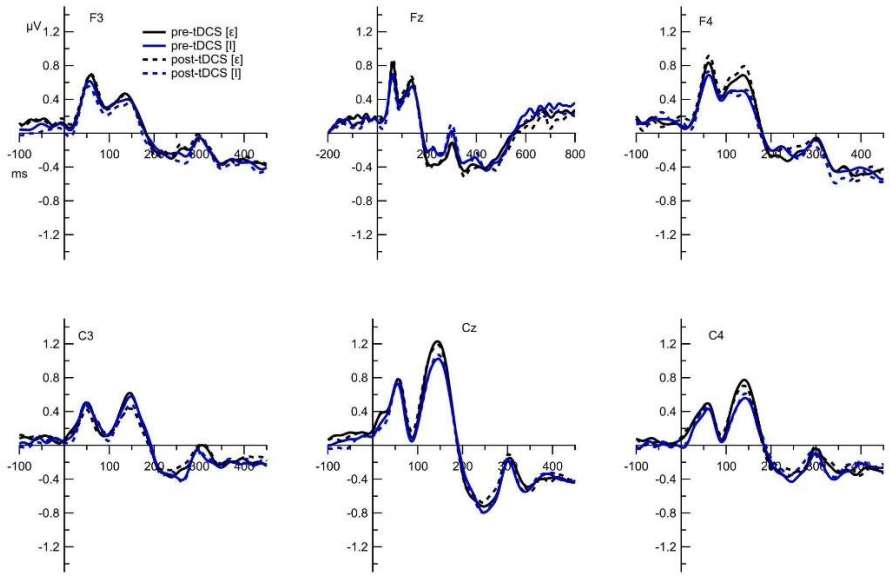
Appendix D

The amplitudes of T-complex at T7 and T8

				T7 amplitude			T8 amplitude	
PrePost	Stimuli	Order	Na	Ta	Tb	Na	Ta	Tb
pre	i	eeei	-1.52	0.11	-1.38	-1.05	0.04	-1.28
		SD	*0.63*	*1.06*	*0.90*	*0.80*	*0.71*	*0.99*
post	i	eeei	-1.44	0.00	-1.42	-0.96	0.01	-1.12
		SD	*0.49*	*0.53*	*0.77*	*0.55*	*0.56*	*0.74*
pre	i	iiie	-1.01	0.08	-0.83	-0.82	0.19	-0.80
		SD	*0.74*	*0.55*	*0.51*	*0.34*	*0.53*	*0.43*
post	i	iiie	-0.95	0.05	-0.81	-0.85	0.17	-0.75
		SD	*0.25*	*0.38*	*0.33*	*0.47*	*0.80*	*0.48*
pre	e	eeei	-1.19	0.29	-1.13	-0.75	0.16	-0.66
		SD	*0.28*	*0.71*	*0.71*	*0.50*	*0.60*	*0.72*
post	e	eeei	-1.37	0.21	-1.13	-0.77	0.18	-0.87
		SD	*0.60*	*0.58*	*0.71*	*0.58*	*0.41*	*0.69*
pre	e	iiie	-1.37	-0.18	-1.35	-1.05	0.08	-1.19
		SD	*0.80*	*0.45*	*0.70*	*0.35*	*0.48*	*0.74*
post	e	iiie	-1.26	0.07	-1.31	-0.61	0.20	-0.94
		SD	*0.49*	*0.67*	*0.68*	*0.71*	*0.92*	*0.85*

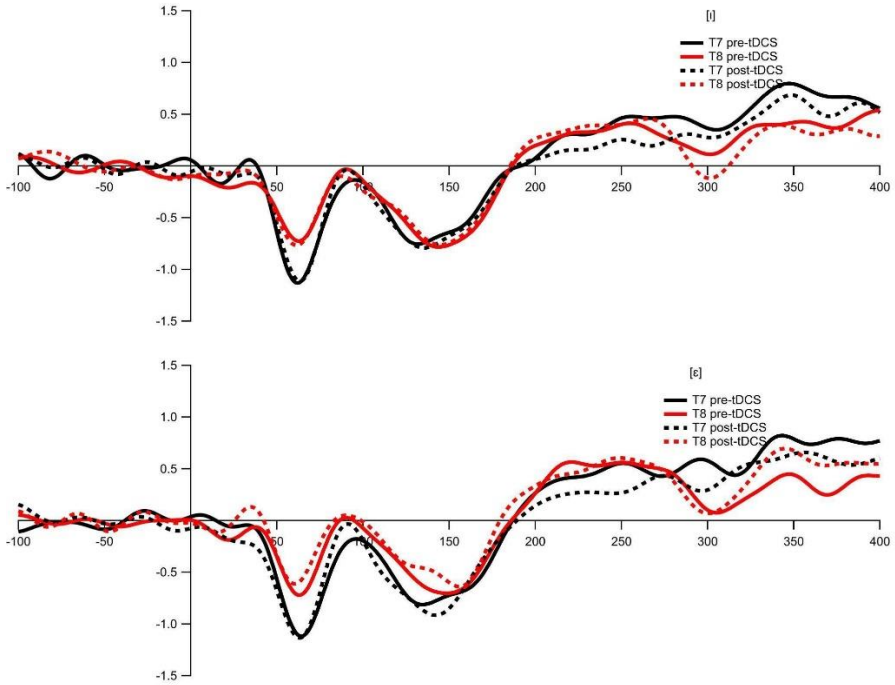
Appendix E

The waveforms of P1-N1-P2 complex at six fronto-central sites



Appendix F

The waveforms of T-complex at left and right hemispheres



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