Changed temporal processing in the human auditory cortex by transcranial direct current stimulation

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium
(Dr. rer. nat.)

genehmigt durch die Fakultät für Naturwissenschaften
der Otto-von-Guericke-Universität Magdeburg

von M.Sc. Kai Heimrath

geb. am 14.06.1984 in Haldensleben

Gutachter: Prof. Dr. habil. Tömme Noesselt

Prof. Dr. Martin Meyer

eingereicht am: 07.06.2016

verteidigt am: 11.01.2017

WESSEN GUTE WERKE MEHR SIND ALS WEISHEIT, DESSEN WEISHEIT HAT BESTAND; UND WESSEN WEISHEIT MEHR IST ALS SEINE GUTEN WERKE, DESSEN WEISHEIT HAT KEINEN BESTAND.

TALMUD

Acknowledgement

An dieser Stelle möchte ich nun den Menschen danken, die mich während der letzten $4^{1/2}$ Jahre jedwede Unterstützung erfuhren ließen um die vorliegende Doktorarbeit zu ermöglichen.

Zu allererst möchte ich meinem Betreuer Dr. Tino Zähle besonderen Dank aussprechen. Er hat mir vom ersten Tag an fachlich sowie auch freundschaftlich zur Seite gestanden.

Mein weiterer Dank gilt dem SFB/TR 31-TPA9 "The Human Auditory Cortex", der mich in dem ersten Jahr mit einem Promotionsstipendium unterstützte.

Anna Fischer und Carolin Breitling danke ich für die tolle Zusammenarbeit bei der EEG-Datenerhebung.

Ein ganz herzliches Dankeschön geht auch an die Kollegen aus der AG Neuropsychologie. Neben den fachlich inspirierenden Gesprächen haben mir vor allem die amüsanten Kaffeepausen, das gemeinsame Eis essen oder die manchmal etwas zu ausschweifenden Bierabende die Arbeit erleichtert.

Zu guter Letzt möchte ich meiner Familie und meinen Freunden danken, die mich in allen Belangen unterstützt haben. Insbesondere bedanke ich mich bei meinen Eltern und Alex für den immerwährenden moralischen Beistand.

Table of Content

LIST OF FIGURES V

LIST OF ABBREVIATIONS VI

ABSTRACT VIII

1. INTRODUCTION 1

1.1 Structure and function of the auditory system 3

1.2 The structure of the acoustic speech signal 5

1.3 Gap detection paradigm 7

1.4 Deficient temporal information processing (Dyslexia) 9

1.5 Theories of hemispheric asymmetry in speech processing 10
  1.5.1 Structural and functional neuroanatomical evidence 13
  1.5.2 Electrophysiological evidence 16

1.6 Transcranial Direct Current Stimulation (tDCS) 18
  1.6.1 Functional principle of tDCS 18
  1.6.2 What can tDCS application inform about auditory brain function? 20

1.7 Specific aims 21
  1.7.1 Specific aim of experiment 1 21
  1.7.2 Specific aim of experiment 2 22
  1.7.3 Specific aim of experiment 3 23

2. EXPERIMENT 1 25

EFFECT OF TDCS ON TEMPORAL INFORMATION PROCESSING AS MEASURED BY THE GAP DETECTION PARADIGM 25

2.1 Introduction 26

2.2 Methods 27

2.3 Results 30

2.4 Discussion 31

3. EXPERIMENT 2 35

PRE-ATTENTIVE SPECTRO-TEMPORAL FEATURE PROCESSING DURING HD-TDCS 35

3.1 Introduction 36

3.2 Methods 37

3.3 Results 41

3.4 Discussion 44

4. EXPERIMENT 3 48

EFFECT OF BILATERAL TDCS ON PHONETIC PERCEPTION 48

4.1 Introduction 49

4.2 Methods 50

4.3 Results 53

4.4 Discussion 57

5. GENERAL DISCUSSION 60

5.1 Methodological challenges of auditory tDCS 61

5.2 Outline and future perspectives 64
    5.2.1 Specific prerequisites of tDCS for clinical application 64

6. REFERENCES 66

CURRICULUM VITAE 87

LIST OF PUBLICATIONS 89

STATUTORY DECLARATION 90

List of Figures

Figure 1: Illustration of the hierarchical organization of the AC. 4

Figure 2: Exemplary categorical perception of /da/ and /ta/. 6

Figure 3: Illustration of the within-channel design (A) and between-channel design (B). 8

Figure 4: Asymmetric sampling in time (AST) theory. 13

Figure 5: Auditory stimuli and tDCS application. 29

Figure 6: Performance data. 31

Figure 7: Auditory stimuli. 38

Figure 8: (A) Experimental setup for simultaneous HD-tDCS and EEG. 40

Figure 9: Auditory mismatch negativity (MMN) results. 42

Figure 10: Mismatch negativity (MMN) amplitudes separately for temporal and spectral deviant tones during sham, anodal_left, anodal_right, cathodal_left and cathodal_right at electrode site Fz (mean ± SEM). 44

Figure 11: Behavioral results. 54

Figure 12: Electrophysiological results. 56

List of Abbreviations

AC	auditory cortex
AEP	auditory evoked potential
AST	asymmetric sampling in time
ANOVA	analysis of variance
BOLD	blood oxygenation level dependent
Ca^{2+}	calcium ions
cAMP	cyclic adenosine monophosphate
cf	conferre: compare
CV	consonant-vowel
dB	decibel
e.g.	exempli gratia: for example
EEG	electroencephalography
ERP	event-related potential
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GDT	gap detection task
h	hour
HD-tDCS	High-Definition transcranial direct current stimulation
HG	Heschl's gyrus
Hz	Hertz
i.e.	id est: that is
IFG	inferior frontal gyrus
LORETA	low-resolution brain electromagnetic tomography
LTP	long-term potentiation
LTD	long-term depression
MMN	mismatch negativity
MEG	magnetoencephalography
ms	milliseconds
min	minute
NMDA	N-methyl-d-aspartate

NOT	noise onset time
PT	planum temporale
PET	positron emission tomography
REA	right-ear advantage
SEM	standard error of mean
STG	superior temporal gyrus
STS	superior temporal sulcus
tDCS	transcranial direct current stimulation
VOT	voice onset time
µV	microvolt

Abstract

Behavioral and neurophysiological studies revealed functional hemispheric asymmetry between the left and the right auditory-related cortices proposing a relative trade-off between spectral and temporal processing of complex acoustic signals such as speech and music. The left auditory cortical areas are preferentially tuned for temporal resolution, whereas right auditory cortical areas are more amenable to spectral resolution. Even though this lateralized auditory processing within the auditory cortex (AC) is widely accepted, several studies provide contradicting results showing no or reversed functional lateralization. The present thesis is aimed to investigate functional lateralization of the AC in a causal way utilizing transcranial direct current stimulation (tDCS). TDCS is a non-invasive brain stimulation method that delivers low electrical currents to the cerebral cortex resulting in the modulation of cortical excitability. Two experiments were conducted to investigate lateralized low-level feature processing. Behavioral results of the first study show that stimulation of the left but not right AC deteriorated auditory perception of rapidly changing acoustic information in a gap detection task (GDT). In the second study, I assessed the influence of anodal and cathodal high definition (HD)-tDCS delivered over the left or right AC on auditory mismatch negativity (MMN) in response to temporal as well as spectral deviants. The electrophysiological results show that the pre-attentive processing of temporal but not spectral acoustic features is elevated after selectively enhancing the neural reactivity of the left AC only. In sum, the data of both experiments provide a causal demonstration of left-lateralized specialization for temporal information processing. Given the potential of tDCS to modulate temporal resolution abilities of the AC, I conducted an additional experiment to examine effects on speech perception. In three experimental sessions, I assessed phonetic categorization of consonant-vowel (CV)-syllables (/da/, /ta/) with varying voice onset times (VOT) during bilateral sham, anodal, and cathodal tDCS delivered to the AC. Subsequently, I recorded auditory evoked potentials (AEP) in response to voiced (/ba/, /da/, /ga/) and voiceless (/pa/, /ta/, /ka/) CV-syllables. As a result, I demonstrate that bilateral tDCS of the AC can modulate phonetic perception. Cathodal tDCS improved phonetic categorization abilities in a VOT continuum accompanied by an elevation of the P50 amplitude of the AEP to CV-syllables during the anodal tDCS aftereffect. The results indicate the ability of bilateral tDCS over the AC to ameliorate speech perception.

Taken together, this PhD thesis demonstrates tDCS-induced changes in acoustic perception and AC reactivity. The results provide a direct causal evidence for left-lateralized sensitivity to temporal information in the acoustic signal. Moreover, I show that tDCS has the neuromodulatory potential to alter speech perception.

1. Introduction

The cerebral cortex of the human brain is anatomically separated in two distinct hemispheres that are interconnected by the largest fiber system in the brain, the corpus callosum. This bundle of more than 200 million axons transmits information from one hemisphere to the other. This anatomical arrangement is the biological basis for the sophisticated human intellect and enables one to easily carry out multiple complex cognitive tasks simultaneously. The cortical hemispheres act together to direct behavior and cognition, however, both the left and the right hemisphere differ from each other by exhibiting predominant functions. In the auditory domain, the two hemispheres have traditionally been described in terms of their functional specialization for language and speech. In 1861, the French surgeon Paul Broca provided the first empirical evidence for functional lateralization of language areas. He investigated the patient "Tan" who showed a lesion of the left inferior frontal gyrus (IFG). The patient suffered from a speech deficit that was characterized by the loss of the ability to clearly pronounce words, a so called Broca's aphasia (Broca, 1861). Later, the German neurologist Carl Wernicke found that a damage to the posterior temporal lobe (planum temporale, PT) in the left hemisphere may result in deficits of language comprehension, a so called Wernicke's aphasia (Wernicke, 1874). This pioneering work has emphasized left-lateralized speech-processing and advanced future research to investigate language specialization of the cerebral hemispheres. In the early 1960s Doreen Kimura introduced the dichotic listening task, which is a simple method to investigate hemispheric specialization of speech sound perception. The subjects were presented with competing words to the left and right ear simultaneously. When asked to repeat as many words as possible they most frequently reported words presented to the right ear. Since auditory information has greater neural representation in the opposite cerebral hemisphere, it has been suggested that this right ear advantage (REA) indicates a left-lateralized predominance for speech (Kimura, 1961b; a). By the advent of brain imaging and advanced electrophysiological techniques language lateralization has been investigated in a profound way also in the conscious healthy human. In particular, it has been shown that the left AC is pre-dominant for the perception and production of speech, and the right AC is dedicated to the processing of prosodic and emotional content of speech (Galaburda *et al.*, 1978; Ross, 1981; Weintraub *et al.*, 1981; Josse & Tzourio-Mazoyer, 2004). However, to date it is still discussed how this functional asymmetry is realized in the brain. Since cortical asymmetry is not limited to higher-level cognitive functions, the perception of natural sounds requires the processing of specific spectral distributions that change over time according to specific temporal sequences (Santoro *et al.*, 2014). Hence, functional or perceptual asymmetry of the AC can be described along a low-level acoustic processing dimension that shows a relative trade-off between spectral feature processing in the right hemisphere and temporal feature processing in the left hemisphere. Previous research showed that speech related disorders have been associated with altered low-level temporal processing abilities (Tallal & Piercy, 1973; Tallal, 1980; Tallal & Stark, 1981; Ben-Yehudah *et al.*, 2004). With the advent of modern neuromodulation techniques, such as direct current stimulation (tDCS), new approaches have been performed to investigate auditory functionality. Unraveling the functional lateralization by tDCS may contribute to a better understanding of acoustic processing in the auditory system and thus may facilitate potential add-ons to conventional therapies.

In the present PhD thesis, by systematically altering the neural activity of either the left or right AC, I investigated lateralized spectral and temporal processing in the human AC in a causal way. Furthermore, I assessed the neuromodulatory potential of auditory tDCS to alter speech perception and its underlying AC reactivity.

In the introduction section, I will describe the structure and function of the auditory system, followed by a theoretical overview of the acoustic speech signal. Afterwards, I will introduce the gap detection paradigm, an established method to measure temporal resolution abilities in the human AC. Moreover, I will briefly describe the essential role of temporal information processing in speech perception. I will specifically outline theories that make assertions about asymmetrical representation of spectral and temporal information in the AC and exemplify supporting brain imaging studies. Finally, I will concisely present the function of tDCS and its importance for neuroscientific research.

1.1 Structure and function of the auditory system

The auditory system of the human body is a striking feature that converts pressure waves to acoustic elements which are perceived as speech or music. Thus, it is culturally and socially essential and represents a crucial modality of sensation and perception.

The transformation of sound waves into neural activity in the AC begins in the external ear by funneling the sound waves through the external auditory canal to the tympanic membrane. In the middle ear three ossicles (malleus (hammer), incus (anvil) and stapes (stirrup)) deliver incoming vibrations to the oval window. The vibrations of the oval window causes traveling waves in the fluid-filled sections of the cochlea. This part of the inner ear plays a key role for transforming sonically generated pressure waves into neural impulses. The traveling waves displace the hair cells on the basilar membrane in the cochlea and thereby induce neuronal impulses. The displacement of the basilar membrane is specifically determined by the frequencies of the sound. According to place theory high frequencies maximally displace at the cochlear base, whereas low frequencies maximally displace at the cochlear apex (Bekesy, 1961). The local distribution of the hair cells is the basis for the tonotopic structure of the central auditory system. Once the hair cells converted the traveling wave to neuronal activity, the auditory information flows via the auditory nerve (nervus acusticus) to the cochlear nucleus. This is the place where fibers cross to the contralateral side, ensuring parallel organization of the ascending auditory system and information flow from each ear to both the left and the right cerebral hemisphere. The electrical information travels via the superior olive, the nucleus of lateral leminiscus and the inferior colliculus to the medial geniculate complex of the thalamus. The afferent neurons finally project to the AC being the ultimate target that is involved in receiving the sound signal. The AC is a portion of the superior temporal cortex and is divided into three functional regions including core, belt and parabelt regions. Whereas the belt is concentrically arranged around the core, the parabelt is adjacent to the ventrolateral side of the belt.

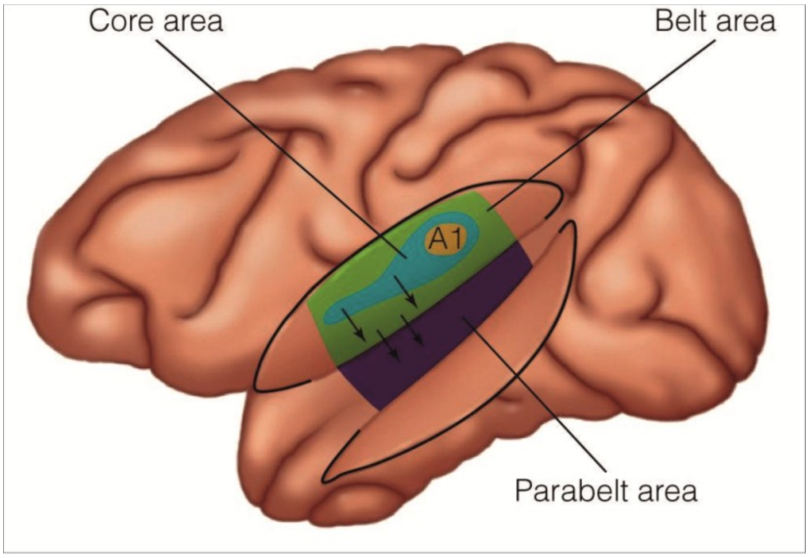

Figure 1: Illustration of the hierarchical organization of the AC. The temporal lobe is pulled back to see the core area, belt area and parabelt area. The arrows indicate the direction of auditory information processing from core to belt and to parabelt (Kaas *et al.*, 1999; Goldstein, 2010).

These regions comprise different subdivisions that process auditory information in parallel. The primary AC lies in the core area on the Heschl's gyrus (HG, BA 41) and is tonotopically organized according to the frequency arrangement in the cochlea. When complex acoustic information reaches the AC, fine-grained analysis along the spectral and temporal dimensions begins in the primary AC. While spectral information is encoded by the tonotopic map, temporal information is represented by rapidly changing patterns of neural activity. The auditory information processing is hierarchical organized starting with basic acoustic signal analysis within the primary AC (core) (Warrier *et al.*, 2009) followed by an activation of non-primary areas (belt, parabelt) to more complex auditory information as included in speech and music (Peretz & Zatorre, 2005; Zhang *et al.*, 2011; Steinschneider *et al.*, 2013) (cf. Figure 1).

1.2 The structure of the acoustic speech signal

Speech and language processing is a unique and complex function of the human brain involving prosodic, syntactic, and semantic elements. Moreover, an important element is phonology describing the structure of sounds that can be used to produce an acoustic speech signal. The acoustic speech signal can be basically described by three main characteristics, namely, as phonemes, as phonetic features and as acoustic signal.

Phonemes are the smallest distinguishable unit of speech. For instance, considering the word /b/oy and /t/oy, one can recognize that the phoneme /b/ is replaced by /t/ resulting in an entirely different word meaning.

Phonetic features describe how sounds are produced by physical movements of the vocal tract. Vowels are produced by a relatively wide open vocal tract, whereby the form of the opening of the vocal tract determines which vowels are produced. The production of consonants is based on three characteristics: voicing (sonority), place of articulation and type of articulation. Voicing is an articulatory process that relies on vibrations of the vocal cord. Consonants that cause a vibration of the vocal cord are voiced (e.g. /d/), whereas consonants that are produced without vibration are voiceless (e.g. /t/).The place of articulation is the location where the obstruction of the sounds in the vocal tract occurs. For instance, the production of /d/ is alveolar because the tongue is against the upper gum ridge. The manner of articulation describes how air escapes as it flows from the vocal tract out of the mouth and nose. A consonant sound such as /p/ represents a stop or plosive, whereas the consonant sound such as /f/ is a fricative. Finally, each phoneme can be classified by a unique combination of these three characteristics. Moreover, phonemes can be characterized by the acoustic speech signal that relies on physical features.

The acoustic speech signal carries specific spectral distributions that change over time according to specific temporal sequences. In detail, time, frequency and amplitude of the waveform are vital to process a speech signal. Importantly, the acoustic signal waveform can be illustrated as a function of time and frequency in a spectrogram. Within the scope of speech perception a fundamental component of vowels in a spectrogram are formants that are depicted by horizontal frequency bands with distinctive frequency ranges. Whereas the time course of formants (formant transition), which represents rapid changes of frequencies, and the voice onset time (VOT) are essential characteristics for consonants. The VOT is a main feature to categorize stop-consonants and is defined as the duration of the delay between release of closure and start of voicing. It characterizes voicing differences in a wide variety of languages and helps to distinguish voiced stop consonants (/b/, /d/, /g/) from their voiceless counterparts (/p/, /t/, /k/) (Lisker & Abramson, 1964). Figure 2 shows exemplary categorical perception identifying consonant-vowel (CV) syllables /da/ (voiced) and /ta/ (voiceless) in the order of tens of ms. There exist a perceptibility constant of the syllables with short VOTs identified as /da/ and those with long VOTs as /ta/. The perception shift at identifying /da/ or /ta/ is the phonetic boundary. At this point the subjects cannot unambiguously report which syllable was perceived. Categorical perception is crucial in speech perception, as it ensures that speech related acoustic signals are not perceived as an acoustic continuum but rather as clearly separable acoustic information (Davis & Johnsrude, 2007).

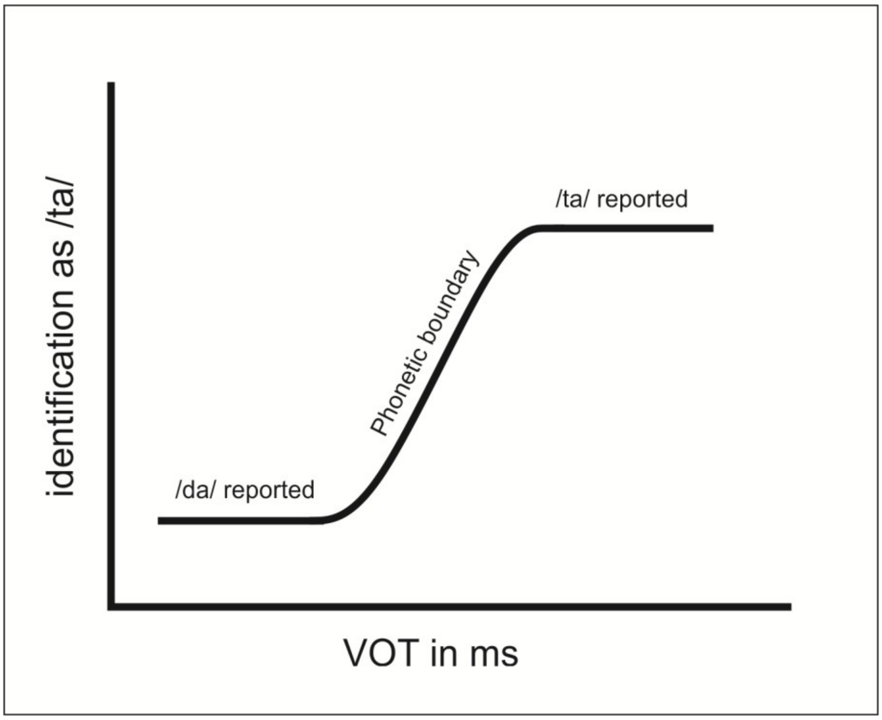

Figure 2: Exemplary categorical perception of /da/ and /ta/. Syllables with short VOTs are identified as /da/, whereas syllables with long VOTs are identified as /ta/. The phonetic boundary is the shift between the /da/ and /ta/ percept (cf. Eimas and Corbit, 1973).

This section emphasizes the importance of temporal characteristics of formants, formant transition and particularly VOT suggesting that correct processing of rapidly changing acoustic information is essential for efficient speech perception.

1.3 Gap detection paradigm

As described in the previous chapter the perception of phonemes depends to a large extent on VOT that constitutes a short silent gap in the acoustic signal. One of the most common methods used to determine the individual temporal resolution ability is a gap detection paradigm.

Generally, a gap detection task (GDT) refers to the discrimination of an interruption between two markers (leading element and trailing element) and is a widely accepted method to measure temporal resolution ability in healthy controls as well as patients with auditory processing deficits (Phillips *et al.*, 1997; Phillips *et al.*, 1998; Zaehle *et al.*, 2004; Sharma *et al.*, 2006). During the GDT the listener is presented with a series of two streams of sounds, one of which contains a silent interval (short gap in ms). The task is to identify the shortest detectable gap (gap detection threshold).
Phillips et al. (1997, 1998) demonstrated that the gap detection threshold is strongly influenced by the spectral features of the markers and the temporal position of the gap. If the leading and trailing element that surround the gap are noise bands with similar frequencies, the temporal operation is a discontinuity detection within one perceptual or neural channel (within-channel paradigm). The performance of this paradigm is relatively simple and the gap detection threshold is only a low around a few ms. Whereas if markers have different frequencies the temporal operation requires a relative timing of the offset of the leading element and the onset of the trailing element (cf. Figure 3). Therefore, the relative timing operation requires a central comparison between two perceptual channels, since there are no lateral neural connections between cochlear output fibers. This between-channel or central gap detection is more difficult resulting in increased gap detection threshold around tens of ms. Moreover, in contrast to the within-channel gap threshold, the between-channel gap threshold is highly sensitive to the duration of the leading element. In particular, the between-channel gap threshold inversely varies with duration of the

leading element less than about 30 ms. In order to investigate possibly shared temporal processing between non-speech gap detection and speech specific VOT detection gap stimuli were designed that resemble the structure of CV-syllables.

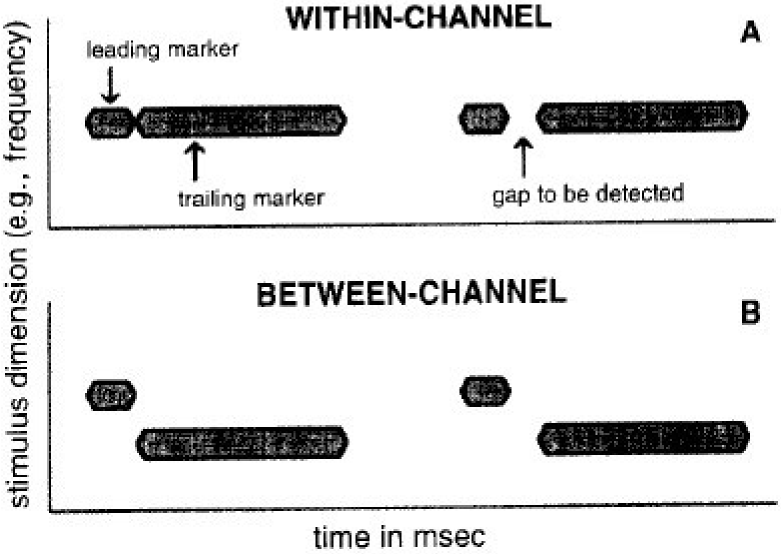

Figure 3: Illustration of the within-channel design (A) and between-channel design (B). In the within-channel design the short leading and the long trailing element have the same frequency, whereas in the between-channel design the markers differ in frequency (Phillips, 1999).

These stimuli have a short broadband leading element (resembling a consonant burst), followed by a brief silent interval (VOT), and a relatively long, low-frequency trailing element (vowel). In result, gap detection thresholds are long for short leading element durations, and short for long leading element durations indicating an inverse relation of gap detection threshold and leading element duration. For leading elements with a short duration (5 ms) the average gap detection threshold was around 30 ms. Notably, this value is close to the value defining the phonetic boundary between some voiced and voiceless CV-syllables around 25-25 ms in human as well as animals (Eimas & Corbit, 1973; Kuhl & Miller, 1978; Eggermont, 1995; Elangovan & Stuart, 2008).

In sum, a between-channel paradigm is a fundamentally different task compared to the within-channel paradigm. The results further suggest a general neural basis for low-level temporal processing of speech and non-speech sounds. Consequently, a between-channel GDT is an optimal method to assess individual temporal processing ability in human central auditory system. Moreover, using the between-channel paradigm revealed a right-ear advantage (REA), i.e. predominance of the left AC for temporal processing.

1.4 Deficient temporal information processing (Dyslexia)

Evidence for the essential relation between speech perception and basic temporal processing has been provided by studies investigating patients with auditory related disorders. Psychometric data show abnormal VOT identification of reading disabled subjects compared to typical reading subjects (Joanisse *et al.*, 2000; Breier *et al.*, 2001; Chiappe *et al.*, 2001; Bogliotti *et al.*, 2008). Moreover, temporal resolution as measured by a between channel GDT is impaired in patients suffering from dyslexia (Phillips *et al.*, 2010; Hamalainen *et al.*, 2013).

Dyslexia is a learning disorder characterized by severe and persistent reading and spelling problems. The prevalence of dyslexia has been estimated to be approximately 5 to 10% (Elliott & Grigorenko, 2014). Despite the fact that the current focus of research lies on child and adolescent dyslexics, most affected subjects report persistent restrictions in reading and writing in adulthood. One of the most dominant cognitive symptoms of dyslexia is the phonological processing deficit. The impaired phonological skills are the consequence of a more basic auditory processing constraint that disrupts essential components for literacy, starting with the acquisition of phonological representations (Ramus, 2003; Tallal, 2004; Tallal & Gaab, 2006). At the neurological level, the perceptual deficit is related to a dysfunction of left hemispheric perisylvian brain areas that underlie phonological representations (Ramus, 2003). The impaired auditory processing impedes speech perception by degrading the ability to accurately segment the speech stream into its important phonetic components such as rhymes, syllables and phonemes. Accordingly, individuals with dyslexia have difficulties in processing rapidly changing information in speech - such as the spectral changes of formant transitions (Farmer & Klein, 1995; Tallal & Gaab, 2006), and cues that vary over time such as amplitude and frequency modulations (Studdert-Kennedy & Mody, 1995) - as well as in non-speech sounds (Tallal & Piercy, 1974; Breier *et al.*, 2001; Chandrasekaran *et al.*, 2009). Consequently, basic auditory processing problems can be considered to be causally responsible for phonological deficits (Farmer & Klein, 1995; Tallal, 2004; Tallal & Gaab, 2006).

The data of patients with dyslexia emphasize the importance of temporal information in the acoustic speech signal as well as the predominant role the left AC in speech perception.

1.5 Theories of hemispheric asymmetry in speech processing

The first neurophysiological insights of speech processing have been attributed to the correlation of certain brain lesions and specific dysfunction of speech perception or speech production.

In the 19th century, the Wernicke-Lichtheim model (1885) has been introduced describing left lateralized speech processing based on postmortem sections. This classical model proposes three different anatomical structures on the left perisylvian cortex comprising Broca's area (responsible for speech production), Wernicke's area (responsible for speech perception) and the arcuate fasciculus, a fiber tract connecting both areas. Beyond the Wernicke aphasia and Broca aphasia, the dysfunction of the arcuate fasciculus leads to a conductivity aphasia that results in poor speech repetition (Geschwind, 1979). In the 1960s more support of left hemisphere specialization for speech processing has been provided by behavioral studies using dichotic listening techniques (Kimura, 1961b; a; Bryden, 1982). The results show that participants exhibit a right-ear advantage (REA) for most speech stimuli indicating greater left hemispheric processing. However, it has been discussed that the REA for speech as measured in a dichotic listening task is not the result of the speech sound stimuli per se but rather depends on spectro-temporal characteristics. In a latter dichotic listening study, a reduced REA was found to phonemically similar CV-syllables with extended duration of the formant transition compared to characteristic short duration. This study pioneers the left hemispheric preference for speech to basic temporal structure of the acoustic speech signal (Schwartz & Tallal, 1980). In contrast, by using a dichotic pitch recognition task a left-ear advantage was revealed indicating a predominant role for spectral processing in the right hemisphere (Sidtis, 1981). During the last decades new brain imaging studies emerged using PET, fMRI, EEG, and MEG and gained more detailed insights about AC specialization in terms of acoustic features.

One of the first prominent studies was carried out by Zatorre et al. (2001), who examined the response of the left and right AC to spectro-temporal features using PET. The participants were presented with pure tone patterns that changed in frequency or duration. The results show that distinct subareas of the AC in both hemispheres responded to spectral and temporal variations. The primary AC (HG) was preferentially recruited by increasing temporal variation, whereas anterior STG areas and right STS region covaried with spectral changes. While the signal in the left hemisphere was higher for temporal, the activation in the right hemisphere was greater for spectral changes. Primary AC areas (core areas) in both hemispheres preferentially respond to acoustic temporal features, whereas more anterior STG regions (belt and parabelt areas) respond preferentially to spectral features. This paper has been very influential, contrasting spectral processing and temporal processing in the AC. It is suggested to consider a functional asymmetry on auditory low-level with left-lateralized temporal processing and right lateralized spectral processing.

In contrast, Hickok and Poeppel (2000) suggest a model that accounts for a bilateral contribution of the posterior-superior temporal lobe for sound based representations of speech. This approach involves two left lateralized pathways that participate in speech perception in a task dependent manner. The ventral pathway involves the cortex in the vicinity of the temporal-parietal-occipital junction. This pathway is important for interfacing sound-based representations of speech with widely distributed conceptual representations and therefore is involved in tasks that require access to the mental lexicon. The dorsal pathway involves the inferior parietal and frontal systems and appears to play a greater role in tasks that require explicit access to certain sub-lexical speech segments.

Following these thoughts, Poeppel (2003) introduced the asymmetric sampling in time (AST) theory and proposed that the input speech signal has a neural representation being bilaterally symmetric at an early representational level in the primary AC area. Beyond the initial representation non-primary areas further elaborate the temporal information asymmetrically. Neuronal ensembles in left non-primary AC areas (belt, parabelt) preferentially extract information from a short temporal integration window from ~20-40 ms, which is relevant for encoding formant transition of stop consonants. Whereas neuronal ensembles in the right hemisphere preferentially extract information from a long integration window in the order of ~150-250 ms that occur to syllabicity and prosodic phenomena (cf. Figure 4). Moreover, AST model can be further characterized by time dependent integration due to oscillatory neuronal activity in different frequency bands. While the left hemisphere areas sample the spectro-temporal cortical representations built in core AC at higher frequencies around 40 Hz (gamma band), the right hemisphere areas sample at lower frequencies around 4-10 Hz (theta and alpha bands). In conclusion, it is supposed that high temporal resolution power in left AC might be essential to resolve rapid frequency changes typical for e.g. encoding formant transition of stop consonants and VOT, whereas slow frequency changes can be better distinguished in the right AC in the context of prosodic information or music perception.

The traditional concepts of both Zatorre et al. (2001, 2002) and Poppel (2003) predict that even though speech perception is bilaterally organized the hemispheres are not equally engaged in acoustic feature processing. They suggest that speech perception on the basis of spectro-temporal aspects is laterally processed with complementary contribution of left and right AC areas. However, the AST theory seems more suited to explain functional lateralization 1) as it incorporates physiologically motivated temporal integration windows and 2) it avoids categorical dichotomy (Liem et al., 2014). In order to examine the concept of functional lateralization, a series of hemodynamic and electrophysiological studies was carried out providing evidence to a large extent.

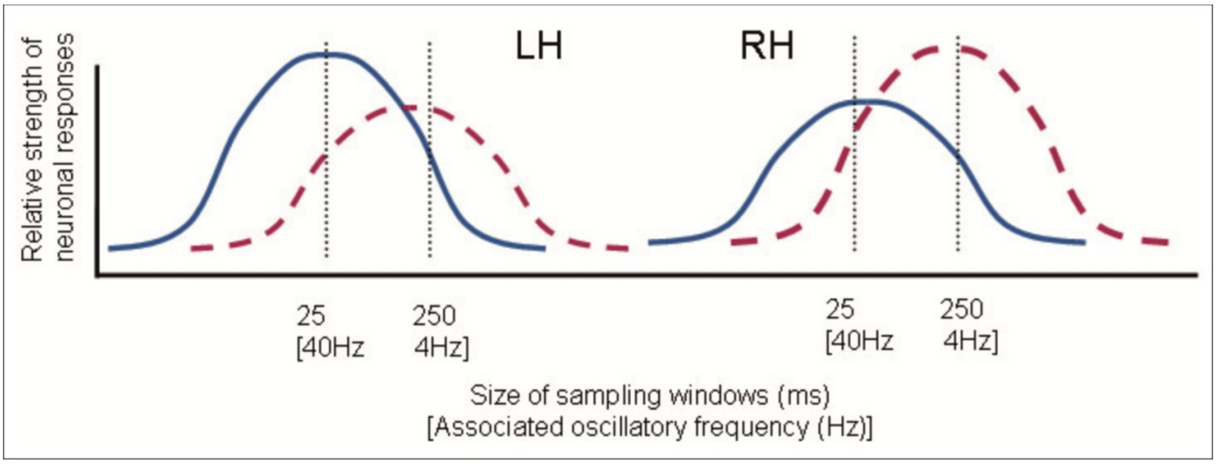

Figure 4: Asymmetric sampling in time (AST) theory. The illustration depicts the differential preferences of the two hemispheres with the left posterior auditory-related cortex being preferentially driven by rapidly changing cues and the right posterior auditory related cortex being more amenable to slowly changing acoustic cues (Meyer, 2008).

1.5.1 Structural and functional neuroanatomical evidence

In this section, I will exemplify studies that examined hemodynamic responses in the auditory system related to changes of spectral and temporal information in speech and non-speech sounds. Here, I refer not only to functional lateralization in the AC, but also to structural differences between the left and right temporal lobe.

According to the proposed functional lateralization, an fMRI study investigated to what extent rapid auditory information in speech sounds compared to non-speech sounds is processed laterally (Zaehle *et al.*, 2004). For that purpose the authors assessed temporal information processing by utilizing 1) a between-channel GDT as described above and 2) a phonetic discrimination task with CV syllables with manipulated VOT (/da/ = 30 ms, /ta/ = 40 ms). It has been revealed that rapid temporal information in speech as well as non-speech sounds is preferentially processed in the left primary AC (HG) and non-primary area (PT). Moreover, the authors suggest a general sensitivity of language related areas for rapid temporal information irrespective of linguistic content (Zaehle *et al.*, 2004).

These results have been confirmed by Meyer et al. (2005). In this study, an auditory discrimination task was performed on a set of sine-wave analogues with different spectro-temporal features that could be perceived as either non-speech or speech (say and stay). In a first condition, naive listeners perceived the sound as unnatural or non-speech sound, while in the second condition informed listeners recognized them consistently as speech. Importantly, the informed listeners were instructed to pay attention precisely on the brief temporal gaps that help to discriminate the speech sounds. The behavioral data indicate that the temporal integration as occurred during informed condition is essential for speech perception. The fMRI signal in response to the perceptual switch from non-speech (spectral processing) to speech (spectro-temporal processing) led to an activation increase in the adjacent portions of the left posterior AC areas (HG, PT, STS). The authors conclude that the left posterior superior temporal lobe is preferentially sensitive for briefly changing temporal cues during speech.

Another study was carried out with meaningful word items that were degraded along the spectral and temporal dimension (Obleser *et al.*, 2008). In a listening task, the speech stimuli were presented and the subjects were required to indicate how comprehensible the word had been. The analysis of the BOLD signal to spectro-temporal modulated speech stimuli revealed a subtle functional lateralization of AC areas. The signal to temporal variations was most effective in driving brain activation of the left anterolateral superior temporal sulcus (STS), whereas the right was more sensitive to changes in spectral details. The results underline a hemispheric asymmetry in the sensitivity to spectral and temporal details in the speech signal.

Zaehle et al. (2008) corroborate the relative trade-off between spectral and temporal processing during sublexical auditory perception. The subjects had to discriminate verbal (CV-syllables) and nonverbal (gap stimuli) auditory stimuli with respect to spectral or temporal acoustic features. The fMRI data show a significant activation in the dorsal stream involving the left inferior frontal gyrus (IFG) and the left parietal operculum when participants had to discriminate speech and non-speech stimuli based on subtle temporal acoustic features. In contrast, when subjects perceived the same stimuli based on changes in the frequency, bilateral activations along the middle temporal gyrus and STS were observed. These findings demonstrate an involvement of the dorsal pathway in the segmental sublexical analysis of speech sounds as well as in the segmental acoustic analysis of non-speech sounds with analogous spectro-temporal characteristics. Finally, this study emphasizes that segmental processing according to temporal features requires the left-hemispheric dorsal processing network.

Direct evidence for the AST model has been provided by Boemio et al. (2005), who showed that both hemispheres remarkably contribute to temporal processing. In particular, subjects were presented with temporal varying narrow-band noise stimuli which either have a constant frequency throughout the signal or a frequency that was swept linearly upward or downward randomly. The fMRI results show an activation to temporal and spectral structure in the left and right superior temporal gyrus (STG). Moreover, lateralized activity to slowly modulated signals has been found in the right STS indicating consistency with the AST model that predicts a rightward lateralization of function for long-duration segments.

Further confirmation for the AST theory has been provided by Liem et al. (2014) who combined functional and structural MRI. In order to investigate the functional lateralization, auditory sentences were split into segments with varying length (100, 150, 200, 250 ms). In a pattern-matching task the subjects had to indicate whether the probe stimulus was a sample from the original version of the sentence. The results revealed no functional lateralization in the primary AC (HG). In contrast, a functional shift was observed in non-primary AC areas involving the PT and the posterior STG when diminishing temporal information with increasing time window. This result corresponds to the AST theory suggesting that right non-primary AC areas preferentially process slowly changing cues. Moreover, a structural-behavioral relationship was found by showing that subjects with smaller cortical thickness in the right PT compared to the left PT showed increased performance (Liem *et al.*, 2014). Generally, the structural data revealed a leftward surface area asymmetry in 74% of subjects and a rightward cortical thickness asymmetry in 61% of subjects (Liem *et al.*, 2014). Such structural asymmetries in auditory-related regions (HG, PT, STG) that seem to covary with functional lateralization have also been demonstrated in previous postmortem, neuropsychological and neuroimaging studies (Hutsler & Gazzaniga, 1996; von Steinbuchel *et al.*, 1999; Hutsler, 2003; Sigalovsky *et al.*, 2006; Takao *et al.*, 2011; Meyer *et al.*, 2013). For instance, data from post-mortem brains demonstrate a rightward asymmetry of cortical thickness in the PT (Harasty *et al.*, 2003). Moreover, Warrier et al. (2009) assessed the relationship between auditory cortical structure and spectro-temporal processing by fMRI. As a result, the authors demonstrate a functional lateralization as proposed by Zatorre et al. (2001, 2002) and Poeppel (2003). Particularly, while larger leftward asymmetry of volume in the HG was associated with temporal processing, rightward asymmetry was associated with spectral processing.

White matter structural characteristics are considered to be important for processing temporal acoustic features (Penhune *et al.*, 1996; Warrier *et al.*, 2009). It is suggested that greater volume in the left AC areas is due to greater myelination causing faster conductivity and thereby enhanced sensitivity to rapidly changing acoustic information (Zatorre & Belin, 2001).

1.5.2 Electrophysiological evidence

FMRI measurements have become one of the most valuable neuroimaging techniques to localize neural activity in human brain. However, this method cannot precisely detect auditory temporal operation to rapidly changing acoustic cues. FMRI detects neural activity indirectly hemodynamic resulting in a rather poor temporal resolution. Whereas MEG and EEG recording allows a direct measurement of neural activity with very high temporal resolution in the order of ms. This section outlines electrophysiological studies providing evidence for hemispheric specialization to spectro-temporal processing in the AC.

Sandmann et al. (2007) assessed auditory lateralization of prelexical speech processing. For that purpose a dichotic listening task was performed with concurrent EEG measurement. The listeners heard dichotic pairs of six CV-syllables with varying VOT that initially started with a voiced (/ba/, /da/, /ga/) or a voiceless stop consonant (/pa/, /ta/, /ka/). The analysis of the auditory evoked potentials (AEPs) showed that the fronto-central N1 amplitudes were larger for syllables with voiced than voiceless initial consonants. Furthermore, low resolution electromagnetic tomography (LORETA) revealed a lateralization effect with stronger leftward lateralization for voiced than voiceless CV-syllables indicating that auditory lateralization is affected by temporal cues (VOT) in CV-syllables.

In order to investigate the spatio-temporal pattern of acoustic feature processing CV syllables with varying VOT (5 ms, 30 ms and 60 ms) and non-speech analogues with varying noise-onset-time (NOT) (5 ms, 30 ms and 60 ms) were presented (Zaehle *et al.*, 2007). The data revealed an early and a late negative deflection (N1a, N1b) of AEPs, both significantly correlating to the duration of VOT/NOT. LORETA analysis showed overlapping supratemporal networks that are involved in the perception of both speech and non-speech sounds with a bilateral activation pattern during the N1a time window and leftward asymmetry during the N1b time window. Furthermore, elaborated regional statistical analysis of the data further point to strong left lateralized responses over the middle supratemporal plane for both the N1a and N1b component, and a functional leftward asymmetry over the posterior supratemporal plane for the N1b component. Finally, the authors suggest a predominant role of the left middle and posterior AC in speech and nonspeech discrimination based on temporal features.

Furthermore, functional hemispheric asymmetries were examined on basic neural processing of fundamental sound features (Okamoto *et al.*, 2009). During MEG recording tonal stimuli and pulse trains stimuli with spectral or temporal change were presented. The neural responses elicited by spectral and temporal stimulus change were lateralized. The N1m amplitude evoked by the spectral stimulus change was comparably larger in the right hemisphere, whereas the N1m amplitude evoked by the temporal stimulus change was larger in the left. The data demonstrate that the human AC of the left hemisphere has superior temporal resolution capabilities, whereas the AC of the right hemisphere has better spectral resolution capabilities at early basic neural processing levels.

Moreover, functional lateralization is not limited to conscious cognitive processes but can be even assessed during pre-attentive processing without any attentional fluctuations. For that purpose, auditory mismatch negativity (MMN) is a valuable electrophysiological measure that can be elicited when violations of regularities in a stream of sounds occur. In a recent study, auditory MMN elicited by band-pass deviant sounds that either varied in temporal or spectral information were recorded by MEG and revealed hemispheric lateralization. In particular, spectral deviants were preferentially processed in the right hemisphere, whereas temporal deviants were processed in the left hemisphere (Okamoto *et al.*, 2013).

In congruency with current fMRI studies, the electrophysiological data suggest that similar mechanisms underlie the perception of linguistically different but acoustically equivalent auditory stimuli. Moreover, it can be resumed that on the level of basic auditory analysis the left and right AC are differentially engaged as postulated by Zatorre et al. (2001, 2002) and Poeppel (2003). However, the results have been challenged regarding several issues of data acquisition such as different stimulus material (speech vs. non-speech sounds), task demands (active vs. passive task demands) and task dependent attention (attention to the left vs. right ear) (Bryden *et al.*, 1983; Woldorff *et al.*, 1993; Poeppel *et al.*, 1996; Scott & McGettigan, 2013). Moreover, most neuroimaging studies do not provide a causal link between the neural activity in the AC and spectro-temporal information processing. To explore functional asymmetry in the AC, a causal impact such as altering the neural activity by non-invasive brain stimulation constitutes a promising opportunity to add robust information about functional specialization of the AC.

1.6 Transcranial Direct Current Stimulation (tDCS)

At the start of the new millennium non-invasive brain stimulation techniques revived and have been successfully employed to directly influence cortical excitability. TDCS is probably the most frequently used technique. By applying low-intensity electrical currents through the skull tDCS is capable to directly influence brain activity and its related alterations in behavior. In this section, I will give a brief overview of the functional principle and significance in basic neuroscience.

1.6.1 Functional principle of tDCS

TDCS can influence cortical activity by delivering low currents to the cerebral cortex (Nitsche *et al.*, 2008). The current flows between an active and a reference electrode. While a part of this current is shunted through the scalp, the rest is delivered to the brain tissue (Miranda *et al.*, 2006; Neuling *et al.*, 2012), thereby inducing diminutions or enhancements of cortical excitability (Nitsche *et al.*, 2008). The direction of the tDCS-induced effect depends on the current polarity. Anodal tDCS typically has an excitatory effect while cathodal tDCS decreases the cortical excitability in the region under the electrode (Nitsche & Paulus, 2000; Nitsche *et al.*, 2003b). Specifically, anodal tDCS causes a depolarization of the resting membrane potential and increases the firing rate, whereas cathodal tDCS decreases the firing rate via hyperpolarization of the resting membrane potential (Bindman *et al.*, 1962; Purpura *et al.*, 1965). The effects of tDCS are not limited to modulations of cortical excitability during stimulation (online effect), but outlast the stimulation period by several minutes or hours (Bindman *et al.*, 1962; 1964; Nitsche & Paulus, 2000; 2001). This aftereffect or offline effect of tDCS relies on long-term synaptic changes associated with long-term potentiation (LTP) and long-term depression (LTD). Specifically, tDCS induced post-synaptic polarization is caused by altered pre-synaptic input due to changed firing rates which leads to enhanced N-methyl-Daspartate (NMDA) receptor-efficiency resulting in an increase of the intracellular Ca^{2+} level. While anodal aftereffects are suggested to induce LTP due to enhanced firing rate, cathodal tDCS reduces firing rate followed by LTD (Liebetanz *et al.*, 2002; Nitsche *et al.*, 2002; Nitsche *et al.*, 2003a; Stagg & Nitsche, 2011; Monte-Silva *et al.*, 2013). Moreover, pharmacological investigations reported tDCS induced changes of neurotransmission. Anodal stimulation leads to a significant decrease in GABA (inhibitory neurotransmitter) concentration resulting in enhanced neural activity, whereas cathodal stimulation decreases Glutamate (excitatory Neurotransmitter) concentration following diminished neural activity (Filmer *et al.*, 2014). Behavioral and direct neurophysiological changes induced by tDCS have been successfully demonstrated in the motor (Nitsche and Paulus, 2000; Sehm et al., 2013b), visual (Antal et al., 2003; Peters et al., 2013), and somatosensory system (Dieckhofer et al., 2006; Antal et al., 2008; Sehm et al., 2013a) as well as in the cognitive domain (Heimrath et al., 2012; Floel, 2014). The application of tDCS on the auditory system is relatively sparse.

In a first meaningful approach Zaehle et al. (2011) investigated cortical reactivity of the human AC after anodal and cathodal tDCS. For this purpose active tDCS electrodes were placed over a temporal or a temporo-parietal location and a reference electrode over the contralateral supraorbital area. Each of the participants performed four consecutive sessions at one-week intervals and received in two out of four sessions tDCS over the primary AC, while in the two remaining sessions, tDC-stimulation was applied over a secondary auditory region. Furthermore, in each session, participants underwent one sham, and one verum stimulation with the sham condition always preceding the verum stimulation condition to avoid carryover effects of tDCS. After receiving tDCS AEPs were recorded in response to sinusoidal tones of 1 kHz and found tDCS-induced modulations of auditory evoked brain activity as a function of stimulation site and condition (offline effect). Both, anodal and cathodal stimulation over the primary and secondary AC affected sensory acoustic processing. Consequently, by revealing polarity-specific effects of anodal and cathodal tDCS on AC reactivity, the authors demonstrated for the first time, that the excitability of the AC can be directly modulated by tDCS. While anodal tDCS over the temporal lobe increased the P50 amplitude, cathodal stimulation over the temporo-parietal area increased the N1 component of the AEP (Heimrath *et al.*, 2016).

Besides these direct electrophysiological evidences for tDCS-related alterations of the human AC, several behavioral studies reported effects of auditory tDCS on different aspects of acoustic perception (Heimrath *et al.*, 2016).

1.6.2 What can tDCS application inform about auditory brain function?

The advent of functional brain imaging extended our knowledge about specific neural mechanisms involved in cognitive, motor, and perceptual processes. However, neuroimaging results are inherently correlational showing that activity in specific brain areas is associated with certain perceptions and behaviors. Accordingly, inferences of causality cannot be drawn from imaging studies. The possibility to directly modulate circumscribed brain areas by tDCS offers a powerful research tool to investigate brain functions. Transient neuromodulation enables us to alter the excitability of brain areas and to observe the effects on behavior. Therefore, tDCS can be utilized to make causal inferences about the relationship between neural activity of certain brain areas and the behavioural outcome. Thus, tDCS now opens new strategies for testing hypotheses on the causal relation of cortical reactivity and function (Fox, 2011; Miniussi & Ruzzoli, 2013; Filmer *et al.*, 2014). Moreover, a multimodal approach combining tDCS and EEG enables a gain of more detailed understanding of neural mechanisms involved in these alterations (Miniussi *et al.*, 2012). Such approach can directly link the obtained EEG signal to the modulated neural activity.

Applying tDCS, separately and in combination with EEG, constitutes a promising method to investigate neural activity of the AC involved in auditory low-level processing.

1.7 Specific aims

This PhD project aims at investigating tDCS-dependent alterations on low-level acoustic processing and cortical reactivity of the AC. Particularly, the two big goals are to examine hemispheric specialization for spectro-temporal processing in a causal way and to prove whether tDCS has the potential to change the temporal resolution of the AC in response to speech and non-speech sounds. For this purpose, I conducted three experiments gathering behavioral as well as electrophysiological data (for an overview of experimental designs see Table 1).

1.7.1 Specific aim of experiment 1

I want to examine the functional lateralization of the AC for the perception of rapidly changing acoustic information in non-speech sounds by tDCS.

While there is much behavioral, electrophysiological as well as hemodynamic evidence of the left-hemisphere dominance for temporal processing, there is a lack of direct causal inference of the functional outcome and the underlying neural representation. In the first experiment the left and right AC was separately tDC-stimulated while participants performed a between-channel GDT. A between-channel GDT has been reliably shown to reflect temporal resolution ability of the central auditory system (Phillips *et al.*, 1997; Zaehle *et al.*, 2004).

Hypothesis:

Based on theories about functional specialization by Zatorre et al. (2001, 2002) and Poeppel (2003), I expect that anodal tDCS of the left, but not the right AC reactivity will alter the participants' temporal resolution abilities as measured by the individual gap detection threshold.

1.7.2 Specific aim of experiment 2

I want to investigate the functional lateralization of the AC for pre-attentive spectro-temporal feature processing without any task or attentional demands by high-definition (HD)-tDCS.

It has been shown that the investigation of lateralized spectro-temporal processing can be influenced by task demands and task dependent attention (Bryden *et al.*, 1983; Woldorff *et al.*, 1993; Poeppel *et al.*, 1996). To specifically address this issue, acoustic perception without attentional fluctuations can be assessed by recording the auditory mismatch negativity (MMN), a pre-attentive measure of event-related potentials (Kujala *et al.*, 2007). This parameter can be elicited without task or attentional demands and is an extremely robust parameter to asses central auditory processing. By utilizing high-definition (HD)-tDCS in this second experiment, I systematically modulated neural activity of the left and right AC. The application of HD-tDCS compared to conventional tDCS enables a more focused current flow to the target area and thus enhances cortical reactivity (Datta *et al.*, 2012; Kuo *et al.*, 2013). Anodal and cathodal HD-tDCS was delivered over the left or right AC on auditory MMN in response to temporal as well as spectral deviants.

Hypothesis:

I hypothesize that HD-tDCS modulation of the left AC will alter MMN response to temporal deviants, whereas HD-tDCS over the right AC will influence MMN in response to spectral deviants.

1.7.3 Specific aim of experiment 3

I want to assess the effects of bilateral tDCS over the temporal cortex on phonetic categorization of CV-syllables in a VOT continuum and on AEPs in response to voiced and voiceless CV-syllables.

The first two experiments investigated the influence of tDCS on low-level acoustic processing only. However, the results of experiment 1 and 2 do not provide information about the efficacy of auditory tDCS on speech perception (Heimrath *et al.*, 2016). As discussed in the introduction speech perception is strongly influenced by the temporal features of the acoustic sound. VOT is a temporal feature to categorize CV-syllables in a continuum and has been shown to be crucial for speech perception. The processing of different VOTs in speech stimuli is reflected by the P50-N1 complex of AEPs (Sandmann *et al.*, 2007; Zaehle *et al.*, 2007; King *et al.*, 2008). To my knowledge there are neither behavioral nor electrophysiological data that show tDCS induced modulation of speech perception in healthy subjects. In the third experiment, I systematically investigated the effects of anodal and cathodal tDCS over the bilateral temporal cortex on phonetic categorization in a VOT continuum and on the P50-N1 complex of AEPs in response to voiced and voiceless CV-syllables.

Hypothesis 1:

I assume tDCS-dependent alterations in the performance of a phonetic categorization task.

Hypothesis 2:

Furthermore, I expect tDCS-induced changes in the neural reactivity of the AC reflected by modulations of the P50-N1 complex.

Table 1: Overview of experimental designs

Experiment	Sample size	Electrode position of the active electrode	Stimulation intensity	Paradigm
1	15	T7, T8	1.5 mA	between-channel GDT
2	12	C5, C6	0.5 mA	MMN paradigm (spectral and temporal deviants)
3	13	simultaneous T7, T8	1.5 mA	phonetic perception task

Note: Electrode positions refer to the international 10-20 system.

2. Experiment 1

Effect of tDCS on temporal information processing as measured by the gap detection paradigm

Specific aim:

I want to examine the functional lateralization of the AC for the perception of rapidly changing acoustic information in non-speech sounds by tDCS.

The content of this chapter has been published as: Heimrath, K., Kuehne, M., Heinze, H.J., and Zaehle, T. (2014). Transcranial direct current stimulation (tDCS) traces the predominance of the left auditory cortex for processing of rapidly changing acoustic information. Neuroscience 261, 68-73. doi: 10.1016/j.neuroscience.2013.12.031.

Abstract

In the present study, I investigated the effects of anodal tDCS over the AC on the perception of rapidly changing acoustic cues. For this purpose, in 15 native German speakers the left or right AC was separately stimulated while participants performed a between-channel gap detection task. Results show that stimulation of the left but not right AC deteriorated the auditory perception of rapidly changing acoustic information. The data indicate a left hemispheric dominance for the processing of rapid temporal cues in auditory non-speech sounds. Moreover, I demonstrate the ability of non-invasive brain stimulation to change human temporal information processing in the auditory domain.

2.1 Introduction

The two cerebral hemispheres of the human brain have traditionally been described in terms of their functional specialization with the AC of the left hemisphere being predominant for the perception and production of speech, and the AC of the right hemisphere dedicated to the processing of prosodic and emotional content of speech (Galaburda *et al.*, 1978; Ross, 1981; Weintraub *et al.*, 1981). However, research in the past decades clearly suggests that the functional asymmetries of the left and right auditory system can be described along a low-level acoustic processing dimension (Zatorre & Belin, 2001; Tallal & Gaab, 2006; Zatorre & Gandour, 2008). In this regard, recent neurobiological frameworks of auditory cognition propose a ‘‘division of labor’’ between the left and the right auditory-related cortices, encompassing a relative trade-off in spectral and temporal processing of complex acoustic signals such as speech and music, with left auditory cortical areas being highly tuned for temporal resolution and right auditory cortical areas being more amenable to spectral resolution (Zatorre & Belin, 2001; Meyer, 2008). According to the ‘‘asymmetric sampling in time’’ (AST) hypothesis, asymmetries in the auditory system may be accounted for by hemispheric differences in sampling time: the left auditory areas preferentially extract information from short and the right auditory areas from long temporal integration windows (Poeppel, 2003a; Luo & Poeppel, 2012). Moreover, the authors have argued that these time windows also correspond to different spectral resolution constants (25-ms time window corresponds to 40-Hz spectral resolution; 200-ms time window corresponds to 5-Hz spectral resolution), which leads generally to a ‘‘division of labor’’ as mentioned by Zatorre and Belin (2001). In contrast to this proposal the more flexible AST model suggests that the spectro-temporal asymmetry is attributed to differences in neuronal integration windows on the left and right auditory-related cortex. However, to this date, the asymmetry of the auditory domain for temporal acoustic features is still controversially discussed (Scott & McGettigan, 2013). While a majority of hemodynamic (Zaehle *et al.*, 2004; Meyer *et al.*, 2005), electrophysiological (Sandmann *et al.*, 2007; Zaehle *et al.*, 2007; Okamoto *et al.*, 2009), behavioral (Schwartz & Tallal, 1980; Sulakhe *et al.*, 2003), as well as animal studies (Wetzel *et al.*, 2008; Rybalko *et al.*, 2010) have shown lateralized auditory processing of spectro-temporal sounds, also several contradicting results have been reported showing no (Uther *et al.*, 2003) or reversed auditory hemispheric lateralization (Reiterer *et al.*, 2005; De Sanctis *et al.*, 2009). In the majority of these studies, the conclusions are drawn on correlational inferences, e.g. statistical relationship between a set of variables that, in principle, do not allow a direct causal inference. In contrast, the possibility to directly modulate circumscribed brain areas by non-invasive electrical stimulation offers a research tool for investigating such causal relations (Fox, 2011). TDCS can influence cortical activity via weak direct current to the head. In the auditory system it has been shown that tDCS can alter primary AC reactivity (Zaehle et al., 2011) as well as temporo-spectral perception (Ladeira *et al.*, 2011; Tang & Hammond, 2013). In particular, using silent gaps in white noise clicks, anodal but not cathodal tDCS improved gap detection performance (Ladeira et al., 2011). Electrophysiologically, anodal stimulation over temporal cortex specifically enhances the P50 component of AEPs, with no effect of cathodal tDCS (Zähle et al., 2011).

In the present study, I investigated the effects of anodal tDCS over the AC of both hemispheres on the perception of rapidly changing acoustic cues. Here, by systematically modulating the neural activity of either the left or right AC, I studied hemispheric lateralization for the processing of rapidly changing acoustic cues in non-speech sounds. According to the neurophysiological frameworks mentioned above I hypothesized that the modulation of the left, but not the right AC reactivity by means of tDCS will alter participant's temporal resolution abilities.

2.2 Methods

Subjects

Fifteen native German speakers (mean age 24.4; range 20–29; 7 male) participated in this study. After explanations about risk of the research, the subjects gave written informed consent to the study. All subjects were right-handed and had no history of neurological, psychological or hearing impairment.

Stimuli

To study individual temporal processing abilities, I utilized a between-channel gap detection task (Phillips *et al.*, 1997; Zaehle *et al.*, 2004). Generally, a gap detection task (GDT) is the most common method used to measure auditory temporal resolution. Two different GDT approaches exist, a traditional paradigm with temporal operation executed in a discontinuity detection within one perceptual or neural channel caused by one stimulus frequency (within-channel paradigm). On the contrary, there is a paradigm presenting stimuli with a gap between markers (leading and trailing element) with different frequency content, which requires different perceptual channels (between-channel paradigm). Performing a between-channel GDT imperatively requires a relative timing of the offset of activity evoked by the leading element and the onset of activity mediating the trailing element (Phillips et al., 1997, 1998). The auditory stimuli were generated with a sampling depth of 16 bits and a sampling rate of 44.1 kHz using the SoundForge 4.5. Software (Sonic Foundry Inc., www.sonicfoundry.com). The leading element was wideband noise burst with a length of 7 ms. The trailing element was a band-passed noise centered on 1000 Hz and a width of 500 Hz with a length of 300 ms. Figure 5A illustrates spectrogram and waveform of a Gap stimulus. I determined the individual gap detection threshold as an adaptive measurement of temporal resolution abilities by using an up/down staircase procedure. The listener was presented with two streams of sounds, one of which had a brief silent period (‘gap’). The listener’s task was to identify this signal and the shortest detectable gap (‘gap threshold’) is determined. The first detectable stimulus was presented with the initial gap of 100 ms and were than adjusted stepwise by an up/down staircase: if the gap was identified correctly, the gap in the next trail was decreased; if the gap was identified incorrectly, the gap in the next trial was increased. The trails were terminated following 10 reversals and the gap detection threshold was computed by the arithmetic mean of the last four reversals (Treutwein, 1995). All sessions were performed in an acoustically and electromagnetic shielded room. GDT was applied by a Notebook (Samsung RC730, with Intel (R) Core i7 2.2 GHz processor) connected with headphones (Sennheiser, HD 65TV) and with a sound pressure level of 80 dB.

tDCS procedure

All participants received on three different days one session of either sham (S), anodal stimulation over the left (tDCS_left) or right (tDCS_right) AC in a randomized order. TDCS was applied by a battery driven constant current stimulator (ELDITH, NeuroConn GmbH, Ilmenau, Germany) using two rubber electrodes placed in 0.9% saline-soaked synthetic sponges. The 5 x 5-cm stimulation electrode was placed over T7/T8 according to the 10–20 system for EEG electrode placement, the 5 x 10 cm reference electrode was placed contralateral to the stimulation over C4/C3. The active electrode placement has been shown to modulate AC reactivity (Zaehle et al., 2011). The reference position was chosen to minimize tDCS effects in the contralateral auditory area. Figure 5B illustrates electrode positioning and modeled current density for the left anodal stimulation.

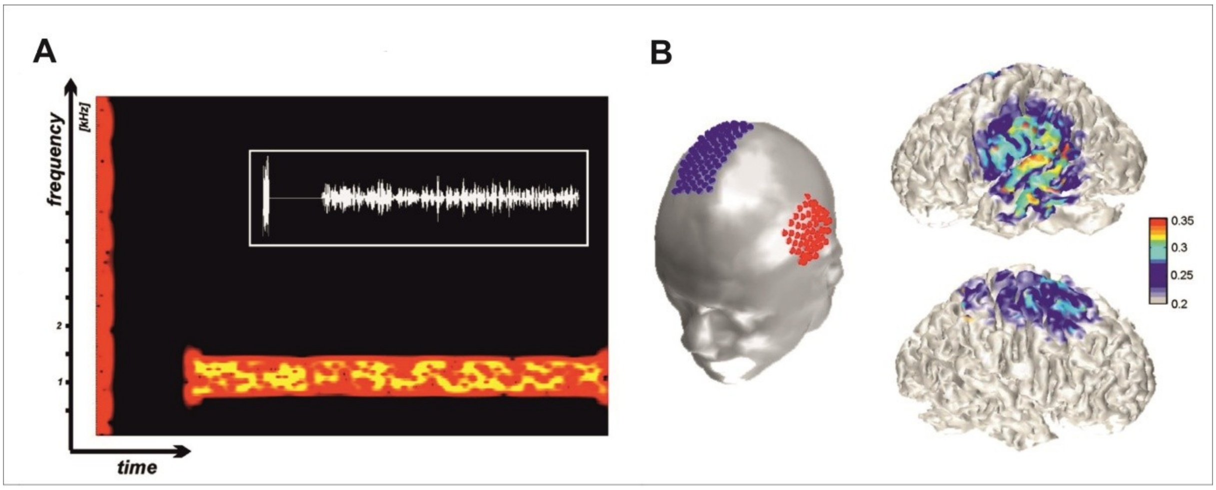

Figure 5: Auditory stimuli and tDCS application. (A) Shows exemplary spectrogram and waveform of a gap-stimulus. (B) Illustrates electrode positioning and modeled current density for the left anodal stimulation.

The direct current was applied with a strength of 1.5 mA with a 10-s fade in/out. After 10 min stimulation, the GDT started, while the stimulation continued. For sham condition the stimulation stopped after 15 s with a 5-s fade out. This procedure ensured that in the sham and stimulation conditions, participants experienced the initial itching that recedes over the first seconds of tDCS. Accordingly, none of the participants were able to determine whether or not they received active or sham stimulation. Prior to every session the participants had 1 min for practicing the GDT by the help of the study coordinator.

Statistical analysis

Statistical analysis of gap detection thresholds was performed by SPSS software (Version 21.0). Individual gap-detection thresholds were entered into a repeated measures ANOVA (analysis of variance) with the within subject factor stimulation (S, tDCS_left, tDCS_right). For post hoc analysis paired samples t-tests were performed. Normal distribution was tested by Kolmogorov–Smirnov-Test (sham: p = 0.71, anodal left: p= 0.99, anodal right: p = 0.99).

2.3 Results

Mean and SEM of gap detection threshold separately for three stimulation conditions are shown in Figure 6. Repeated measures ANOVA reveals significant main effect of the factor stimulation (F(1.2, 17.1) = 4.863; p = 0.035). Post hoc t-tests revealed increased gap detection threshold after left-sided anodal tDCS in contrast to sham tDCS (t(14) = -2.323; p = 0.036) and right-sided anodal tDCS (t(14) = -2.171; p = 0.048), whereas gap detection thresholds after right-sided anodal tDCS did not differ from individual thresholds after sham (t(14) = -1.850; p = 0.086).

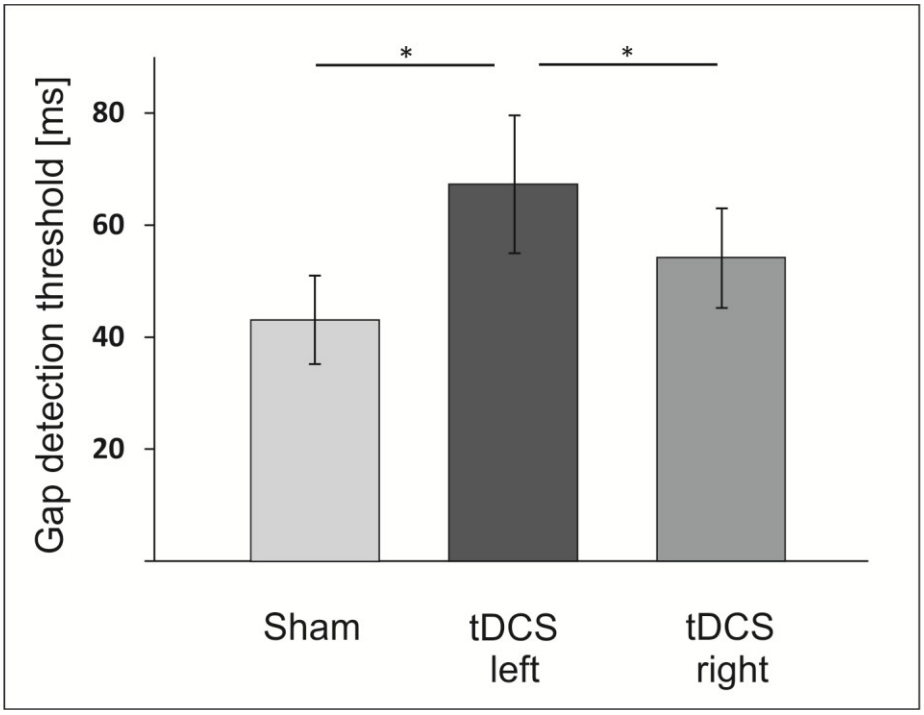

Figure 6: Performance data. Individual gap detection thresholds (mean ± SEM) separately for sham, anodal tDCS over the left AC (tDCS_left), and anodal tDCS over the right AC (tDCS_right).

2.4 Discussion

In the present study, I examined the functional lateralization of the AC for the perception of rapidly changing acoustic cues in a causal way utilizing tDCS. The results show that neuromodulation of the left, but not right, AC induced altered individual gap detection thresholds. These data suggest predominance of the left AC for processing rapid temporal acoustic information in non-speech sounds. The results are in good agreement with previous studies showing correlative associations between the left AC/hemisphere and advanced processing for rapidly changing acoustic stimuli (Jancke *et al.*, 2001; Zaehle *et al.*, 2004; Zaehle *et al.*, 2008; Okamoto *et al.*, 2009; Warrier *et al.*, 2009). This functional lateralization can be dedicated to structural differences between the left and right temporal lobes. Post mortem and brain imaging studies exhibit increased white matter extension in HG, PT and STG causing larger cortical volume and surface area on the left compared to the right hemisphere (Buxhoeveden & Casanova, 2000; Harasty *et al.*, 2003; Warrier *et* *al.*, 2009; Meyer *et al.*, 2013). Further fMRI studies showed greater gray and white-matter volume on the left compared to the right hemisphere caused by greater myelination (Sigalovsky *et al.*, 2006; Takao *et al.*, 2011). On cellular level, the left AC contains increased number and size of layer-III pyramidal cells (Hutsler & Gazzaniga, 1996; Hutsler, 2003). It has been hypothesized that this morphological leftward asymmetry leads to differences in functional rapid auditory processing due to greater myelination, which allows faster conductivity and thereby enhanced sensitivity to rapidly changing acoustic information (Zatorre and Belin, 2001). Neuropsychological studies support this assumption: patients with lesions of the left temporal lobe have deficits in auditory processing of temporal information, whereas right-lesioned patients are impaired to perceive spectral information (Robin *et al.*, 1990; Tallal *et al.*, 1993; von Steinbuchel *et al.*, 1999). With the advent of modern neuromodulation techniques, such as tDCS, new approaches have been performed to investigate auditory functionality. By applying unilateral auditory tDCS on spectro-temporal processing, Tang and Hammond (2013) demonstrated that anodal tDCS over the right AC causes diminished frequency discrimination. Furthermore, it has been demonstrated that simultaneous anodal stimulation of the bilateral AC improves up to 22.5%, whereas cathodal stimulation decreased 54.5% participants' performance in a random GDT (Ladeira et al., 2011). However, these alleged contrary results of an observed deterioration in the present study on one hand and an elevation of temporal resolution after anodal tDCS on the other hand might be based on fundamental difference in GDT paradigm applied. In contrast to the between-channel paradigm used in the present study, Ladeira et al. (2011) applied a within-channel paradigm to measure temporal resolution abilities. In this within channel paradigm the listener is presented with two streams of otherwise homogeneous sound, one of which contains a silent period (gap) at its temporal midpoint (signal); the other (standard) does not and the task of the listener is to specify which interval contained the gap. Such task requires a discontinuity detection within one perceptual channel. In contrast, in a between-channel paradigm the sounds (markers) bounding the gap are spectrally different from each other. There is thus a discontinuity in both the signal and the standard, but only the signal contains a nonzero duration silent period (Phillips *et al.*, 1997; Phillips *et al.*, 2010). Individual thresholds in a between-channel paradigm are often an order of magnitude higher and likely reflect a relative timing of the offset of activity aroused by the leading marker and the onset of activity aroused by the trailing marker (Phillips *et al.*, 1997; Grose *et al.*, 2001; Carmichael *et al.*, 2008). Moreover, such between channel gap thresholds, but not thresholds of a within channel paradigm, are highly correlated with VOT phonetic boundaries (Phillips *et al.*, 1997; Phillips & Smith, 2004), recruit overlapping neural network (Zaehle *et al.*, 2004) and, consequently, are correlated with phonological reading in normally developing children (Walker *et al.*, 2006). Based on this it has been suggested that only a between-channel paradigm allows a unique probe into temporal auditory processing (Phillips et al., 2010). Besides these divergent paradigms, Ladeira and colleagues stimulated both auditory cortices simultaneously, not allowing a systematic investigation of functional lateralization. Remarkably, in the present study anodal tDCS caused a reduction of the temporal resolution abilities. Thus the tDCS-related increased cortical excitation of the left AC resulted in a deteriorated auditory performance. Given an optimal and unaffected level of these auditory processes in the sample of young healthy subjects, this observation might be related to an inverted U-shaped dose-response relationship between AC reactivity and auditory perception. Such inverted U-shaped relationship has been reported for the relation of the dose of a pharmacological treatment and altered cognitive functions (Goldman-Rakic *et al.*, 2000; Cools *et al.*, 2001). Although the influence of tDCS on auditory activity state is possibly a multifactorial phenomenon, the arousal level crucially interacts with cognitive processes and influences the effectiveness at a given dosage. The performance will improve as arousal increases until it reaches a point where optimum performance is achieved, and arousal is at its optimum level. If arousal increases beyond this point, e.g. due to external electric stimulation, performance will begin to deteriorate. This hypothesis implies that enhanced excitability does not increase performance per se. Monte-Silva et al. (2009) demonstrated dose-dependent impairment by a dopamine D2-like agonist on anodal tDCS-induced motor-cortex excitability. The findings revealed an inverted U-shaped curve with enhanced activity by anodal tDCS at an optimal dose of D2-like agonists, whereas lower and higher doses resulted in less activity (Monte-Silva *et al.*, 2009; Krause *et al.*, 2013b). Following this, one might further speculate that in deficient auditory processing associated with hypofunctioning of the auditory-related cortex (Gaab *et al.*, 2007; Chobert *et al.*, 2012; Raschle *et al.*, 2013), an enhancement of left AC reactivity will result in an improvement of such perceptual processes. Thus the findings also might have clinical implications by fostering potential approaches for a treatment of speech-related pathologies such as dyslexia. Dyslectic children as well as adults exhibit deficits in the processing of rapid auditory information accompanied with deficient phonological processing (Gaab et al., 2007; Chobert et al., 2012; Raschle et al., 2013). The data demonstrate the neuromodulatory effect of auditory tDCS on rapid temporal processes involved in stop-consonant discrimination and thus provides a possible method for the treatment of dyslexia. However, specific clinical efficacy of tDCS has to be proven by further studies consulting brain imaging and behavioral data.

3. Experiment 2

Pre-attentive spectro-temporal feature processing during HD-tDCS

Specific aim:

I want to investigate the functional lateralization of the AC for pre-attentive spectro-temporal feature processing without any task or attentional demands by high-definition (HD)-tDCS.

The content of this chapter has been published as: Heimrath, K., Breitling, C., Krauel, K., Heinze, H.J., and Zaehle, T. (2015). Modulation of pre-attentive spectro-temporal feature processing in the human auditory system by HD-tDCS. Eur J Neurosci 41, 1580-1586. doi: 10.1111/ejn.12908.

Abstract

The present study examined the functional lateralization of the human AC for pre-attentive spectro-temporal feature processing. By using High-definition (HD)-tDCS) I systematically modulated neural activity of the bilateral AC. I assessed the influence of anodal and cathodal HD-tDCS delivered over the left or right AC on auditory mismatch negativity (MMN) in response to temporal as well as spectral deviants in 12 healthy subjects. The results showed that MMN to temporal deviants was significantly enhanced by anodal HD-tDCS applied over the left AC only. The data indicate a left hemispheric dominance for the pre-attentive processing of low-level temporal information.

3.1 Introduction

The human auditory system has been traditionally described as functionally lateralized for the processing of separate features in the acoustic signal. Classical neurobiological frameworks of auditory cognition propose a ‘‘division of labor’’ between the left and right auditory-related cortices, encompassing a relative trade-off in spectral and temporal processing of complex acoustic signals such as speech and music. Left auditory cortical areas are highly tuned for temporal processing and right auditory cortical areas are more amenable to spectral processing (Zatorre & Belin, 2001; Zatorre *et al.*, 2002; Poeppel, 2003b). This lateralized spectro-temporal processing within the AC has been proven by several studies (Schonwiesner *et al.*, 2005; Sandmann *et al.*, 2007; Zaehle *et al.*, 2007; Obleser *et al.*, 2008; Okamoto *et al.*, 2009), while other studies provide contradicting results showing no or reversed auditory lateralization (Harrington *et al.*, 2004; Reiterer *et al.*, 2005; Meyer, 2008; Zatorre & Gandour, 2008; Scott & McGettigan, 2013). Task demands and task dependent attention can systematically cause these outcome variations. Contradicting results have been shown, e.g. for active vs. passive task demands and attention to the left vs. right ear. (Bryden *et al.*, 1983; Woldorff *et al.*, 1993; Poeppel *et al.*, 1996). It has been argued that attention related modulations are based on the gain of neural activity elicited by the attended sound. If the task only requires divided attention or passive listening, these effects are less robust or even not present. To address this issue, asymmetric involvement of the AC in low-level acoustic perception without attentional demands can be assessed by recording the mismatch negativity (MMN), a pre-attentive measure of event related potentials (ERP) (Kujala *et al.*, 2007). MMN occurs as a negative component that can be elicited by infrequently deviant tones in a sequence of frequently occurring standard tones.

Besides the possible modulating influences of task-demands and attention, in most studies on auditory spectro-temporal asymmetry, conclusions are drawn on correlational inferences. However, such statistical relationship between a set of variables, in principle, does not allow for a direct causal inference of the functional outcome and the underlying neural representation. The advent of tDCS opens new strategies for investigating causal relations between cortical reactivity and function (Filmer *et al.*, 2014). By applying low currents through the skull to the brain, tDCS directly modulates cortical excitability (Bindman *et al.*, 1962; Nitsche *et al.*, 2008). In classical tDCS applications, relative large electrode pads were used that spatially imprecise stimulate rather broad cortical areas. To improve the spatial preciseness, high-definition (HD)-tDCS has been introduced recently (Datta *et al.*, 2009).

Here, I examined functional lateralization of the AC for pre-attentive spectro-temporal feature processing. By systematically modulating the neural reactivity of either the left or right AC, I assessed asymmetric processing of the auditory system in a causal way. Based on the evidence mentioned above, I hypothesized that HD-tDCS modulation of the left AC will alter MMN response to temporal deviants, whereas HD-tDCS over the right AC will influence MMN response to spectral deviants.

3.2 Methods

Subjects

12 subjects (mean age 25.9; range 22 - 32; 7 male) participated in this study. Participants gave written informed consent in accordance with the 2013 World Medical Association Declaration of Helsinki. All subjects were native German speakers and had no history of neurological, psychological or hearing impairment.

Stimuli

The auditory stimuli were generated (sampling depth of 32 bits and a sampling rate of 44.1 kHz) using Praat (Version 5.3.63). The set of stimuli comprised one standard tone with a duration of 75 ms and a frequency of 1000 Hz, two temporal deviants (25 ms/1000 Hz, 125 ms/1000 Hz) and two spectral deviants (75 ms/1100 Hz, 75 ms/900 Hz) (cf. Figure 7). Linear rise-fall times were 5 ms and the stimuli were presented binaurally via headphones (Sennheiser, HD 65TV) with a sound pressure level of 80dB.

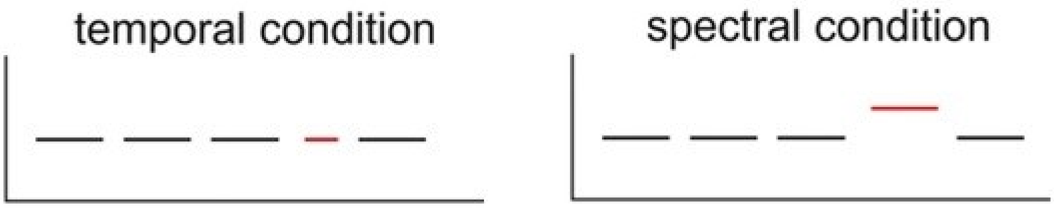

Figure 7: Auditory stimuli. Exemplary temporal and spectral deviant tones (red line) compared to standard tone (black line).

tDCS

To increase spatial specificity of the applied electrical currents “HD-tDCS” has been introduced (Datta *et al.*, 2009; Kuo *et al.*, 2013). Conventional tDCS procedures most commonly used large electrode pads (25 cm^2-35 cm^2), which stimulate relatively broad areas between the active and reference electrode. While a part of this current is shunted through the scalp, the rest is delivered to the brain tissue inducing rather diffuse changes in cortical excitability (Miranda *et al.*, 2006). A 4x1 ring configuration (HD-tDCS) with a center electrode overlying the targeted brain area surrounded by four reference electrodes enables a more restricted cortical neuromodulation (Kuo *et al.*, 2013) and leads to higher electric fields in comparison to electrode pads (Datta *et al.*, 2012). Furthermore, HD-tDCS over auditory cortical areas directly allows for parallel MMN recording at central electrodes (cf. Figure 8A). Thus, in the present study by applying HD-tDCS, electrophysiological recordings could be acquired directly during stimulation without relying on transient after-effects. Each participant performed five sessions: (i) sham, (ii) anodal HD-tDCS over the left AC (aHD-tDCS_left), (iii) anodal HD-tDCS over the right AC (aHD-tDCS_right), (iv) cathodal HD-tDCS over the left AC (cHD-tDCS_left) and (v) cathodal HD-tDCS over the right AC (cHD-tDCS_right). All sessions were separated by at least 24 hours. Session order for sessions i-iii was counterbalanced across participants; sessions iii and iv were acquired 6-8 months after the initial session, in a counterbalanced order. The current strength was 0.5 mA for 21 min, with a linear fade in/fade out time of 10 s. The central active electrode was placed over the AC (C5/C6) and surrounded by 4 reference electrodes (FC5/FC6, C3/C4, CP5/CP6, T7/T8) according to the international 10-10 system. The active electrode placement was chosen to affect the temporal cortex, which has shown to be responsible for MMN generation to temporal and spectral modulated deviants (Molholm *et al.*, 2005; Grimm *et al.*, 2006; Naatanen *et al.*, 2007). The stimulation electrodes were sintered Ag/AgCl ring electrodes (outer radius: 12 mm, inner radius: 6 mm). The ring electrodes were fixed on an EEG cap and were filled with EEG electrolyte gel (Easy Cap, Abralyt 2000) to ensure conductivity to the skull. For the sham condition, the stimulation was turned off after 30 s with linear fade out time of 10 s to the unawareness of the participants. This procedure ensured that in the sham and stimulation conditions, participants experienced the initial itching that recedes over the first seconds of HD-tDCS. After session iii, participants were asked to indicate in which of the sessions they felt an active tDCS. Out of the 12 subjects, only one identified the correct order of active and sham tDCS.

Procedure

To asses an asymmetric involvement of the AC in low-level acoustic perception without attentional demands I recorded the mismatch negativity (MMN), a pre-attentive measure of event related potentials (ERP) (Kujala *et al.*, 2007). MMN occurs as a negative component that can be elicited by infrequently deviant tones in a sequence of frequently occurring standard tones. Here, the central auditory system forms a representation of repetitive aspects of stimulation, and in cases where the representation is violated by a physical different feature of a rare stimulus a MMN is elicited (Kujala *et al.*, 2007; Naatanen *et al.*, 2007). MMNs are independent of attentive control and can be obtained even when ignoring the stimuli while performing unrelated tasks (Garrido *et al.*, 2009b), during sleep (Campbell & Colrain, 2002; Ruby *et al.*, 2008; Sculthorpe *et al.*, 2009) or without consciousness (Fischer *et al.*, 2004; Naccache *et al.*, 2005; Fischer *et al.*, 2006; Tzovara *et al.*, 2013). Traditionally, the MMN has been assumed to originate bilaterally in the supratemporal cortices, and AC (Naatanen *et al.*, 2007; Naatanen *et al.*, 2011). Importantly, auditory MMN can be used to investigate function and acoustic dependent brain asymmetry (Todd *et al.*, 2011; Gu *et al.*, 2013; Musacchia *et al.*, 2013).

In the present study, the participants performed an auditory MMN paradigm (Naatanen *et al.*, 2007) with spectral and temporal deviants. After 10 min of consecutive HD-tDC-stimulation, the MMN paradigm started, while the HD-tDC-stimulation continued. MMN block consisted of 940 stimuli starting with 8 initial standard tones. Four different deviants occurred in 30% of the trials, accordingly 7.5% for each specific deviant. The stimuli were pseudo randomized within the block with at least two standard stimuli occurring between two deviants. The duration of the MMN block was 11 min and stimuli were presented with a stimulus onset interval of 750 ms.

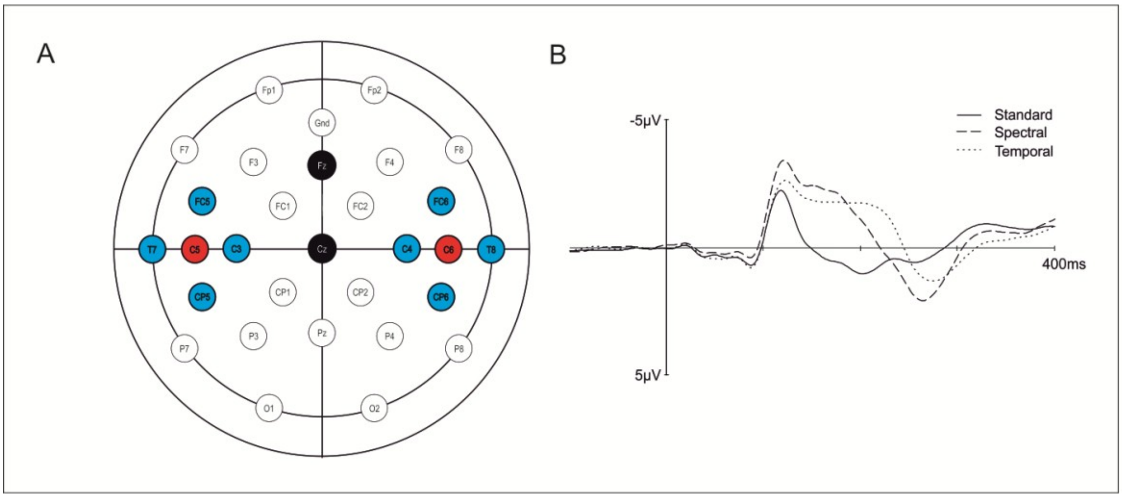

Figure 8: (A) Experimental setup for simultaneous HD-tDCS and EEG. Placement of HD-tDCS ring electrodes over left and right AC in a 4×1 configuration. The active electrode (red) is surrounded by four reference electrodes (blue). EEG was measured at location Fz and Cz (black). (B) AEPs group averages across each stimulation session at electrode site Fz for standard tones, spectral and temporal deviant tones separately.

EEG recordings

EEG was recorded in parallel to HD-tDCS from the standard scalp locations Fz and Cz, according to the international 10-10 system, using Ag/AgCl electrodes mounted in an elastic cap. The electrooculogram was recorded with one electrode placed below and approximately 1 cm to the external canthus of the left eye. EEG data were recorded by a Brainamp DC amplifier (Brainproducts) and the corresponding software (Brainproducts, Brain Vision Recorder 1.20). Data were referenced to the linked mastoids and sampled at 500 Hz. Impedances were kept below 5 kΩ.

Data analysis

EEG preprocessing and data analysis were carried out using EEGlab V.12 (http://sccn.ucsd.edu/eeglab/). EEG data were off-line filtered from 0,01 Hz to 40 Hz. Segments containing ocular artifacts, movement artifacts, or amplifier . saturation were excluded from the averaged ERP waveforms. EEG recordings were sectioned into 600 ms epochs (200 ms pre-stimulus and 400 ms poststimulus) and a baseline correction using the pre-stimulus portion of the signal was carried out. ERPs for each stimulus category were averaged for each subject and grand-averaged across subjects. MMN waves were individually calculated by subtracting the ERP to standard stimuli from that of deviant stimuli. In accordance with reported MMN magnitude at fronto-central sites (Naatanen *et al.*, 2007) larger amplitudes across grand-averages waves were found at Fz and thus I restricted the analysis to this EEG position. For each condition I measured the peak amplitude from a 40 ms window centered at the individual MMN latency of each subject (Gu *et al.*, 2013). MMN peak latency for each condition was obtained by the most negative peak in the latency window from 130-230 ms after the onset of the stimulus. To analyze the effects of active HD-tDCS on hemispheres, I calculated a 2x2x2 repeated measures ANOVA with the factor *stimulation* (anodal, cathodal), *hemisphere* (tDCS_left, tDCS_right) and *deviant* (temporal, spectral). Subsequently, to compare active and sham stimulation two repeated measures 3x2 ANOVAs with the factor *stimulation* (sham, tDCS_left, tDCS_right) and *deviant* (temporal, spectral) were calculated separate for anodal and cathodal tDCS. To further explore significant main effects and interactions I compared the MMN amplitudes by performing *t*-tests (one-tailed, Bonferroni-Holm corrected).

3.3 Results

Figure 8B shows the averaged AEPs to standard and deviant tones for the temporal and spectral conditions averaged across all tDCS sessions at electrode site Fz. As shown in Figure 9, temporal and spectral deviants elicited considerable MMN responses between 100–250 ms after the onset of auditory stimuli during anodal (A) and cathodal (B) tDCS.

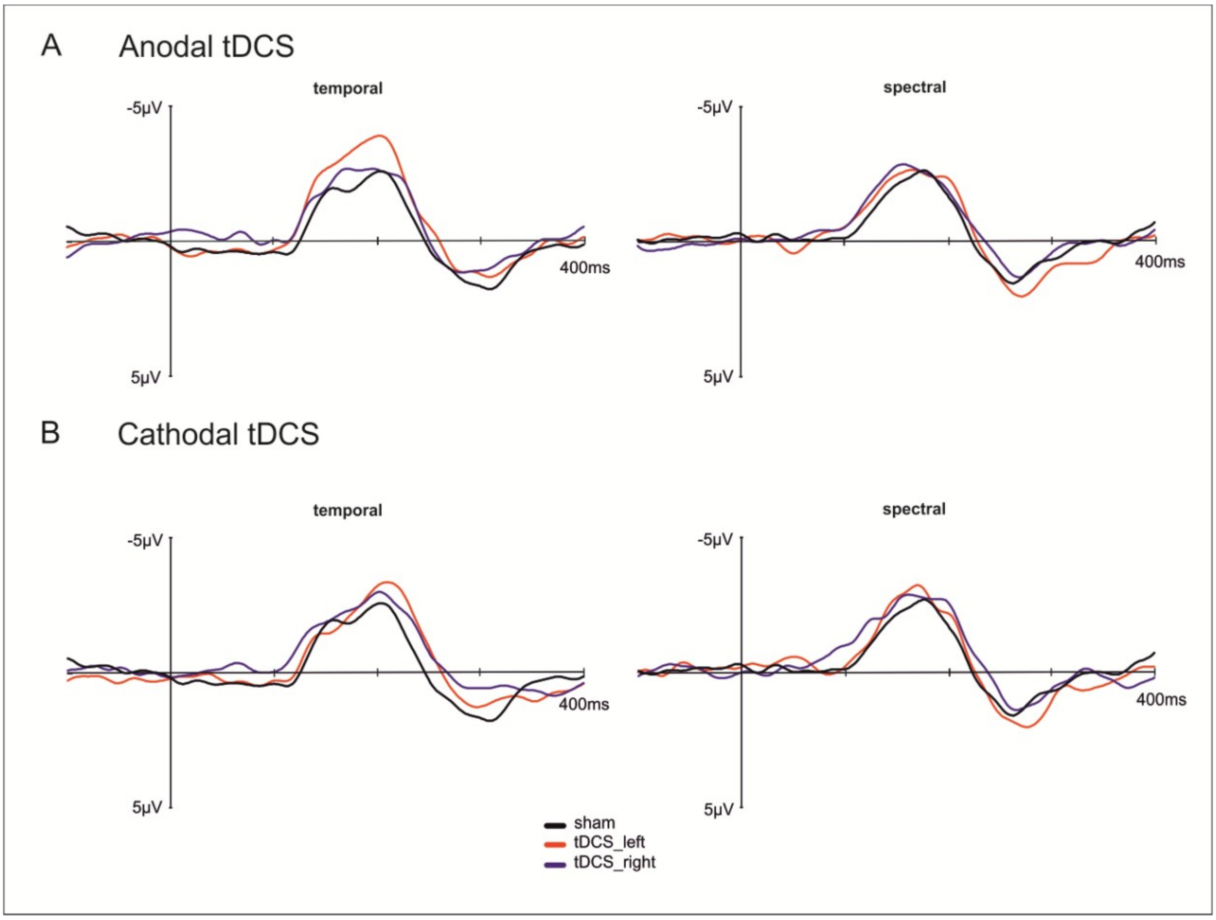

Figure 9: Auditory mismatch negativity (MMN) results. MMN in response to temporal and spectral deviant tones at electrode site Fz during anodal transcranial direct current stimulation (tDCS; A), cathodal tDCS (B) over the left (red) and right auditory cortex (AC; blue) in comparison to sham tDCS (black).

Figure 10 illustrates the mean MMN amplitudes separately for temporal (top) and spectral (bottom) deviants during sham, and active tDCS at electrode Fz. The 2x2x2 repeated measures ANOVA revealed no significant main effects of the factors *stimulation* [F(1,11) = 0.006, p = 0.94], *hemisphere* [F(1,11) = 1.557, p = 0.21], *deviant* [F(1,11) = 0.581, p = 0.46], nor for the *stimulation x hemisphere* [F(1,11) = 0.402, p = 0.54], *stimulation x deviant* [F(1,11) = 0.335, p = 0.57] and *hemisphere x deviant* interaction [F(1,11) = 2.446, p = 0.15], but a significant interaction between *stimulation x hemisphere x deviant* [F(1,11) = 4.474, p = 0.05]. For anodal tDCS the 3x2 repeated measures ANOVA with the factors *stimulation* (sham, tDCS_left, tDCS_right) and *deviants* (temporal, spectral) revealed no significant main effect of the factors *stimulation* [F(2,22) = 2.151, p = 0.14], and *deviant* [F(1,11) = 0.378, p = 0.55] but a significant *stimulation* x *deviant* interaction [F(2,22) = 3.470, p = 0.05]. For cathodal tDCS a 3x2 repeated measures ANOVA revealed neither a significant main effect of the factors *stimulation* [F(2,22) = 0.324, p = 0.73] and *deviant* [F(2,22) = 0.001, p = 0.99] nor an interaction of *stimulation x deviant* [F(2,22) = 0.198, p = 0.82]. Separate post hoc t-statistics of the MMN amplitudes in the temporal condition demonstrated increased amplitudes during left anodal tDCS compared to right anodal tDCS (t(11) = -3.254; p = 0.02) and sham stimulation (t(11) = 2.486; p = 0.03). MMN amplitude during right anodal tDCS did not differ from MMN amplitudes during sham stimulation (t(11) = -0.034; p = 0.49). In the spectral condition, post-hoc *t-tests* showed no significant increment of MMN amplitude by left anodal tDCS compared to right anodal tDCS (t(11) = 0.482; p = 0.64) and to sham stimulation (t(11) = -0.061; p = 0.48). Right anodal tDCS compared to sham showed no significant difference (t(11) = 0.537, p = 0.9). In summary, MMN amplitudes in response to temporal deviants were increased by anodal tDCS over the left but not right AC. Furthermore, neither anodal tDCS over the left nor the right AC altered MMN amplitudes to spectral deviants. Cathodal tDCS over the left and right AC had no effect on MMN amplitude to neither spectral nor temporal deviants. The results of the 2x2x2 repeated measure ANOVA on MMN peak latencies reveal no main effect of *stimulation* [F(1,11) = 0.221, p = 0.65], *hemisphere* [F(1,11) = 1.716, p = 0.22], but a significant main effect of *deviant* [F(1,11) = 9.908, p = 0.01] due to longer peak latencies for temporal as for spectral deviants. I found no interaction for *stimulation x hemisphere* [F(1,11) = 0.797, p = 0.39], *stimulation x deviant* [F(1,11) = 0.001, p = 0.99], *hemisphere x deviant* [F(1,11) = 0.320, p = 0.58] and *stimulation x hemisphere x deviant* [F(1,11) = 0.024, p = 0.88].

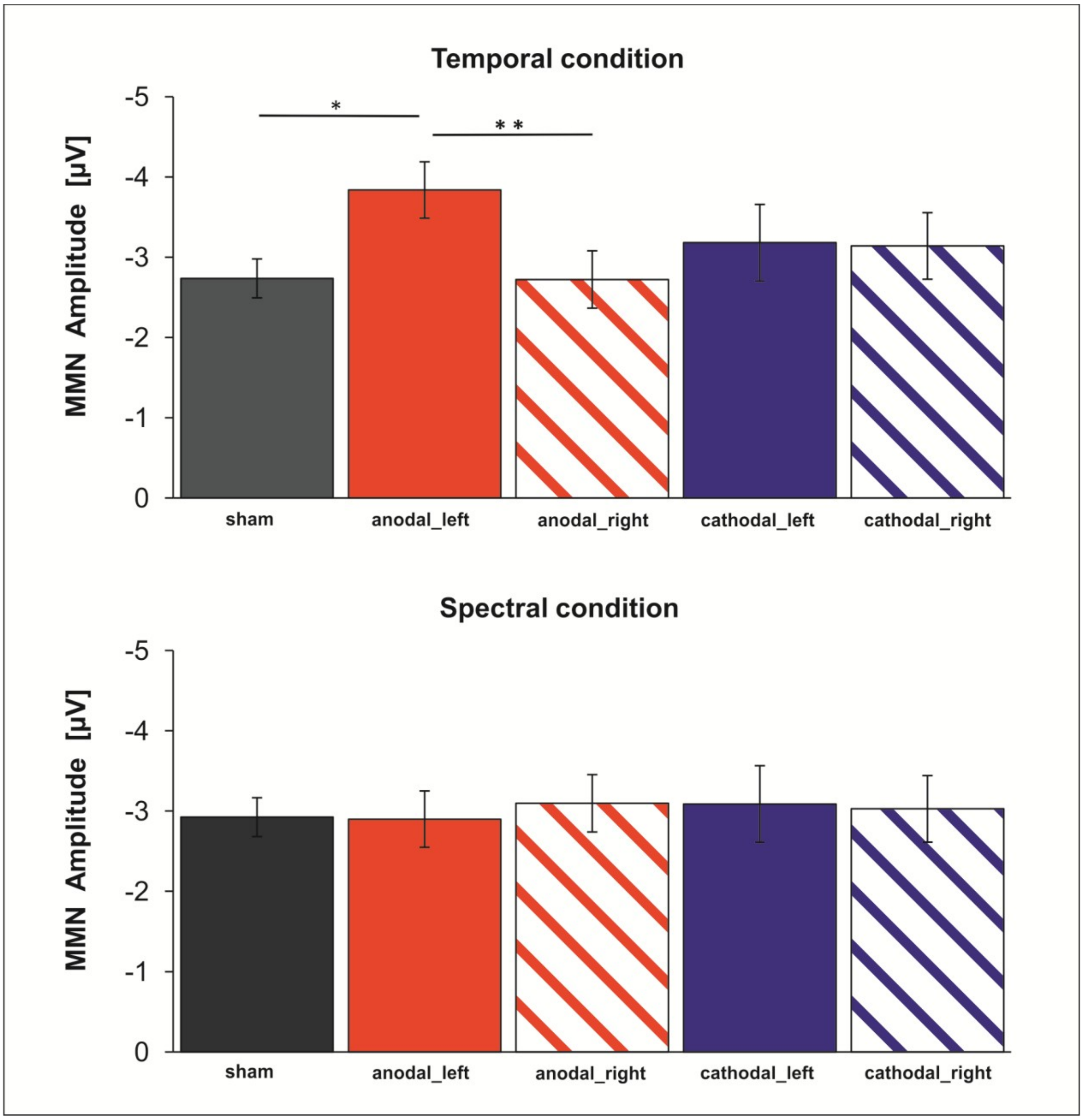

Figure 10: Mismatch negativity (MMN) amplitudes separately for temporal and spectral deviant tones during sham, anodal_left, anodal_right, cathodal_left and cathodal_right at electrode site Fz (mean ± SEM).

3.4 Discussion

In the present study, I examined the functional lateralization of the AC for pre-attentive spectro-temporal feature processing. By systematically modulating the neural activity of the AC, I showed that MMN amplitudes in response to temporal, but not spectral deviant tones were increased by anodal tDCS applied over the left AC only. This finding supports the assumption that depending on the acoustic properties of the signal, the two cerebral hemispheres are differentially engaged in the pre-attentive processing of change detection and provides further evidence for the feature-specific structure of hemispheric asymmetry in auditory processing.

The results of a specific involvement of the left AC in the processing of temporal acoustic characteristics are in good agreement with former neurophysiological studies (Jancke *et al.*, 2001; Zatorre & Belin, 2001; Giraud *et al.*, 2005; Gaab *et al.*, 2007; Zaehle *et al.*, 2008; Okamoto *et al.*, 2009; Warrier *et al.*, 2009). Moreover, by directly modulating the reactivity of the underlying neural cortex, I provide direct causal evidence for a relationship between the activity of the left AC and its functional specification. It has been assumed that this left hemisphere sensitivity for rapidly changing acoustic cues is the basis of the well documented hemispheric specialization for speech perception (Schwartz & Tallal, 1980) and has been shown to be deficient in phonological disorders (Tallal & Newcombe, 1978; Schwartz & Tallal, 1980). Left-lateralized brain response to rapidly changing acoustic information has been even shown in early developmental stage in 4-month infants (Musacchia *et al.*, 2013). The functional leftward asymmetry for the temporal analysis has been dedicated to structural differences between the left and right temporal lobe (Buxhoeveden & Casanova, 2000; Harasty *et al.*, 2003; Warrier *et al.*, 2009; Meyer *et al.*, 2013) with greater gray and white-matter volume on the left compared to the right hemisphere (Sigalovsky *et al.*, 2006; Takao *et al.*, 2011). Accordingly, this morphological asymmetry leads to functional differences of spectro-temporal resolution due to greater myelination, which allows for faster conductivity and thereby enhanced sensitivity to rapidly changing acoustic information (Penhune *et al.*, 1996; Anderson *et al.*, 1999; Klingberg *et al.*, 2000; Zatorre & Belin, 2001). In experiment 1, utilizing conventional tDCS, I already demonstrated left hemispheric dominance for the processing of rapid temporal cues in a causal way and showed that neuromodulation of the left, but not right, AC induced altered individual gap detection thresholds. In the present study, I extended this approach by using EEG and avoiding effects of attention or task demands. Furthermore, HD-tDCS was used to target the AC. In contrast to conventional tDCS protocols, HD-tDCS enables neuromodulation of specific cortical areas and thus enhances induced plasticity

(Miranda *et al.*, 2006; Datta *et al.*, 2012; Kuo *et al.*, 2013) and prevents potential effects of the tDCS reference electrode. Furthermore, the 4 x 1 configuration allows the parallel assessment of EEG during the tDCS application.

The demonstration of a predominance of the left hemisphere for the processing of temporal information in the auditory system is in line with the proposed "division of labour" accounts (Zatorre & Belin, 2001; Poeppel, 2003b). However, while these models suggest a relative trade-off between the two hemispheres for temporal and spectral analysis, the present study did not observe a modulatory effect of either the left or right AC reactivity modulations on the MMN amplitudes to spectral deviants. Lateralized spectro-temporal processing within the AC has been proven by several imaging studies (Schonwiesner *et al.*, 2005; Sandmann *et al.*, 2007; Zaehle *et al.*, 2007; Obleser *et al.*, 2008; Okamoto *et al.*, 2009). However, even though several investigations demonstrated a right sided dominance for spectral processing within the auditory domain (Grimm *et al.*, 2006; Zaehle *et al.*, 2009; Okamoto & Kakigi, 2013; Cha *et al.*, 2014), also bilateral contributions of the STG/STS during spectral analysis have been evidenced (Zatorre & Belin, 2001; Jamison *et al.*, 2006; Zaehle *et al.*, 2008). Analogously, for the pre-attentional processing of spectro-temporal acoustic features, several studies reported lateralized MMN responses with enhanced MMN amplitude to temporal modulated sounds in the left- and enhanced MMN amplitude to spectral modulated sounds in the right hemisphere (Todd *et al.*, 2011; Okamoto & Kakigi, 2013). Moreover, MMN generators have been located within the left hemisphere for the processing of temporal acoustic properties and the right hemisphere for the processing of spectral characteristics (Molholm *et al.*, 2005; Zaehle *et al.*, 2009). Nevertheless, also absent or reversed spectro-temporal MMN asymmetries have been reported. Commonly, these variations have been attributed to fundamentally different stimulus material and task requirements (Uther *et al.*, 2003; Takegata *et al.*, 2004; Grimm *et al.*, 2006; Maess *et al.*, 2007; De Sanctis *et al.*, 2009; Sorokin *et al.*, 2010; Kuuluvainen *et al.*, 2014). Moreover, it has been assumed that hemispheric lateralization for spectral MMN response might be more depending on linguistic relevance and familiarity of the acoustic sound feature (Tervaniemi & Hugdahl, 2003; Zatorre & Gandour, 2008; Kujala & Naatanen, 2010). Accordingly, pre-attentive spectral auditory processing might be less lateralized in the auditory domain. Consequently, recent tDCS studies investigating lateralized auditory perception reported rather inconsistent results. Whereas Mathys et al. (2010) showed a decrement of pitch discrimination induced by cathodal tDCS over the left and right AC, anodal tDCS had no effect on task performance. In contrast, Tang and Hammond (2013) reported that anodal tDCS over the right AC causes diminished frequency discrimination by decreasing sensitivity to temporal fine structure, but did not affect spectral selectivity. Impey & Knott (2015) demonstarted that anodal tDCS over the left AC enhances MMN to spectral deviants only in individuals with low MMN baseline amplitudes. It can be assumed that different stimulation parameter such as stimulation power, electrode size, and electrode placement especially of the reference electrode, as well as the individual auditory stimuli contribute to these varying tDCS-effects. Finally, the auditory evoked MMN does not exclusively originate in temporal regions. The prefrontal cortex has been associated with generation of auditory evoked MMN as well (Doeller *et al.*, 2003; Deouell, 2007; Garrido *et al.*, 2009a; Garrido *et al.*, 2009b). Anodal tDCS over the right frontal cortex exclusively affects MMN to spectral deviants whereas neither anodal nor cathodal tDCS modulate MMN to temporal deviants (Chen *et al.*, 2013). Thus, specifically for spectral processing, varying stimulation locations over the temporo-frontal network seem to influence tDCS induced effects on the MMN measurement considerably.

To this date, the asymmetry of the auditory domain for low-level acoustic features is still controversially discussed (Scott & McGettigan, 2013). By directly modulating the reactivity of the underlying neural cortex, HD-tDCS can provide causal evidence for a relationship between the activity of the left and right auditory cortices and its functional specification. Thus studies using HD-tDCS might help to advance our understanding of hemispheric lateralization for low-level acoustic feature processing.

Conclusion

In the present study, I applied HD-tDCS over the AC to examine functional asymmetry of spectro-temporal feature processing. The results show that the pre-attentive processing of temporal but not spectral acoustic features is elevated after selectively enhancing the neural reactivity of the left AC only, providing a causal demonstration of the left-lateralized sensitivity to temporal features in the acoustic signal.

4. Experiment 3

Effect of bilateral tDCS on phonetic perception

Specific aim:

I want to assess the effects of bilateral tDCS over the temporal cortex on phonetic categorization of CV-syllables in a VOT continuum and on AEPs in response to voiced and voiceless CV-syllables.

The content of this chapter has been published as: Heimrath, K., Fischer, A., Heinze, H.J., and Zaehle, T. (2016). Changed categorical perception of consonant-vowel syllables induced by transcranial direct current stimulation (tDCS). BMC Neurosci 17, 8. doi: 10.1186/s12868-016-0241-3.

Abstract

Speech-related disorders may refer to impairment of temporal analysis in the human auditory system. By the advance of non-invasive brain stimulation new forms of therapy arise. In the present study, I examined the neuromodulatory effect of auditory tDCS on the perception of temporal modulated speech syllables. In three experimental sessions I assessed phonetic categorization of consonant–vowels (CV)-syllables (/da/,/ta/) with varying voice onset times (VOT) during bilateral sham, anodal, and cathodal tDCS delivered to the AC. Subsequently, I recorded AEPs in response to voiced (/ba/,/da/,/ga/) and voiceless (/pa/,/ta/,/ka/) CV-syllables. In result, I demonstrate that bilateral tDCS of the AC can modulate CV-syllable perception. Behaviorally, cathodal tDCS improved phonetic categorization abilities in a VOT continuum accompanied by an elevation of the P50 amplitude of the AEP to CV-syllables during the anodal tDCS after effect. The present study demonstrates the ability of bilateral tDCS over the AC to ameliorate speech perception. The results may have clinical implications by fostering potential approaches for a treatment of speech-related pathologies with a deficit of temporal processing.

4.1 Introduction

Speech perception requires the recognition and discrimination of phonemes, in particular the encoding of temporal information in short linguistic elements such as consonants and vowels. A main feature to categorize stop-consonants is the voice onset time (VOT), which is defined as the duration of the delay between release of closure and start of voicing. It characterizes voicing differences in a variety of languages and distinguishes voiced stop consonants (/b/, /d/, /g/) from their voiceless counterparts (/p/, /t/, /k/) (Lisker & Abramson, 1964). Discriminating voiced and unvoiced syllables in a consonant-vowel (CV)-VOT continuum is categorical by exhibiting two qualitatively discrete percepts. The neural activity of the auditory cortices during the processing of different VOT's in speech stimuli is reflected by the P50-N1 complex of the AEP (Sharma & Dorman, 1999; Sandmann *et al.*, 2007; Zaehle *et al.*, 2007; King *et al.*, 2008; Toscano *et al.*, 2010). Accordingly, the P50-N1 complex has been successfully shown to reflect neural representation of feature processing of the acoustic stimulus (Sharma *et al.*, 2000; Elangovan & Stuart, 2011). Speech related disorders have been associated with altered acoustic processing abilities. Children with general language-learning disabilities (Tallal & Piercy, 1973; Tallal & Stark, 1981) and children and adults with dyslexia (Tallal, 1980; Ben-Yehudah *et al.*, 2004) show an impaired auditory processing of temporal information during speech perception. Specifically, these patients demonstrated deficient phoneme perception abilities, reflected by inconsistent labeling of CV-syllables in a VOT continuum (Joanisse *et al.*, 2000; Breier *et al.*, 2001; Chiappe *et al.*, 2001; Bogliotti *et al.*, 2008). As a completion to conventional approaches that treat temporal processing deficits in dyslexics by perceptual training (Tallal *et al.*, 1996; Fricke *et al.*, 2013; Chobert *et al.*, 2014; Duff *et al.*, 2014), tDCS might be a promising therapeutic tool.

Given the neuromodulatory potential of tDCS to alter AC reactivity (Zaehle *et al.*, 2011) as well as spectro-temporal perception (Ladeira *et al.*, 2011; Impey & Knott, 2015), in the present study, I investigated the effects of tDCS over the bilateral temporal cortex on phonetic categorization of CV-syllables in a VOT continuum. I hypothesized tDCS-dependent alterations in the performance of a phonetic categorization task. Furthermore, I recorded and compared AEPs in response to voiced and voiceless CV-syllables after tDCS application and expect tDCS induced changes in the neural reactivity of the AC reflected by modulations of the P50-N1 complex.

4.2 Methods

Subjects

13 human subjects (mean age 25.92 ± 3.15; 7 male) participated in this study. Participants gave written informed consent in accordance with the 2013 World Medical Association Declaration of Helsinki. All subjects were native German speakers and had no history of neurological, psychological or hearing impairment. All procedures were approved by the ethics committee of the University of Magdeburg.

Stimuli

The auditory stimuli were generated (sampling depth of 32 bits and a sampling rate of 44.1 kHz) using Software SoundForge 4.5 (Sonic Foundry Inc., 1999) and Praat (Version 5.3.63). The duration of each single stimulus was 330ms. Stimulus presentation was controlled by the Presentation software (Neurobehavioral Systems, USA). The stimuli were presented binaurally via headphones (Sennheiser, HD 65TV) with a sound pressure level of 75dB.

tDCS

All participants received on three different days one session of either bilateral sham, anodal or cathodal stimulation over the AC in a randomized order. The sessions were separated by at least 48h to avoid carry over effects. TDCS was applied by a battery driven constant current stimulator (ELDITH, NeuroConn GmbH, Germany) using three rubber electrodes placed in 0.9% saline-soaked synthetic sponges. Two 5 x 5 cm stimulation electrodes were placed over T7 and T8 according to the 10-20 system for EEG electrode placement. A 5 x 10 cm reference electrode was placed longitudinally over electrode site Cz. The stimulation electrode placement has been shown to modulate low-level processing and cortical reactivity in the AC (Ladeira *et al.*, 2011; Zaehle *et al.*, 2011). The direct current was applied with a strength of 1.5

mA and 10 s fade in/out. For sham condition, the stimulation was turned off after 30s without the awareness of the participants with linear fade out time of 10 s. This procedure ensured that in the sham and stimulation conditions, participants experienced the initial itching that recedes over the first seconds of tDCS. Accordingly, none of the participants were able to reliably determine whether or not they received active or sham stimulation.

Procedure

To familiarize the participants with the task, prior to every session participants practiced the phonetic categorization. Then tDCS application was started. After 10 min of consecutive tDCS, a phonetic categorization task (CV-task I) started, while tDC-stimulation continued. For the CV-task, a synthetic VOT continuum was used ranging from 20 to 40 ms VOT in 1 ms steps (Zaehle *et al.*, 2007). Participants were instructed to listen to each syllable and to decide whether the syllable was the voiced syllable /da/ or the voiceless syllable /ta/ by pressing a corresponding button. Each of the 21 CV-syllable was presented 18 times in a randomized order. The task duration was 12 min. Subsequently, tDCS-electrodes were removed and EEG-electrodes were mounted. The time interval between the end of the tDCS and the start of the EEG session was 11,7 min ± 3,6 min. During the second task (CV-task II) AEPs were recorded in response to voiced (/da/, /ba/, /ga/) and voiceless (/ta/, /pa/,/ka/) natural CV-syllables. Participants had to decide whether the CV-syllable was voiced or voiceless by pressing the corresponding button. Each CV-syllable was presented 50 times in a randomized order with a delay time of 1000ms after subjects' response. Performance rate was equal above 97% in all three stimulation conditions (sham 97.75%, anodal: 97.31%, cathodal 98.1%, $F(2, 24) = 1.974$, $p = 0.161$).

Data analysis

Behavioral data

To examine performance in the CV-task-I I analyzed the slope parameter ($\beta1$) of the individual identification curves. This parameter provides a reliable measure for the preciseness of categorical perception in a VOT continuum (Joanisse *et al.*, 2000; Breier *et al.*, 2001; Bogliotti *et al.*, 2008; McCarthy *et al.*, 2014), with high values of β1 indicating a steep increase of the identification curve and reflecting high preciseness in categorical perception, and low values of β1 denoting a shallow, more fuzzy categorical perception. For this, I fitted each individual identification curve with the following formula:

$$x(y) = \frac{1}{(1+e^{(-(\beta 1 * \mathrm{x} + \beta 0)})} ,$$

and calculated the individual category boundary x(y = 0,5), which is the point of 50% correct responses or the point of maximal confusion. On average across the three tDCS conditions (sham, anodal, and cathodal) this point was found on a VOT of 29.2 ms (cf. Figure 11A). Subsequently, I extracted the individual slope parameter (β1) at this category boundary (VOT 29ms +/- 2ms). For analysis, the categorization parameter was normalized to the individual data during sham condition (baseline) to control for inter-individual variance, and compared between stimulation conditions by means of paired-sample t-tests.

Electrophysiological data

EEG preprocessing and data analysis were carried out using EEGlab V.12 (http://sccn.ucsd.edu/eeglab/). EEG data were off-line filtered from 0,01 Hz to 40 Hz. Segments containing ocular artifacts, movement artifacts, or amplifier saturation were excluded from the averaged ERP waveforms. The EEG recordings were sectioned into 600 ms epochs (200 ms pre-stimulus and 400 ms post-stimulus) and a baseline correction using the pre-stimulus portion of the signal was carried out. ERPs in response to all CV- syllables were averaged for each subject and grand-averaged across subjects. A peak analysis was performed on single-subject averages measured at channel Cz, which showed the largest deflections in the grand average. AEPs were quantified by measuring the baseline-to-peak amplitudes for the most positive (P50) and negative peak (N1) occurring at specific latency ranges (P50: 20–70 ms; N1: 80–140 ms). In the end, amplitude of the P50 and N1 components were analyzed using separate repeated-measures ANOVAs with a within-subject factor *tDCS* (sham, anodal, and cathodal). For post hoc analysis paired samples t-tests were performed.

4.3 Results

Behavioral data

Figure 11A shows the averaged CV-syllable identification curve for the percental /ta/ identification illustrating that, overall, participants successfully categorized phonetic stimuli. The analysis revealed a mean slope parameter (β1) for tDCS conditions (sham = 1.23, SE ± 0.14; anodal = 1.31, SE ± 0.27; cathodal = 1.74, SE ± 0.27). As shown in Figure 11B, cathodal tDCS steepened the slope parameter (β1) of the identification curves by 50 % compared to sham baseline performance (t(1,12) = 2.387, p = 0.03). Furthermore, simultaneous cathodal tDCS had a significant stronger effect on β1 than anodal tDCS (t(1,12) = 2.53, p = 0.03). Simultaneous anodal tDCS caused no considerable changes from sham baseline performance (t(1,12) = 0.464, p = 0.65). Thus, concurrent cathodal tDCS improved the categorical perception of a CV-VOT continuum demonstrating the ability to sharpen phonetic perception by means of bilateral auditory cathodal tDCS.

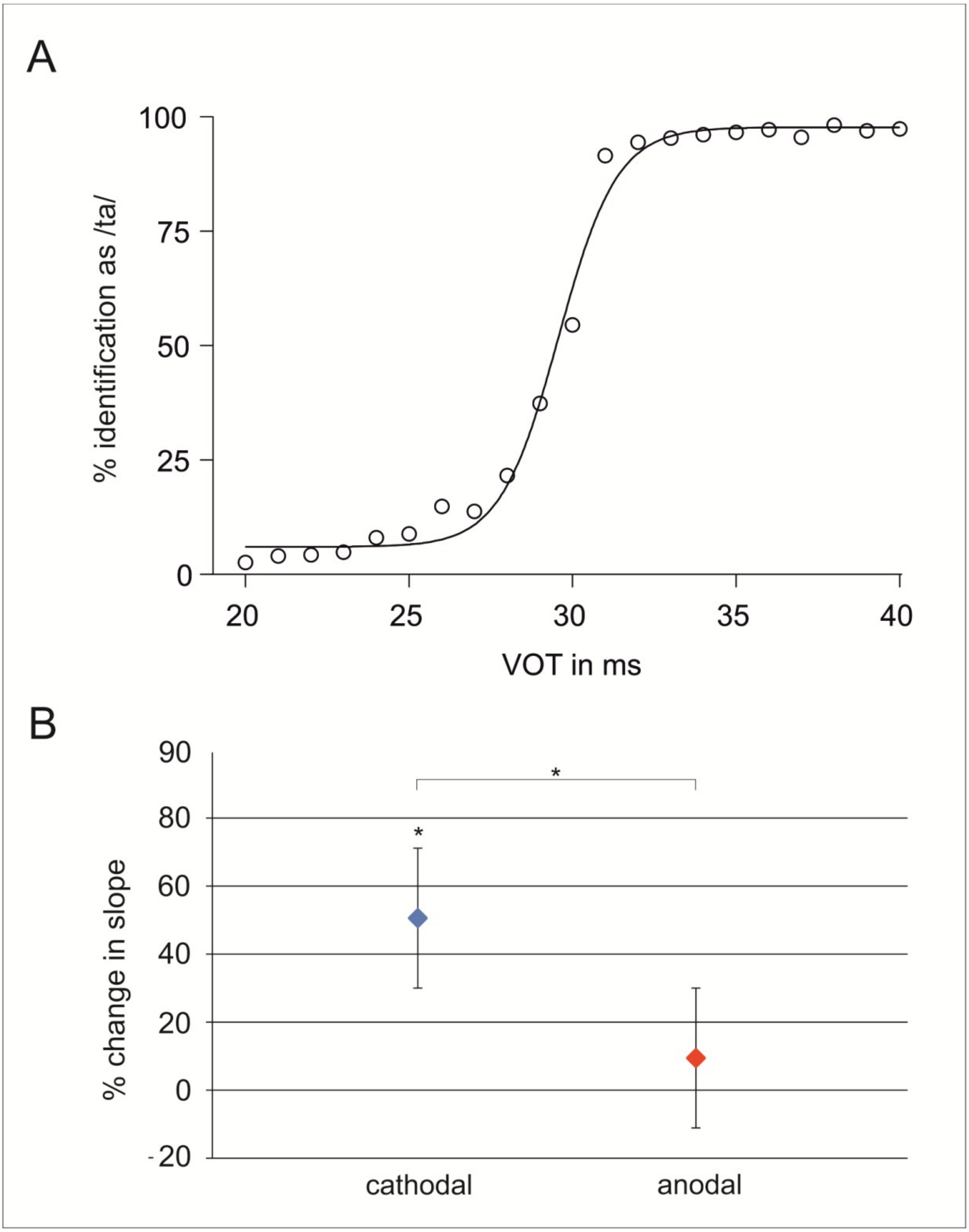

Figure 11: Behavioral results. (A) Subjects performance on phonetic categorization averaged across tDCS conditions (sham, anodal, and cathodal). The *graph* indicates the percentage of CV-syllables that were identified as /ta/ in relation to their VOT (*circles*) and the logistic curve fit. (B) Effect of active tDCS on phonetic categorization. Individual changes in slope are plotted relative to normalized sham condition (Mean ± SEM).

Auditory evoked potentials

AEPs in response to CV-syllables are illustrated in Figure 12. All stimuli evoked measurable P50 and N1 components. Repeated measures ANOVA with the factor *tDCS* (sham, anodal, cathodal) for P50 amplitude revealed a significant main effect [F(2,24) = 5.985, p = 0.01] due to significant larger P50 amplitude after anodal in contrast to sham tDCS (t(12) = 2.441, p = 0.03) and cathodal tDCS (t(12) = 3.676; p = 0.01). P50 amplitude after cathodal tDCS did not differ compared to sham tDCS (t(12) = 0.114; p = 0.89). For the N1 amplitude repeated measures ANOVA showed no tDCS effect [F(1,12) = 0.488, p = 0.62] (cf. Figure 12B). No differences in the P50 (F(2,24) = 0.053, p = 0.95) and N1 latencies (F(2,24) = 2.037, p = 0.15) could be observed.

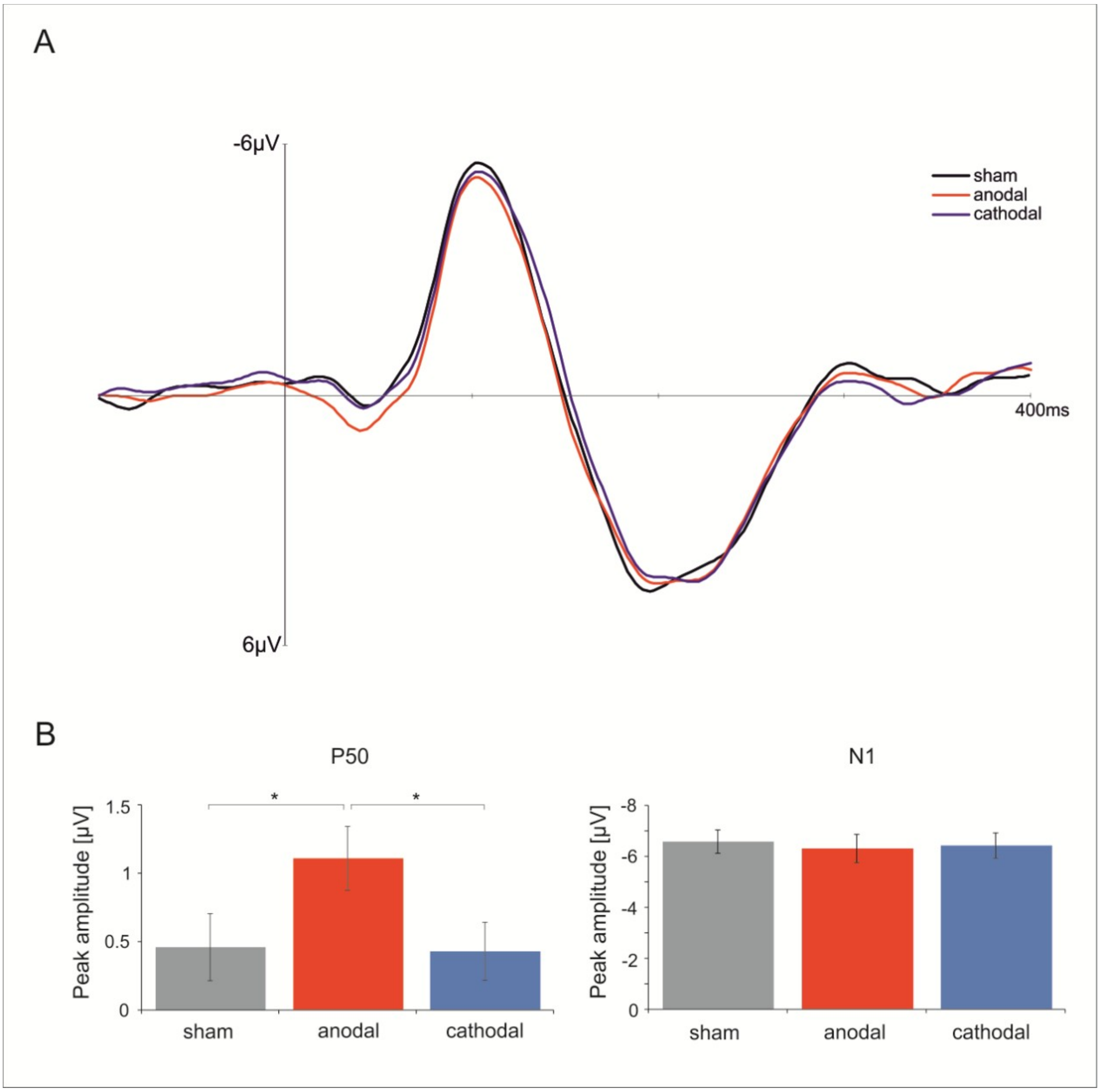

Figure 12: Electrophysiological results. (A) Grand average AEPs recorded at channel Cz are shown for different conditions (sham, anodal, and cathodal). (B) P50 and N1 amplitudes recorded at channel Cz for different tDCS conditions (sham, anodal, and cathodal) (Mean ± SEM).

4.4 Discussion

In the present study, I demonstrate that phonetic perception can be modulated by bilateral tDCS of the AC. Categorization of CV-syllables in a VOT continuum was enhanced by cathodal tDC-stimulation. In particular, concurrent cathodal tDCS steepened the slope of the identification curve indicating more consistent categorization of the syllables /ta/ and /da/. This sharpening of the phonetic perception was accompanied by increased P50 amplitude in response to natural CV syllables after anodal stimulation.

In the present study, cathodal tDCS improved preciseness of phonetic categorization, with no influences of anodal tDCS. In a first attempt this result might be contradictive in the light of the polarity-specific dichotomy assuming that anodal tDCS typically improves while cathodal tDCS worsens the behavioral outcome in a specific task. Notably, these dual-polarity effects have mainly been demonstrated in the motor domain but less on cognitive functions (Jacobson *et al.*, 2012). Particular in the auditory domain, several studies demonstrated a decrement of performance induced by cathodal tDCS on auditory function (Mathys *et al.*, 2010; Ladeira *et al.*, 2011), but there is also evidence for an opposite effect showing improved performance after cathodal stimulation (Alexander *et al.*, 2012). It can be assumed that different stimulation parameter such as stimulation power, electrode size, and electrode placement especially of the reference electrode, as well as the individual auditory stimuli contribute to the varying tDCS-effects. Furthermore, the tDCS-related alterations of the neurotransmitter level may impact homeostatic plasticity in the auditory domain. Whereas anodal tDCS reduces local concentrations of the inhibitory neurotransmitter gamma-amino butyric acid (GABA), thus, inducing improvement, cathodal tDCS reduces excitatory glutamate levels followed by impoverishment of the behavioral outcome. However, there is also evidence that cathodal tDCS can decrease GABA concentration and thus may induce improved performance as well (Stagg *et al.*, 2009; Filmer *et al.*, 2014). Thus, given that regional cortical excitation/inhibition balance, measured by ratios of glutamate/GABA, provide meaningful interpretations of individual cognitive as well as perceptual performance (Krause *et al.*, 2013a), cathodal tDCS may artificially change the excitation/inhibition balance towards a more optimal level in the AC.

The present results extend the view of tDCS induced modulations on temporal processing by showing improved phonetic categorization of CV-syllables with varying VOTs. This might reflect a facilitation of low-level acoustic processing of temporal features in the AC. Moreover, I assessed the electrophysiological brain activity in order to investigate tDCS induced aftereffects on CV-syllable perception. It has been proposed that anodal tDCS over the temporal cortex can alter AC reactivity resulting in modulation of the AEPs. As has been demonstrated previously using sinus tones (Zaehle *et al.*, 2011), I found enhanced P50 amplitudes after anodal tDCS indicating changes in the AC through an early stage of perceptual processing. Remarkably, the present study shows enhancement of the AC reactivity after anodal- but not cathodal tDCS. Such anodal tDCS-related increase in cortical excitation could be assumed to be the cause of an improved auditory performance. However, the behavioral data during tDCS showed no change of performance during anodal condition. Accordingly, I cannot directly relate the observed electrophysiological modulations after tDCS to the improved auditory phonetic categorization abilities described with concurrent stimulation. However, tDCS efficiency on cortical excitability critically depends on the timing of the stimulation. Several studies showed that tDCS can result in contradictive effects during (online) and after the application of tDCS (offline). For instance, simultaneous anodal tDCS leads to an improvement in motor learning and working memory performance, whereas during the aftereffect anodal tDCS results in no or opposite effects (Kuo *et al.*, 2008; Stagg *et al.*, 2011; Martin *et al.*, 2014). Such opposite online vs. offline effects has been found for the visual domain showing improved perceptual learning after but not during anodal tDCS (Pirulli *et al.*, 2013). Analogously, online tDCS decreased motor learning, whereas motor performance was worsened during the aftereffect (Reis & Fritsch, 2011; Stagg *et al.*, 2011). These opposing effects might be related to the underlying physiological actions of online vs. offline tDCS. While acute effects during stimulation (online) are primary based on changed membrane potentials, post-stimulation aftereffects are related to NMDA-receptor activation indicating a LTP-like mechanism for learning (Nitsche *et al.*, 2003a; Stagg & Nitsche, 2011; Monte-Silva *et al.*, 2013). The results demonstrate that simultaneous cathodal tDCS can induce an enhancement of auditory performance, whereas anodal tDCS induces aftereffects that enhance AC reactivity. Nevertheless, the present findings may have clinical implications for the treatment of speech-related pathologies such as dyslexia. Dyslectic children as well as adults exhibit deficits in the processing of rapid auditory information accompanied with deficient phonological processing (Breier *et al.*, 2001; Tallal & Gaab, 2006; Bogliotti *et al.*, 2008). Those patients may benefit from tDCS administration as add-on to conventional therapy. Notwithstanding the fact that the neurophysiological mechanisms are still not fully understood the current results show that tDCS can be successfully used to modulate rapid temporal processing of speech sounds. Consequently, by modulating the excitability of the temporal cortex via non-invasive brain stimulation, the present study provides a novel approach that can be simply administered to address stunted temporal processing abilities in auditory disorders in the human brain.

Conclusion

To my knowledge this is the first study investigating tDCS effects on phonetic perception by behavioral and electrophysiological parameter. The results show that bilateral tDCS of the temporal lobe can change the cortical reactivity and the performance associated with phonetic categorization. Additional studies are needed to provide a better understanding of the behavioral and neurophysiological basis of tDCS efficiency in the human AC.

5. General Discussion

In the current PhD thesis, I assessed tDCS-induced changes in acoustic perception and AC reactivity. Specifically, I investigated hemispheric lateralization of spectro-temporal processing in a causal way. Furthermore, I examined the neuromodulatory potential of tDCS to alter phonetic perception. Here, I utilized a novel tDCS approach by directly changing the neural activity of the AC. In three experiments, behavioral and electrophysiological data were collected. The main findings can be summarized as follows.

In the first experiment, I assessed left-lateralized dominance for temporal processing in a between-channel GDT by selectively stimulating either the left or the right AC. Anodal tDCS of the left, but not right, AC altered individual temporal resolution abilities suggesting a predominance of the left AC for processing rapid temporal acoustic information in non-speech sounds. This result agrees with the concept of a left hemispheric dominance for the processing of rapid temporal information as proposed by Zatorre et al. (2001, 2002) and Poeppel (2003). To further test functional lateralization in the human auditory system, in the second experiment I investigated the influence of anodal and cathodal HD-tDCS delivered over the left or right AC on auditory MMN in response to temporal as well as spectral deviants. The results show that MMN amplitude in response to temporal but not spectral acoustic features was elevated during anodal HD-tDCS of the left AC only. The data provide further causal evidence for a left hemispheric dominance for pre-attentive processing of low-level temporal information. Moreover, this multimodal approach highlights the feasibility of recording EEG during auditory tDCS to gain more detailed information about the underlying neural mechanisms involved in these alterations.The data of the first two experiments support the theory of a left-lateralized temporal processing and thus contribute to a better understanding of functional lateralization of the human AC.

Beyond the modulation of these acoustic processing abilities, in the third experiment I assessed the usability of auditory tDCS to generally change acoustic speech perception. Here, I could demonstrate that cathodal tDCS improved phonetic categorization abilities by increasing the preciseness of the individual categorization abilities, whereas anodal tDCS selectively modulated the P50 amplitude of the AEP

to CV-syllables. While several studies investigated the influence of tDCS on low-level acoustic processing, this study provides for the first time behavioral and electrophysiological evidence for a neuromodulatory effect of auditory tDCS on acoustic speech perception.
Acoustic aspects play a fundamental role in speech perception, however, this process critically depends on a number of subcomponents involved in sensory and cognitive functions. The underlying cortical network for speech processing is not exclusively restricted to the AC but is widely distributed extending from the posterior part of the AC to the prefrontal cortex (Zhang et al., 2011). Importantly, in addition to the analysis of acoustic content, also semantics, syntax, orthography, and prosody are crucial for the perception and comprehension of speech. In the context of the vast literature on low-level processing the present findings significantly enhance the knowledge in this field. Moreover, by demonstrating neuromodulatory effects of tDCS over the AC, this approach has been shown its potential to identify auditory functions.

In sum, the results of these studies provide a better understanding of low-level temporal information processing in the AC and demonstrate its potential at fostering therapeutic application of tDCS in language related disorders such as dyslexia. Despite the novel insights that were provided by this project, it is important to note challenges and limitations of the methodology.

5.1 Methodological challenges of auditory tDCS

Generally, stimulation parameters such as stimulation intensity, electrode size, electrode placement especially of the reference electrode as well as interindividual variability of subjects need to be systemically investigated for the implementation of optimal tDCS protocols on the auditory system. One main challenge in future research and clinical application of tDCS is the improvement of stimulation focality (Heimrath *et al.*, 2016). HD-tDCS, as applied in the second experiment, has been advanced to overcome this issue by utilizing small ring electrodes that increase spatial specificity of the current over the targeted cortical area (Datta *et al.*, 2009). Moreover, depending on the current flow in the cortex which is either radial oriented or tangential oriented, tDCS may produce distinct electrophysiological effects (Rahman *et* *al.*, 2013). Radial inward current induces somatic depolarization that facilitates synaptic efficacy, whereas tangential current flow (transverse) modulates synaptic efficacy in a pathway-manner by hyperpolarization of afferent neurons. It has been shown that it is not the polarity of tDCS which determines the direction of the effect per se but rather the orientation of the long axis of the neuron (Kabakov *et al.*, 2012). Contradictory polarity effects have been revealed in cell-culture experiments showing that anodal tDCS hyperpolarizes the membrane potential in apical dendritic regions and depolarizes the somatic regions, whereas cathodal tDCS was followed by the reversed effect (Radman *et al.*, 2009). The current flow in the human brain is dominantly tangential to the cortical surface. This implies that tangentially aligned neurons will be influenced more efficiently by tDCS compared to radially aligned neurons. Thus, the radial and tangential orientation in sulci and gyri has a strong impact on the current flow. While tDCS over gyri induces radial currents, the current flow in sulci is exclusively tangential (Miranda, 2013; Rahman *et al.*, 2013). As the results of the present thesis do not show the prevalent polarity-specific dichotomy assuming that anodal tDCS typically improves while cathodal tDCS worsens the behavioral outcome, I presume that distinct pattern of gyri and sulci in auditory related cortices might be caused the heterogeneity of neuromodulatory effects. Consequently, using state of the art simulations of current density distributions on individual anatomical data may help to improve current tDCS schemes.

In order to further optimize tDCS schemes on the auditory system it should be considered that auditory processing is a complex cognitive function mediated by multiple functionally connected brain areas rather than one individual region, which is typically targeted in tDCS studies (Vanneste & De Ridder, 2011). TDCS over e.g. the perisylvian region does not only modulate brain activity in the region under the electrode but also in other functionally related areas (Wu *et al.*, 2015). Accordingly, a combination of tDCS and neuroimaging techniques is recommended to explore the connections between different areas of the auditory network and to understand whether and how tDCS may influence auditory network excitability. This might further enable the development of efficient tDCS protocols to target specific connections between brain areas within the auditory network (Luft *et al.*, 2014; Heimrath *et al.*, 2016).

Importantly, in the vast majority of literature tDCS online effects on auditory perception were reported only, whereas electrophysiological investigations of tDCS online effects are sparse. Due to the strong artifacts induced by tDCS, such electrophysiological data were only measurable offline, after terminating the stimulation. Thus, the effect of tDCS on the underlying neural mechanism remains an important, but yet fairly under investigated question. Further knowledge about tDCS effects on brain functions may improve the specificity of stimulation protocols for clinical samples with auditory processing disorders. While several studies reporting pre-to-post changes in ERPs or resting-EEG data used offline measurements, to date, there are only a limited number of studies combining tDCS and electrophysiological data (Heimrath *et al.*, 2016). As I demonstrated, the application of HD-tDCS electrode application might be a further promising approach for the parallel assessment of EEG during tDCS. Moreover, it has been suggested that MEG is able to overcome this shortcoming due to its measurement of neuromagnetic activity via sensors (i.e. superconducting quantum interference devices, SQUIDS) not directly placed at the scalp (Soekadar *et al.*, 2013; Neuling *et al.*, 2015; Witkowski *et al.*, 2015; Heimrath *et al.*, 2016).

Finally, besides the contributions of stimulation parameters and task difficulty on the variability of response to tDCS, both interindividual and across multiple testing sessions, also baseline activity changes within the targeted neural network have to be considered. In particular, rather than exerting a homogeneous effect on each neuron underneath the electrodes and across individuals, tDCS interacts with endogenous activity levels within target neuronal populations. This results in tDCS outcomes that are dependent on the pre-existing activation state of the targeted neurons at the moment of stimulation, i.e. on baseline activity (Krause et al. 2013). Again, further research is necessary, in particular combining tDCS and direct neurophysiological measures of brain activity to further examine the relationship between neural baseline activity and effects of stimulation.

5.2 Outline and future perspectives

The neurophysiological mechanisms underlying tDCS induced behavioral and physiological alterations are still not fully understood. The current findings show that tDCS can alter auditory perceptual processing and consequently constitutes a clinical tool for the treatment of auditory related disorders. Given the fact, that the vast majority of dyslexic patients shows a deficit in low-level auditory temporal processing of speech-specific stimuli (Merzenich et al., 1993; Gaab et al., 2007; Vandermosten et al., 2010; Raschle et al., 2014) as well as of non-speech stimuli (Tallal & Piercy, 1974; Breier et al., 2001; Chandrasekaran et al., 2009) and the evidence of tDCS associated alterations of basic auditory performance reviewed above, the application of tDCS seems to be a promising technique and past-due intervention to improve both the AC reactivity in dyslexics and the impaired processing of incoming speech features. However, although there is convincing evidence on the applicability and the potentially beneficial effect of tDCS in dyslexic samples a number of important prerequisites have to be taken into account in order to successfully utilize tDCS in clinical samples. In the following section, I will discuss some of the most relevant prerequisites of tDCS for clinical application.

5.2.1 Specific prerequisites of tDCS for clinical application

The vast majority of all clinical interventions target to normalize pathological processes and to ensure the prolonged impact of the completed intervention. Thus, in order to use tDCS in a clinical setting it is vital to know whether the stimulation schema results in aftereffects of adequate duration. Yet there are no systematic investigations on tDCS long-term effects in the auditory domain.

It is well documented that tDCS over the motor cortex can induce excitability changes from minutes to hours (offline effect) (Nitsche & Paulus, 2000; 2001). In contrast to transient aftereffects (offline effect), long-term effects persisting over a prolonged period (i.e. days and months) are crucial for the clinical application of tDCS. Clinical trials with patients suffering from auditory related disorders show sustained improvement of symptoms lasting up to 16 weeks after the tDCS session (Fridriksson et al., 2011; Garin et al., 2011; Marangolo et al., 2011; Frank et al., 2012; Vestito et al., 2014). Thus, tDCS, especially when applied repetitively on consecutive days seems to be able to induce clinically relevant long-term effects.

Finally, for the clinical application of tDCS, it is desirable to use tDCS already in early stages of the disorder, when the brain's ability to adapt to external events and to develop novel strategies is most pronounced. While the application of tDCS usually aims to improve perceptual or cognitive abilities it seems important to consider probable unwanted side effects in the vulnerable child's and adolescent's brain. Despite first promising results in pediatric samples there is still a lack of systematic studies on the effect of tDCS on the developing brain (Heimrath et al., 2016).

In order to assess both the effect and tolerability of tDCS in the developing brain, Moliadze et al. (2015) investigated immediate effects as well as aftereffects on the excitability of the motor cortex in a sample of children and adolescents (aged 11 – 16 years). Neither anodal tDCS nor cathodal tDCS with 1 mA for 10 min showed any adverse effects or pathological neural activity. In a further study, they reported increased motor evoked potentials to be observed up to one hour after 1 mA anodal and cathodal tDCS (Moliadze et al., 2015b). In sum, all children and adolescents tolerated the stimulation well and tDCS consistently induced functional changes in this pediatric sample. None of the participants reported any visual sensations, headache or symptoms of hyperactivity. This, in turn, seems to allow for the application in clinical interventions. Accordingly the clinical efficacy of tDCS in adolescent patients with attention deficit hyperactivity disorder has already been successfully demonstrated (Munz et al., 2015; Breitling et al., 2016).

Taken together, the use of tDCS in vulnerable persons and especially children should always be performed with great caution, taking into account all the relevant factors which might have immediate as well as long-term unwanted side effects.

6. References

Alexander, T., Avirame, K. & Lavidor, M. (2012) Improving emotional prosody detection in the attending ear by cathodal tDCS suppression of the competing channel. Neuroscience letters, 508, 52-55.

Anderson, B., Southern, B.D. & Powers, R.E. (1999) Anatomic asymmetries of the posterior superior temporal lobes: a postmortem study. Neuropsychiatry, neuropsychology, and behavioral neurology, 12, 247-254.

Bekesy, G. (1961) Concerning the pleasures of observing, and the meachnics of the inner ear. Nobel Lect.

Ben-Yehudah, G., Banai, K. & Ahissar, M. (2004) Patterns of deficit in auditory temporal processing among dyslexic adults. Neuroreport, 15, 627-631.

Bindman, L.J., Lippold, O.C. & Redfearn, J.W. (1962) Long-lasting changes in the level of the electrical activity of the cerebral cortex produced bypolarizing currents. Nature, 196, 584-585.

Bindman, L.J., Lippold, O.C. & Redfearn, J.W. (1964) The Action of Brief Polarizing Currents on the Cerebral Cortex of the Rat (1) during Current Flow and (2) in the Production of Long-Lasting after-Effects. The Journal of physiology, 172, 369-382.

Boemio, A., Fromm, S., Braun, A. & Poeppel, D. (2005) Hierarchical and asymmetric temporal sensitivity in human auditory cortices. Nature neuroscience, 8, 389-395.

Bogliotti, C., Serniclaes, W., Messaoud-Galusi, S. & Sprenger-Charolles, L. (2008) Discrimination of speech sounds by children with dyslexia: comparisons with chronological age and reading level controls. Journal of experimental child psychology, 101, 137-155.

Breier, J.I., Gray, L., Fletcher, J.M., Diehl, R.L., Klaas, P., Foorman, B.R. & Molis, M.R. (2001) Perception of voice and tone onset time continua in children with dyslexia with and without attention deficit/hyperactivity disorder. Journal of experimental child psychology, 80, 245-270.

Breitling, C., Zaehle, T., Dannhauer, M., Bonath, B., Tegelbeckers, J., Flechtner, H.H. & Krauel, K. (2016) Improving Interference Control in ADHD Patients with Transcranial Direct Current Stimulation (tDCS). Front Cell Neurosci, 10, 72.

Broca, P. (1861) Remarques sur le sie´ge de la faculte´ du langage article´ suivies d'une observation d'aphe´mie (perte de la parole). Bull Soc Anat Paris., 6, 330-357.

Bryden, M.P. (1982) Laterality: Functional Asymmetry in the Intact Brain. . New York: Academic Press.

Bryden, M.P., Munhall, K. & Allard, F. (1983) Attentional biases and the right-ear effect in dichotic listening. Brain and language, 18, 236-248.

Buxhoeveden, D. & Casanova, M. (2000) Comparative lateralisation patterns in the language area of human, chimpanzee, and rhesus monkey brains. Laterality, 5, 315-330.

Campbell, K.B. & Colrain, I.M. (2002) Event-related potential measures of the inhibition of information processing: II. The sleep onset period. International journal of psychophysiology : official journal of the International Organization of Psychophysiology, 46, 197-214.

Carmichael, M.E., Hall, S.E. & Phillips, D.P. (2008) Ear and contralateral masker effects on auditory temporal gap detection thresholds. Hearing research, 245, 18-23.

Cha, K., Zatorre, R.J. & Schonwiesner, M. (2014) Frequency Selectivity of Voxel-by-Voxel Functional Connectivity in Human Auditory Cortex. Cerebral cortex.

Chandrasekaran, C., Trubanova, A., Stillittano, S., Caplier, A. & Ghazanfar, A.A. (2009) The natural statistics of audiovisual speech. PLoS computational biology, 5, e1000436.

Chen, J.C., Hammerer, D., Strigaro, G., Liou, L.M., Tsai, C.H., Rothwell, J.C. & Edwards, M.J. (2013) Domain-specific suppression of auditory mismatch negativity with transcranial direct current stimulation. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 125, 585-592.

Chiappe, P., Chiappe, D.L. & Siegel, L.S. (2001) Speech perception, lexicality, and reading skill. Journal of experimental child psychology, 80, 58-74.

Chobert, J., Francois, C., Habib, M. & Besson, M. (2012) Deficit in the preattentive processing of syllabic duration and VOT in children with dyslexia. Neuropsychologia, 50, 2044-2055.

Chobert, J., Francois, C., Velay, J.L. & Besson, M. (2014) Twelve months of active musical training in 8- to 10-year-old children enhances the preattentive processing of syllabic duration and voice onset time. Cerebral cortex, 24, 956-967.

Cools, R., Barker, R.A., Sahakian, B.J. & Robbins, T.W. (2001) Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cerebral cortex, 11, 1136-1143.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D. & Bikson, M. (2009) Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain stimulation, 2, 201-207, 207 e201.

Datta, A., Truong, D., Minhas, P., Parra, L.C. & Bikson, M. (2012) Inter-Individual Variation during Transcranial Direct Current Stimulation and Normalization of Dose Using MRI-Derived Computational Models. Frontiers in psychiatry / Frontiers Research Foundation, 3, 91.

Davis, M.H. & Johnsrude, I.S. (2007) Hearing speech sounds: top-down influences on the interface between audition and speech perception. Hearing research, 229, 132-147.

De Sanctis, P., Molholm, S., Shpaner, M., Ritter, W. & Foxe, J.J. (2009) Right Hemispheric Contributions to Fine Auditory Temporal Discriminations: High-Density Electrical Mapping of the Duration Mismatch Negativity (MMN). Frontiers in integrative neuroscience, 3, 5.

Deouell, L.Y. (2007) The frontal generator of the mismatch negativity revisited. J. Psychophysiol, 21, 188–203.

Doeller, C.F., Opitz, B., Mecklinger, A., Krick, C., Reith, W. & Schroger, E. (2003) Prefrontal cortex involvement in preattentive auditory deviance detection: neuroimaging and electrophysiological evidence. NeuroImage, 20, 1270-1282.

Duff, F.J., Hulme, C., Grainger, K., Hardwick, S.J., Miles, J.N. & Snowling, M.J. (2014) Reading and language intervention for children at risk of dyslexia: a randomised controlled trial. Journal of child psychology and psychiatry, and allied disciplines.

Eggermont, J.J. (1995) Neural correlates of gap detection and auditory fusion in cat auditory cortex. Neuroreport, 6, 1645-1648.

Eimas, P.D. & Corbit, J.D. (1973) Selective adaptation of lingusitic feature detectors. Cognitive Psychology, 4, 99-109.

Elangovan, S. & Stuart, A. (2008) Natural boundaries in gap detection are related to categorical perception of stop consonants. Ear and hearing, 29, 761-774.

Elangovan, S. & Stuart, A. (2011) A cross-linguistic examination of cortical auditory evoked potentials for a categorical voicing contrast. Neuroscience letters, 490, 140-144.

Elliott, J.G. & Grigorenko, E.L. (2014) The Dyslexia Debate. Cambridge: University press.

Farmer, M.E. & Klein, R.M. (1995) The evidence for a temporal processing deficit linked to dyslexia: A review. Psychon Bull Rev, 2, 460-493.

Filmer, H.L., Dux, P.E. & Mattingley, J.B. (2014) Applications of transcranial direct current stimulation for understanding brain function. Trends in neurosciences, 37, 742-753.

Fischer, C., Luaute, J., Adeleine, P. & Morlet, D. (2004) Predictive value of sensory and cognitive evoked potentials for awakening from coma. Neurology, 63, 669-673.

Fischer, C., Luaute, J., Nemoz, C., Morlet, D., Kirkorian, G. & Mauguiere, F. (2006) Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Critical care medicine, 34, 1520-1524.

Fox (2011) Neuroscience: brain buzz. Nature 472:156–158.

Frank, E., Schecklmann, M., Landgrebe, M., Burger, J., Kreuzer, P., Poeppl, T.B., Kleinjung, T., Hajak, G. & Langguth, B. (2012) Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study. Journal of neurology, 259, 327-333.

Fricke, S., Bowyer-Crane, C., Haley, A.J., Hulme, C. & Snowling, M.J. (2013) Efficacy of language intervention in the early years. Journal of child psychology and psychiatry, and allied disciplines, 54, 280-290.

Fridriksson, J., Richardson, J.D., Baker, J.M. & Rorden, C. (2011) Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. Stroke, 42, 819-821.

Gaab, N., Gabrieli, J.D., Deutsch, G.K., Tallal, P. & Temple, E. (2007) Neural correlates of rapid auditory processing are disrupted in children with developmental dyslexia and ameliorated with training: an fMRI study. Restorative neurology and neuroscience, 25, 295-310.

Galaburda, A.M., LeMay, M., Kemper, T.L. & Geschwind, N. (1978) Right-left asymmetrics in the brain. Science, 199, 852-856.

Garin, P., Gilain, C., Van Damme, J.P., de Fays, K., Jamart, J., Ossemann, M. & Vandermeeren, Y. (2011) Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation. Journal of neurology, 258, 1940-1948.

Garrido, M.I., Kilner, J.M., Kiebel, S.J. & Friston, K.J. (2009a) Dynamic causal modeling of the response to frequency deviants. Journal of neurophysiology, 101, 2620-2631.

Garrido, M.I., Kilner, J.M., Stephan, K.E. & Friston, K.J. (2009b) The mismatch negativity: a review of underlying mechanisms. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 120, 453-463.

Geschwind, N. (1979) Specializations of the human brain. Sci Am, 241, 180-199.

Giraud, K., Demonet, J.F., Habib, M., Marquis, P., Chauvel, P. & Liegeois-Chauvel, C. (2005) Auditory evoked potential patterns to voiced and voiceless speech sounds in adult developmental dyslexics with persistent deficits. Cerebral cortex, 15, 1524-1534.

Goldman-Rakic, P.S., Muly, E.C., 3rd & Williams, G.V. (2000) D(1) receptors in prefrontal cells and circuits. Brain research. Brain research reviews, 31, 295-301.

Goldstein, E.B. (2010) Sensation and Perception. Belmont, CA: Wadsworth, Cengage Learning, 8th ed.

Grimm, S., Roeber, U., Trujillo-Barreto, N.J. & Schroger, E. (2006) Mechanisms for detecting auditory temporal and spectral deviations operate over similar time windows but are divided differently between the two hemispheres. NeuroImage, 32, 275-282.

Grose, J.H., Hall, J.W., 3rd, Buss, E. & Hatch, D. (2001) Gap detection for similar and dissimilar gap markers. The Journal of the Acoustical Society of America, 109, 1587-1595.

Gu, F., Zhang, C., Hu, A. & Zhao, G. (2013) Left hemisphere lateralization for lexical and acoustic pitch processing in Cantonese speakers as revealed by mismatch negativity. NeuroImage, 83, 637-645.

Hamalainen, J.A., Salminen, H.K. & Leppanen, P.H. (2013) Basic auditory processing deficits in dyslexia: systematic review of the behavioral and event-related potential/ field evidence. Journal of learning disabilities, 46, 413-427.

Harasty, J., Seldon, H.L., Chan, P., Halliday, G. & Harding, A. (2003) The left human speech-processing cortex is thinner but longer than the right. Laterality, 8, 247-260.

Harrington, D.L., Boyd, L.A., Mayer, A.R., Sheltraw, D.M., Lee, R.R., Huang, M. & Rao, S.M. (2004) Neural representation of interval encoding and decision making. Brain research. Cognitive brain research, 21, 193-205.

Heimrath, K., Fiene, M., Rufener, K.S. & Zaehle, T. (2016) Modulating Human Auditory Processing by Transcranial Electrical Stimulation. Front Cell Neurosci, 10, 53.

Hickok, G. & Poeppel, D. (2000) Towards a functional neuroanatomy of speech perception. Trends in cognitive sciences, 4, 131-138.

Hutsler, J.J. (2003) The specialized structure of human language cortex: pyramidal cell size asymmetries within auditory and language-associated regions of the temporal lobes. Brain and language, 86, 226-242.

Hutsler, J.J. & Gazzaniga, M.S. (1996) Acetylcholinesterase staining in human auditory and language cortices: regional variation of structural features. Cerebral cortex, 6, 260-270.

Impey, D. & Knott, V. (2015) Effect of transcranial direct current stimulation (tDCS) on MMN-indexed auditory discrimination: a pilot study. Journal of neural transmission.

Jacobson, L., Koslowsky, M. & Lavidor, M. (2012) tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale, 216, 1-10.

Jamison, H.L., Watkins, K.E., Bishop, D.V. & Matthews, P.M. (2006) Hemispheric specialization for processing auditory nonspeech stimuli. Cerebral cortex, 16, 1266-1275.

Jancke, L., Buchanan, T.W., Lutz, K. & Shah, N.J. (2001) Focused and nonfocused attention in verbal and emotional dichotic listening: an FMRI study. Brain and language, 78, 349-363.

Joanisse, M.F., Manis, F.R., Keating, P. & Seidenberg, M.S. (2000) Language deficits in dyslexic children: speech perception, phonology, and morphology. Journal of experimental child psychology, 77, 30-60.

Josse, G. & Tzourio-Mazoyer, N. (2004) Hemispheric specialization for language. Brain research. Brain research reviews, 44, 1-12.

Kaas, J.H., Hackett, T.A. & Tramo, M.J. (1999) Auditory processing in primate cerebral cortex. Current opinion in neurobiology, 9, 164-170.

Kabakov, A.Y., Muller, P.A., Pascual-Leone, A., Jensen, F.E. & Rotenberg, A. (2012) Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. Journal of neurophysiology, 107, 1881-1889.

Kimura, D. (1961a) Cerebral dominance and the perception of verbal stimuli. Canadian Journal of Psychology, 15, 166-171.

Kimura, D. (1961b) Some effects of temporal-lobe damage on auditory perception. Can J Psychol, 15, 156-165.

King, K.A., Campbell, J., Sharma, A., Martin, K., Dorman, M. & Langran, J. (2008) The representation of voice onset time in the cortical auditory evoked potentials of young children. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 119, 2855-2861.

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J.D., Moseley, M.E. & Poldrack, R.A. (2000) Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. Neuron, 25, 493-500.

Krause, B., Marquez-Ruiz, J. & Cohen Kadosh, R. (2013a) The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Frontiers in human neuroscience, 7, 602.

Krause, B., Marquez-Ruiz, J. & Kadosh, R.C. (2013b) The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Frontiers in human neuroscience, 7, 602.

Kuhl, P.K. & Miller, J.D. (1978) Speech perception by the chinchilla: identification function for synthetic VOT stimuli. The Journal of the Acoustical Society of America, 63, 905-917.

Kujala, T. & Naatanen, R. (2010) The adaptive brain: a neurophysiological perspective. Progress in neurobiology, 91, 55-67.

Kujala, T., Tervaniemi, M. & Schroger, E. (2007) The mismatch negativity in cognitive and clinical neuroscience: theoretical and methodological considerations. Biological psychology, 74, 1-19.

Kuo, H.I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M.F. & Nitsche, M.A. (2013) Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. Brain stimulation, 6, 644-648.

Kuo, M.F., Unger, M., Liebetanz, D., Lang, N., Tergau, F., Paulus, W. & Nitsche, M.A. (2008) Limited impact of homeostatic plasticity on motor learning in humans. Neuropsychologia, 46, 2122-2128.

Kuuluvainen, S., Nevalainen, P., Sorokin, A., Mittag, M., Partanen, E., Putkinen, V., Seppanen, M., Kahkonen, S. & Kujala, T. (2014) The neural basis of sublexical speech and corresponding nonspeech processing: A combined EEG-MEG study. Brain and language, 130C, 19-32.

Ladeira, A., Fregni, F., Campanha, C., Valasek, C.A., De Ridder, D., Brunoni, A.R. & Boggio, P.S. (2011) Polarity-dependent transcranial direct current stimulation effects on central auditory processing. PloS one, 6, e25399.

Lichtheim, L. (1885) On aphasia. Brain : a journal of neurology, 7, 433–484.

Liebetanz, D., Nitsche, M.A., Tergau, F. & Paulus, W. (2002) Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain : a journal of neurology, 125, 2238-2247.

Liem, F., Hurschler, M.A., Jancke, L. & Meyer, M. (2014) On the planum temporale lateralization in suprasegmental speech perception: evidence from a study investigating behavior, structure, and function. Human brain mapping, 35, 1779-1789.

Lisker, L. & Abramson, A.S. (1964) A cross-language study of voicing in initial stops: Acoustical measurements. Word 20, 384–422.

Luft, C.D., Pereda, E., Banissy, M.J. & Bhattacharya, J. (2014) Best of both worlds: promise of combining brain stimulation and brain connectome. Front Syst Neurosci, 8, 132.

Luo, H. & Poeppel, D. (2012) Cortical oscillations in auditory perception and speech: evidence for two temporal windows in human auditory cortex. Frontiers in psychology, 3, 170.

Maess, B., Jacobsen, T., Schroger, E. & Friederici, A.D. (2007) Localizing pre-attentive auditory memory-based comparison: magnetic mismatch negativity to pitch change. NeuroImage, 37, 561-571.

Marangolo, P., Marinelli, C.V., Bonifazi, S., Fiori, V., Ceravolo, M.G., Provinciali, L. & Tomaiuolo, F. (2011) Electrical stimulation over the left inferior frontal gyrus (IFG) determines long-term effects in the recovery of speech apraxia in three chronic aphasics. Behavioural brain research, 225, 498-504.

Martin, D.M., Liu, R., Alonzo, A., Green, M. & Loo, C.K. (2014) Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale, 232, 3345-3351.

Mathys, C., Loui, P., Zheng, X. & Schlaug, G. (2010) Non-invasive brain stimulation applied to Heschl's gyrus modulates pitch discrimination. Frontiers in psychology, 1, 193.

McCarthy, K.M., Mahon, M., Rosen, S. & Evans, B.G. (2014) Speech perception and production by sequential bilingual children: a longitudinal study of voice onset time acquisition. Child Dev, 85, 1965-1980.

Merzenich, M.M., Schreiner, C., Jenkins, W. & Wang, X. (1993) Neural mechanisms underlying temporal integration, segmentation, and input sequence representation: some implications for the origin of learning disabilities. Annals of the New York Academy of Sciences, 682, 1-22.

Meyer, M. (2008) Functions of the left and right posterior temporal lobes during segmental and suprasegmental speech perception. Z Neuropsychol 19:101–115.

Meyer, M., Liem, F., Hirsiger, S., Jancke, L. & Hanggi, J. (2013) Cortical Surface Area and Cortical Thickness Demonstrate Differential Structural Asymmetry in Auditory-Related Areas of the Human Cortex. Cerebral cortex, 24, 2541-2552.

Meyer, M., Zaehle, T., Gountouna, V.E., Barron, A., Jancke, L. & Turk, A. (2005) Spectro-temporal processing during speech perception involves left posterior auditory cortex. Neuroreport, 16, 1985-1989.

Miniussi, C., Brignani, D. & Pellicciari, M.C. (2012) Combining transcranial electrical stimulation with electroencephalography: a multimodal approach. Clin EEG Neurosci, 43, 184-191.

Miniussi, C. & Ruzzoli, M. (2013) Transcranial stimulation and cognition. Handbook of clinical neurology, 116, 739-750.

Miranda, P.C. (2013) Physics of effects of transcranial brain stimulation. Handbook of clinical neurology, 116, 353-366.

Miranda, P.C., Lomarev, M. & Hallett, M. (2006) Modeling the current distribution during transcranial direct current stimulation. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 117, 1623-1629.

Molholm, S., Martinez, A., Ritter, W., Javitt, D.C. & Foxe, J.J. (2005) The neural circuitry of pre-attentive auditory change-detection: an fMRI study of pitch and duration mismatch negativity generators. Cerebral cortex, 15, 545-551.

Moliadze, V., Andreas, S., Lyzhko, E., Schmanke, T., Gurashvili, T., Freitag, C.M. & Siniatchkin, M. (2015a) Ten minutes of 1mA transcranial direct current stimulation was well tolerated by children and adolescents: Self-reports and resting state EEG analysis. Brain Res Bull, 119, 25-33.

Moliadze, V., Schmanke, T., Andreas, S., Lyzhko, E., Freitag, C.M. & Siniatchkin, M. (2015b) Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 126, 1392-1399.

Monte-Silva, K., Kuo, M.F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W. & Nitsche, M.A. (2013) Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain stimulation, 6, 424-432.

Monte-Silva, K., Kuo, M.F., Thirugnanasambandam, N., Liebetanz, D., Paulus, W. & Nitsche, M.A. (2009) Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 6124-6131.

Munz, M.T., Prehn-Kristensen, A., Thielking, F., Molle, M., Goder, R. & Baving, L. (2015) Slow oscillating transcranial direct current stimulation during non-rapid eye movement sleep improves behavioral inhibition in attention-deficit/hyperactivity disorder. Front Cell Neurosci, 9, 307.

Musacchia, G., Choudhury, N.A., Ortiz-Mantilla, S., Realpe-Bonilla, T., Roesler, C.P. & Benasich, A.A. (2013) Oscillatory support for rapid frequency change processing in infants. Neuropsychologia, 51, 2812-2824.

Naatanen, R., Kujala, T. & Winkler, I. (2011) Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. Psychophysiology, 48, 4-22.

Naatanen, R., Paavilainen, P., Rinne, T. & Alho, K. (2007) The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118, 2544-2590.

Naccache, L., Puybasset, L., Gaillard, R., Serve, E. & Willer, J.C. (2005) Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 116, 988-989.

Neuling, T., Ruhnau, P., Fusca, M., Demarchi, G., Herrmann, C.S. & Weisz, N. (2015) Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. NeuroImage, 118, 406-413.

Neuling, T., Wagner, S., Wolters, C.H., Zaehle, T. & Herrmann, C.S. (2012) Finite-Element Model Predicts Current Density Distribution for Clinical Applications of tDCS and tACS. Frontiers in psychiatry / Frontiers Research Foundation, 3, 83.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F. & Pascual-Leone, A. (2008) Transcranial direct current stimulation: State of the art 2008. Brain stimulation, 1, 206-223.

Nitsche, M.A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F. & Paulus, W. (2003a) Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. The Journal of physiology, 553, 293-301.

Nitsche, M.A., Liebetanz, D., Antal, A., Lang, N., Tergau, F. & Paulus, W. (2003b) Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects. Supplements to Clinical neurophysiology, 56, 255-276.

Nitsche, M.A., Liebetanz, D., Tergau, F. & Paulus, W. (2002) [Modulation of cortical excitability by transcranial direct current stimulation]. Der Nervenarzt, 73, 332-335.

Nitsche, M.A. & Paulus, W. (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology, 527 Pt 3, 633-639.

Nitsche, M.A. & Paulus, W. (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology, 57, 1899-1901.

Obleser, J., Eisner, F. & Kotz, S.A. (2008) Bilateral speech comprehension reflects differential sensitivity to spectral and temporal features. The Journal of neuroscience : the official journal of the Society for Neuroscience, 28, 8116-8123.

Okamoto, H. & Kakigi, R. (2013) Hemispheric Asymmetry of Auditory Mismatch Negativity Elicited by Spectral and Temporal Deviants: A Magnetoencephalographic Study. Brain topography.

Okamoto, H., Stracke, H., Draganova, R. & Pantev, C. (2009) Hemispheric asymmetry of auditory evoked fields elicited by spectral versus temporal stimulus change. Cerebral cortex, 19, 2290-2297.

Okamoto, H., Teismann, H., Keceli, S., Pantev, C. & Kakigi, R. (2013) Differential effects of temporal regularity on auditory-evoked response amplitude: a decrease in silence and increase in noise. Behavioral and brain functions : BBF, 9, 44.

Penhune, V.B., Zatorre, R.J., MacDonald, J.D. & Evans, A.C. (1996) Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cerebral cortex, 6, 661-672.

Peretz, I. & Zatorre, R.J. (2005) Brain organization for music processing. Annu Rev Psychol, 56, 89-114.

Phillips, D.P. (1999) Auditory gap detection, perceptual channels, and temporal resolution in speech perception. J Am Acad Audiol, 10, 343-354.

Phillips, D.P., Comeau, M. & Andrus, J.N. (2010) Auditory temporal gap detection in children with and without auditory processing disorder. J Am Acad Audiol, 21, 404-408.

Phillips, D.P., Hall, S.E., Harrington, I.A. & Taylor, T.L. (1998) "Central" auditory gap detection: a spatial case. The Journal of the Acoustical Society of America, 103, 2064-2068.

Phillips, D.P. & Smith, J.C. (2004) Correlations among within-channel and between-channel auditory gap-detection thresholds in normal listeners. Perception, 33, 371-378.

Phillips, D.P., Taylor, T.L., Hall, S.E., Carr, M.M. & Mossop, J.E. (1997) Detection of silent intervals between noises activating different perceptual channels: some properties of "central" auditory gap detection. The Journal of the Acoustical Society of America, 101, 3694-3705.

Pirulli, C., Fertonani, A. & Miniussi, C. (2013) The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. Brain stimulation, 6, 683-689.

Poeppel, D. (2003a) The analysis of speech in different temporal integration windows: cerebral lateralization as 'asymmetric sampling in time'. Speech Commun, 41, 245-255.

Poeppel, D. (2003b) The analysis of speech in different temporal integration windows: cerebral lateralization as ‘asymmetric sampling in time’. Speech Commun 41:245–255.

Poeppel, D., Yellin, E., Phillips, C., Roberts, T.P., Rowley, H.A., Wexler, K. & Marantz, A. (1996) Task-induced asymmetry of the auditory evoked M100 neuromagnetic field elicited by speech sounds. Brain research. Cognitive brain research, 4, 231-242.

Purpura, D.P., Scarff, T. & McMurtry, J.G. (1965) Intracellular Study of Internuclear Inhibition in Ventrolateral Thalamic Neurons. Journal of neurophysiology, 28, 487-496.

Radman, T., Datta, A., Ramos, R.L., Brumberg, J.C. & Bikson, M. (2009) One-dimensional representation of a neuron in a uniform electric field. Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference, 2009, 6481-6484.

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C. & Bikson, M. (2013) Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. The Journal of physiology, 591, 2563-2578.

Ramus, F. (2003) Developmental dyslexia: specific phonological deficit or general sensorimotor dysfunction? Current opinion in neurobiology, 13, 212-218.

Raschle, N.M., Stering, P.L., Meissner, S.N. & Gaab, N. (2013) Altered Neuronal Response During Rapid Auditory Processing and Its Relation to Phonological Processing in Prereading Children at Familial Risk for Dyslexia. Cerebral cortex.

Raschle, N.M., Stering, P.L., Meissner, S.N. & Gaab, N. (2014) Altered neuronal response during rapid auditory processing and its relation to phonological processing in prereading children at familial risk for dyslexia. Cerebral cortex, 24, 2489-2501.

Reis, J. & Fritsch, B. (2011) Modulation of motor performance and motor learning by transcranial direct current stimulation. Curr Opin Neurol, 24, 590-596.

Reiterer, S.M., Erb, M., Droll, C.D., Anders, S., Ethofer, T., Grodd, W. & Wildgruber, D. (2005) Impact of task difficulty on lateralization of pitch and duration discrimination. Neuroreport, 16, 239-242.

Robin, D.A., Tranel, D. & Damasio, H. (1990) Auditory perception of temporal and spectral events in patients with focal left and right cerebral lesions. Brain and language, 39, 539-555.

Ross, E.D. (1981) The aprosodias. Functional-anatomic organization of the affective components of language in the right hemisphere. Archives of neurology, 38, 561-569.

Ruby, P., Caclin, A., Boulet, S., Delpuech, C. & Morlet, D. (2008) Odd sound processing in the sleeping brain. Journal of cognitive neuroscience, 20, 296-311.

Rybalko, N., Suta, D., Popelar, J. & Syka, J. (2010) Inactivation of the left auditory cortex impairs temporal discrimination in the rat. Behavioural brain research, 209, 123-130.

Sandmann, P., Eichele, T., Specht, K., Jancke, L., Rimol, L.M., Nordby, H. & Hugdahl, K. (2007) Hemispheric asymmetries in the processing of temporal acoustic cues in consonant-vowel syllables. Restorative neurology and neuroscience, 25, 227-240.

Santoro, R., Moerel, M., De Martino, F., Goebel, R., Ugurbil, K., Yacoub, E. & Formisano, E. (2014) Encoding of natural sounds at multiple spectral and temporal resolutions in the human auditory cortex. PLoS computational biology, 10, e1003412.

Schonwiesner, M., Rubsamen, R. & von Cramon, D.Y. (2005) Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. The European journal of neuroscience, 22, 1521-1528.

Schwartz, J. & Tallal, P. (1980) Rate of acoustic change may underlie hemispheric specialization for speech perception. Science, 207, 1380-1381.

Scott, S.K. & McGettigan, C. (2013) Do temporal processes underlie left hemisphere dominance in speech perception? Brain and language, 127, 36-45.

Sculthorpe, L.D., Ouellet, D.R. & Campbell, K.B. (2009) MMN elicitation during natural sleep to violations of an auditory pattern. Brain research, 1290, 52-62.

Sharma, A. & Dorman, M.F. (1999) Cortical auditory evoked potential correlates of categorical perception of voice-onset time. The Journal of the Acoustical Society of America, 106, 1078-1083.

Sharma, A., Marsh, C.M. & Dorman, M.F. (2000) Relationship between N1 evoked potential morphology and the perception of voicing. The Journal of the Acoustical Society of America, 108, 3030-3035.

Sharma, M., Purdy, S.C., Newall, P., Wheldall, K., Beaman, R. & Dillon, H. (2006) Electrophysiological and behavioral evidence of auditory processing deficits in children with reading disorder. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 117, 1130-1144.

Sidtis, J.J. (1981) The complex tone test: implications for the assessment of auditory laterality effects. Neuropsychologia, 19, 103-111.

Sigalovsky, I.S., Fischl, B. & Melcher, J.R. (2006) Mapping an intrinsic MR property of gray matter in auditory cortex of living humans: a possible marker for primary cortex and hemispheric differences. NeuroImage, 32, 1524-1537.

Soekadar, S.R., Witkowski, M., Cossio, E.G., Birbaumer, N., Robinson, S.E. & Cohen, L.G. (2013) In vivo assessment of human brain oscillations during application of transcranial electric currents. Nature communications, 4, 2032.

Sorokin, A., Alku, P. & Kujala, T. (2010) Change and novelty detection in speech and non-speech sound streams. Brain research, 1327, 77-90.

Stagg, C.J., Best, J.G., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kincses, Z.T., Morris, P.G., Matthews, P.M. & Johansen-Berg, H. (2009) Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 5202-5206.

Stagg, C.J., Jayaram, G., Pastor, D., Kincses, Z.T., Matthews, P.M. & Johansen-Berg, H. (2011) Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia, 49, 800-804.

Stagg, C.J. & Nitsche, M.A. (2011) Physiological basis of transcranial direct current stimulation. Neuroscientist, 17, 37-53.

Steinschneider, M., Nourski, K.V. & Fishman, Y.I. (2013) Representation of speech in human auditory cortex: is it special? Hearing research, 305, 57-73.

Studdert-Kennedy, M. & Mody, M. (1995) Auditory temporal perception deficits in the reading-impaired: A critical review of the evidence. Psychon Bull Rev, 2, 508-514.

Sulakhe, N., Elias, L.J. & Lejbak, L. (2003) Hemispheric asymmetries for gap detection depend on noise type. Brain and cognition, 53, 372-375.

Takao, H., Abe, O., Yamasue, H., Aoki, S., Sasaki, H., Kasai, K., Yoshioka, N. & Ohtomo, K. (2011) Gray and white matter asymmetries in healthy individuals aged 21-29 years: a voxel-based morphometry and diffusion tensor imaging study. Human brain mapping, 32, 1762-1773.

Takegata, R., Nakagawa, S., Tonoike, M. & Naatanen, R. (2004) Hemispheric processing of duration changes in speech and non-speech sounds. Neuroreport, 15, 1683-1686.

Tallal, P. (1980) Auditory temporal perception, phonics, and reading disabilities in children. Brain and language, 9, 182-198.

Tallal, P. (2004) Improving language and literacy is a matter of time. Nature reviews. Neuroscience, 5, 721-728.

Tallal, P. & Gaab, N. (2006) Dynamic auditory processing, musical experience and language development. Trends in neurosciences, 29, 382-390.

Tallal, P., Miller, S. & Fitch, R.H. (1993) Neurobiological basis of speech: a case for the preeminence of temporal processing. Annals of the New York Academy of Sciences, 682, 27-47.

Tallal, P., Miller, S.L., Bedi, G., Byma, G., Wang, X., Nagarajan, S.S., Schreiner, C., Jenkins, W.M. & Merzenich, M.M. (1996) Language comprehension in language-learning impaired children improved with acoustically modified speech. Science, 271, 81-84.

Tallal, P. & Newcombe, F. (1978) Impairment of auditory perception and language comprehension in dysphasia. Brain and language, 5, 13-34.

Tallal, P. & Piercy, M. (1973) Defects of non-verbal auditory perception in children with developmental aphasia. Nature, 241, 468-469.

Tallal, P. & Piercy, M. (1974) Developmental aphasia: rate of auditory processing and selective impairment of consonant perception. Neuropsychologia, 12, 83-93.

Tallal, P. & Stark, R.E. (1981) Speech acoustic-cue discrimination abilities of normally developing and language-impaired children. The Journal of the Acoustical Society of America, 69, 568-574.

Tang, M.F. & Hammond, G.R. (2013) Anodal transcranial direct current stimulation over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding. The European journal of neuroscience, 38, 2802-2811.

Tervaniemi, M. & Hugdahl, K. (2003) Lateralization of auditory-cortex functions. Brain research. Brain research reviews, 43, 231-246.

Todd, J., Finch, B., Smith, E., Budd, T.W. & Schall, U. (2011) Temporal processing ability is related to ear-asymmetry for detecting time cues in sound: a mismatch negativity (MMN) study. Neuropsychologia, 49, 69-82.

Toscano, J.C., McMurray, B., Dennhardt, J. & Luck, S.J. (2010) Continuous perception and graded categorization: electrophysiological evidence for a linear relationship between the acoustic signal and perceptual encoding of speech. Psychological science, 21, 1532-1540.

Tzovara, A., Rossetti, A.O., Spierer, L., Grivel, J., Murray, M.M., Oddo, M. & De Lucia, M. (2013) Progression of auditory discrimination based on neural decoding predicts awakening from coma. Brain : a journal of neurology, 136, 81-89.

Uther, M., Jansen, D.H., Huotilainen, M., Ilmoniemi, R.J. & Naatanen, R. (2003) Mismatch negativity indexes auditory temporal resolution: evidence from event-related potential (ERP) and event-related field (ERF) recordings. Brain research. Cognitive brain research, 17, 685-691.

Vandermosten, M., Boets, B., Luts, H., Poelmans, H., Golestani, N., Wouters, J. & Ghesquiere, P. (2010) Adults with dyslexia are impaired in categorizing speech and nonspeech sounds on the basis of temporal cues. Proceedings of the National Academy of Sciences of the United States of America, 107, 10389-10394.

Vanneste, S. & De Ridder, D. (2011) Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. The European journal of neuroscience, 34, 605-614.

Vestito, L., Rosellini, S., Mantero, M. & Bandini, F. (2014) Long-term effects of transcranial direct-current stimulation in chronic post-stroke aphasia: a pilot study. Frontiers in human neuroscience, 8, 785.

von Steinbuchel, N., Wittmann, M., Strasburger, H. & Szelag, E. (1999) Auditory temporal-order judgement is impaired in patients with cortical lesions in posterior regions of the left hemisphere. Neuroscience letters, 264, 168-171.

Walker, K.M., Hall, S.E., Klein, R.M. & Phillips, D.P. (2006) Development of perceptual correlates of reading performance. Brain research, 1124, 126-141.

Warrier, C., Wong, P., Penhune, V., Zatorre, R., Parrish, T., Abrams, D. & Kraus, N. (2009) Relating structure to function: Heschl's gyrus and acoustic processing. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 61-69.

Weintraub, S., Mesulam, M.M. & Kramer, L. (1981) Disturbances in prosody. A right-hemisphere contribution to language. Archives of neurology, 38, 742-744.

Wernicke, C. (1874) Der Aphasische Symptomenkomplex.Eine psychologische Studie auf anatomischer Basis. . Breslau (Germany): Cohn und Weigert., p 72.

Wetzel, W., Ohl, F.W. & Scheich, H. (2008) Global versus local processing of frequency-modulated tones in gerbils: an animal model of lateralized auditory cortex functions. Proceedings of the National Academy of Sciences of the United States of America, 105, 6753-6758.

Witkowski, M., Garcia-Cossio, E., Chander, B.S., Braun, C., Birbaumer, N., Robinson, S.E. & Soekadar, S.R. (2015) Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS). NeuroImage.

Woldorff, M.G., Gallen, C.C., Hampson, S.A., Hillyard, S.A., Pantev, C., Sobel, D. & Bloom, F.E. (1993) Modulation of early sensory processing in human auditory cortex during auditory selective attention. Proceedings of the National Academy of Sciences of the United States of America, 90, 8722-8726.

Wu, D., Wang, J. & Yuan, Y. (2015) Effects of transcranial direct current stimulation on naming and cortical excitability in stroke patients with aphasia. Neuroscience letters, 589, 115-120.

Zaehle, T., Beretta, M., Jancke, L., Herrmann, C.S. & Sandmann, P. (2011) Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale, 215, 135-140.

Zaehle, T., Geiser, E., Alter, K., Jancke, L. & Meyer, M. (2008) Segmental processing in the human auditory dorsal stream. Brain research, 1220, 179-190.

Zaehle, T., Jancke, L., Herrmann, C.S. & Meyer, M. (2009) Pre-attentive spectro-temporal feature processing in the human auditory system. Brain topography, 22, 97-108.

Zaehle, T., Jancke, L. & Meyer, M. (2007) Electrical brain imaging evidences left auditory cortex involvement in speech and non-speech discrimination based on temporal features. Behavioral and brain functions : BBF, 3, 63.

Zaehle, T., Wustenberg, T., Meyer, M. & Jancke, L. (2004) Evidence for rapid auditory perception as the foundation of speech processing: a sparse temporal sampling fMRI study. The European journal of neuroscience, 20, 2447-2456.

Zatorre, R.J. & Belin, P. (2001) Spectral and temporal processing in human auditory cortex. Cerebral cortex, 11, 946-953.

Zatorre, R.J., Belin, P. & Penhune, V.B. (2002) Structure and function of auditory cortex: music and speech. Trends in cognitive sciences, 6, 37-46.

Zatorre, R.J. & Gandour, J.T. (2008) Neural specializations for speech and pitch: moving beyond the dichotomies. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 363, 1087-1104.

Zhang, L., Xi, J., Xu, G., Shu, H., Wang, X. & Li, P. (2011) Cortical dynamics of acoustic and phonological processing in speech perception. PloS one, 6, e20963.

Curriculum Vitae

M.Sc. Kai Heimrath

Personal data

Date of birth: 06/14/1984

Place of birth: Haldensleben

Gender: male

Marital status: single

Citizenship: german

Education

04/2012 – present	**Otto-von-Guericke University Magdeburg, Germany** Department of Neurology, PhD student (Psychology)
10/2009 – 01/2012	**Otto-von-Guericke University Magdeburg, Germany** Master of Science in Integrative Neuroscience
10/2006 – 10/2009	**Technical University Braunschweig, Germany** Bachelor of Science in Biology

Employment

since 04/2012	**Otto-von-Guericke University Magdeburg, Germany** Department of Neurology *Post-graduate researcher*

09/2014 – 12/2014	**Harvard Medical School, Boston, MA, U.S.** Children’s Hospital Boston Department of Medicine, Division of Developmental Medicine: Laboratories of Cognitive Neuroscience *Research Assistant*
03/2011 – 04/2012	**Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Magdeburg, Germany** *Student Research Assistant*

____

M.Sc. Kai Heimrath

List of Publications

Heimrath, K., Fiene, M., Rufener K., and Zaehle T. (2016). Modulating human auditory processing by transcranial electrical stimulation. *Front Cell Neurosci*. doi: 10.3389/fncel.2016.00053.

Heimrath, K., Fischer, A., Heinze, H.J., and Zaehle, T. (2016). Changed categorical perception of consonant-vowel syllables induced by transcranial direct current stimulation (tDCS). *BMC Neurosci* 17, 8. doi: 10.1186/s12868-016-0241-3.

Heimrath, K., Breitling, C., Krauel, K., Heinze, H.J., and Zaehle, T. (2015). Modulation of pre-attentive spectro-temporal feature processing in the human auditory system by HD-tDCS. *Eur J Neurosci* 41, 1580-1586. doi: 10.1111/ejn.12908.

Kuehne, M., **Heimrath, K.**, Heinze, H.J., and Zaehle, T. (2015). Transcranial direct current stimulation of the left dorsolateral prefrontal cortex shifts preference of moral judgments. *PLoS One* 10, e0127061. doi: 10.1371/journal.pone.0127061.

Heimrath, K., Kuehne, M., Heinze, H.J., and Zaehle, T. (2014). Transcranial direct current stimulation (tDCS) traces the predominance of the left auditory cortex for processing of rapidly changing acoustic information. *Neuroscience* 261, 68-73.doi: 10.1016/j.neuroscience.2013.12.031.

Heimrath K, Sandmann P, Becke A, Müller NG, Zaehle T (2012) Behavioral and electrophysiological effects of transcranial direct current stimulation of the parietal cortex in a visuo-spatial working memory task. *Front Psychiatry.;3:56.*

Statutory declaration

Hiermit erkläre ich, dass ich die von mir eingereichte Dissertation zu dem Thema:

„Changed temporal processing in the human auditory cortex by transcranial direct current stimulation”

selbständig verfasst, nicht bereits als Dissertation verwendet habe und die benutzten Hilfsmittel und Quellen vollständig angegeben wurden. Weiterhin erkläre ich, dass ich weder diese noch eine andere Arbeit zur Erlangung des akademischen Grades doctor rerum naturalium (Dr. rer. nat.) an anderen Einrichtungen eingereicht habe.

Magdeburg, den 07.06.2016

M.Sc. Kai Heimrath