Aus der Klinik für Neurologie mit Experimenteller Neurologie der
Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

“Using Anodal tDCS in an associative learning paradigm in healthy older adults“

zur Erlangung des akademischen Grades

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von

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PREFACE

Partial results of the present work have already been published in the following publication:

Antonenko, D., Hayek, D., Netzband, J., Grittner, U., & Flöel, A. (2019). tDCS-induced episodic memory enhancement and its association with functional network coupling in older adults. Sci Rep, 9(1), 2273. doi:10.1038/s41598-019-38630-7

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AD – Alzheimer's disease

ADLs – Activities of daily living

AG – Angular gyrus

atDCS – Anodal transcranial direct current stimulation

CRUNCH – Compensation-related utilization of neural circuits hypothesis

dlPFC – Dorsolateral prefrontal cortex

dmPFC – Dorsal medial prefrontal cortex

DMN – Default mode network

GDS – Geriatric depression scale

HAROLD – Hemispheric asymmetry reduction in older adults

HPC – Hippocampus

IFG – Inferior frontal gyrus

IPL – Inferior parietal lobule

MCI – Mild cognitive impairment

MRI – Magnetic resonance imaging

MTL – Medial temporal lobe

MWT – Multiple-choice vocabulary intelligence test

NIBS – Non-invasive brain stimulation

PFC – Prefrontal cortex

PSA – Process-specific alliance

RB – Response bias

RT – Reaction time

stDCS – Sham transcranial direct current stimulation

tDCS – Transcranial direct current stimulation

VPC – Ventral parietal cortex

WM – Working memory

ABSTRACT

ENGLISH

Introduction: Anodal transcranial direct current stimulation (atDCS) has been used for years to modulate cognitive performance. To date, research has yielded mixed results due to different experimental designs. This thesis aims to explore open questions in modulating episodic memory in older adults and the varying responsiveness of the ageing brain to atDCS.

Methods: In this study, 34 healthy older adults between 51 and 80 years received 20 min of atDCS over the left temporo-parietal junction (TPJ) with the cathode covering the right fronto-orbital region while performing a picture-word associative learning paradigm. Using a single-blind, randomized and controlled crossover design, each participant underwent an anodal and sham tDCS condition. The episodic memory performance was measured by learning and by immediate and delayed retrieval.

Results: Linear mixed models displayed improved episodic memory performance in healthy older adults. Participants receiving atDCS had superior learning and immediate retrieval performance in a picture-word associative learning paradigm. A 20-min delayed retrieval and both hit and correct-rejection rates, according to signal detection theory, revealed no significant results.

Discussion: In summary, evidence exists that a single session of atDCS, applied over the left TPJ, can modulate episodic memory performance in healthy older adults. Nevertheless, there are many unsolved issues causing variation in the aged brain's responsiveness to atDCS, and these issues must be addressed in future studies. Finally, atDCS might serve as a cognitive enhancement device for vulnerable populations, such as older adults in general and patients with early stages of Alzheimer's disease (AD) or post-stroke aphasia.

GERMAN

Einleitung: Die anodale transkranielle Gleichstromstimulation (atDCS) wird seit mehreren Jahren als eine vielversprechende Technik zur Modulation von kognitiven Leistungen verwendet. Es gibt Hinweise, dass Unterschiede in der Wirksamkeit für atDCS in jüngeren und älteren Erwachsenen bestehen. Zudem bleiben, aufgrund von

heterogenen Forschungsdesigns, viele methodische Aspekte ungeklärt. Diese Doktorarbeit bearbeitet offene Fragen über episodische Gedächtnisleistungen von älteren Erwachsenen und bespricht mögliche Ursachen veränderter Wirksamkeit von atDCS.

Methoden: In einer einfach verblindeten, randomisierten und kontrollierten Studie im Crossover-Design wurde der Effekt von atDCS über dem linken posterioren temporoparietalen Kortex (TPJ) mit kontralateraler supraorbitaler Kathode untersucht. 34 gesunde ältere Probanden zwischen 51 und 80 Jahren, bekamen jeweils in zwei Versuchsbedingungen für 20 Minuten atDCS oder eine Scheinstimulation (stDCS) appliziert. Die Lernaufgabe, bestand in einem assoziativen Verknüpfen eines bekannten Objektes mit einem Kunstwort. Es wurde der Lernerfolg, sowie die Leistungen im anschließenden und verzögerten Abruf gemessen.

Ergebnisse: Gemischte lineare Modelle zeigten eine Verbesserung der episodischen Gedächtnisleistung von gesunden älteren Erwachsenen. Unter atDCS zeigten die Teilnehmenden bessere Leistungen beim Lernen und anschließenden Abrufen in einem assoziativen Lernparadigma. Ein verzögerter Abruf und die Auswertung der in der Signalentdeckungstheorie verwendeten einzelnen Maßzahlen zeigten keine signifikanten Unterschiede zwischen den Stimulationsbedingungen.

Diskussion: Zusammenfassend lässt sich sagen, dass atDCS über dem linken posterioren temporoparietalen Kortex nach einer einzelnen Sitzung zu einer Verbesserung der episodische Gedächtnisleistung bei älteren Erwachsenen führt. Trotzdem gibt es weiterhin offene Fragen bezüglich der unterschiedlichen Wirksamkeit in den verschiedenen Altersgruppen. In Zukunft besteht die Möglichkeit, dass vulnerable Gruppen wie ältere, gesunde Erwachsene, Patienten im frühen Stadium einer Demenz vom Alzheimer-Typ (AD) oder einer Aphasie nach einem Schlaganfall von einer Steigerung der kognitiven Fähigkeiten durch atDCS profitieren könnten.

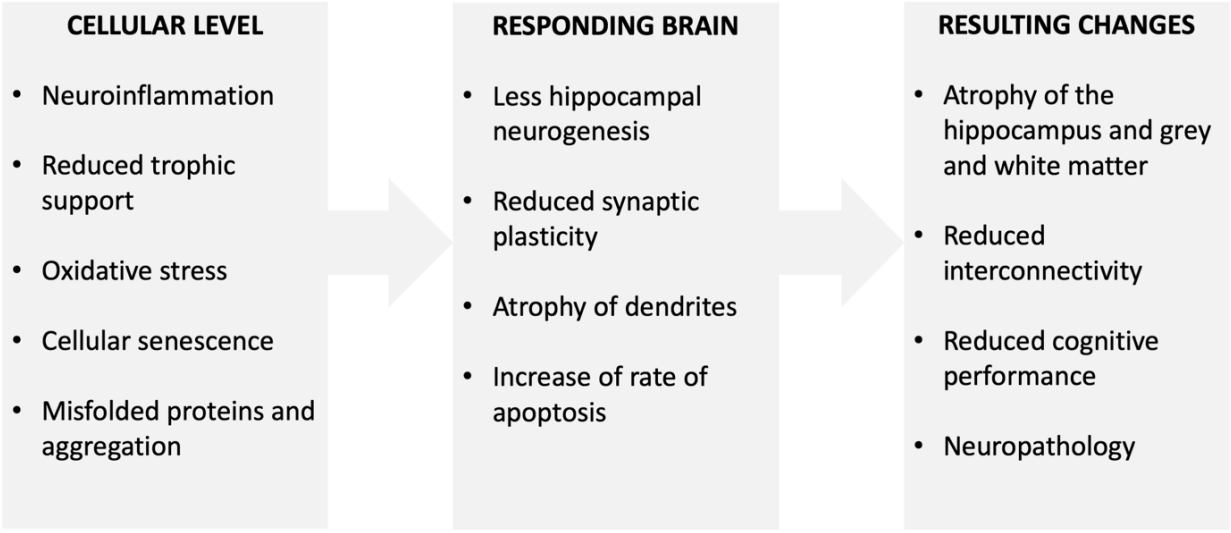
1. INTRODUCTION

For an independent life, intact memory and the ability to learn new things are of great importance. From childhood to older age, the brain is faced with different demands. While language learning processes are established in the first few years of life (Buchweitz, 2016), maintaining memory and cognition as we age is a lifelong task (Grotz et al., 2018). Considering that cognitive abilities, functional connections and the structure of the brain change during one's lifespan (Gutchess, 2014), a broad overview for older adults and its compensation is provided. The focus is on areas and processes that are thought to be related to the task used in this thesis.

1.1 The ageing brain and theories of compensation

Normal ageing from a cognitive view is highly heterogeneous among individuals and therefore described by changes that do not impair one's ability to perform activities of daily living (ADLs; (Harada, Natelson Love, & Triebel, 2013). As with other organ systems, the brain is exposed to different stressors during a person's lifespan and undergoes several processes contributing to functional and structural changes. Neuronal cells are exposed to oxidative stress, reduced trophic support or aggregation of misfolded proteins (Figure 1; (Bettio, Rajendran, & Gil-Mohapel, 2017).

Figure 1 Processes of the ageing brain; adapted from Bettio et al. (2017).



During the ageing process, the brain is exposed to several factors contributing to functional and structural changes. These processes can be regulated or delayed by interventions such as physical activities, cognitive stimulation or diet.

A series of common changes have been described and quantitively linked to cognitive decline, including a decrease in grey matter volume, white matter integrity and atrophy of

the whole brain (Fotenos, Snyder, Girton, Morris, & Buckner, 2005). However, brain volume reduction is not equally spread over the whole brain: while the prefrontal cortex (PFC) and superior temporal gyri (including the primary auditory cortex and Wernicke's area) are most dramatically affected, other parts, such as the temporal, parahippocampal, entorhinal and anterior cingulate gyrus, are relatively well preserved (Fjell et al., 2009).

Apart from structural changes, the task-associated activation patterns of brain areas and networks also change (Cheryl L. Grady, Bernstein, Beig, & Siegenthaler, 2002). For instance, a bihemispheric activation of the temporoparietal cortex during memory performance was observed in older adults, while only left hemisphere activation was present in young participants. Elsewhere, grey matter atrophy of memory-associated areas such as the middle frontal gyrus is positively correlated with increased activity of the inferior parietal PFC and the dorsolateral PFC (dlPFC; (C. Grady, 2012). Furthermore, altered activation and reduced interconnectivity are not strictly correlated with behavioural deficits and decreased ability in aspects of cognitive performance such as language learning (Fjell et al., 2009). However, evidence suggests that age-related cortical thinning of frontal cortex areas and reduced network connectivity separates poor from high cognitive performers in a working memory (WM) performance test for older adults (Nissim et al., 2016). In studies on ageing, hippocampus (HPC) atrophy was associated with a reduction in learning and memory abilities (Bettio et al., 2017). The vulnerability of the HPC is supported by the fact that this region presented a breakdown in blood barrier during both normal and pathological ageing (Montagne et al., 2015).

In general, evidence exists that the brain in older adults reorganizes to compensate for loss of volume as well as structural and functional connectivity to maintain cognitive performance (Gutchess, 2014; Ji et al., 2018). The difference in the decline of single cognitive domains varies and is influenced by changes in non-cognitive domains such as semantic knowledge or emotional regulation (Martins, Joanette, & Monchi, 2015). Different theories have been used to explain variations in cognitive performance in older healthy individuals.

A common and widely discussed theory regarding the variation in cognitive performance in older adults is the compensation-related utilization of neural circuits hypothesis (CRUNCH). It states that older people over-activate task-specific pathways to overcome the reduced efficiency that appears with ageing (Reuter-Lorenz & Cappell, 2008). However, with a higher task load at a certain point (the CRUNCH point), the circuit is

overloaded, which leads to an under-recruitment and worsening of performance results. This phenomenon of over-recruitment is also seen in young adults, albeit starting at a higher task demand (Martins et al., 2015).

Other theories that should be mentioned are the concept of cognitive reserve, the posterior-to-anterior shift and the hemispheric asymmetry reduction in older adults (HAROLD). The concept of cognitive reserve revolves around physical preservation of brain tissue over one's lifespan. It postulates that the quantitative difference in neurons, synapses and brain volume is connected to neuronal reserve (the flexibility, efficiency and capacity of networks) and to neural compensation; with more tissue, the brain has increased abilities to cope with different brain pathologies, including ageing itself (McGarrigle, Irving, van Boxtel, & Boran, 2019; Stern, 2009). Moreover, the posterior-to-anterior shift in ageing describes a reduction in posterior activity and an increase in anterior activity. This is interpreted as a compensatory mechanism of the frontal lobe to overcome neuronal decline in other areas. The phenomenon does not seem to be task- or difficulty-related; however, debate is ongoing (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). Finally, the HAROLD states a decrease in the lateralization of PFC activity during performance. Older age is associated with more symmetric activation patterns in the PFC. This is interpreted either as a compensation or as a result of dedifferentiation (Cabeza, 2002).

1.2 Language, memory processes and underlying neuronal mechanisms

From a naturalistic standpoint, learning a language is described as a fluid construct of multiple pathways (Casaletto et al., 2017). Understanding cortical language representation is thus challenging (Wortman-Jutt & Edwards, 2017). Price (2000) proposed a model based on lesion and imaging studies. Depending on the stimulus modality, specific areas related to a different function in the language network are activated. In language learning, the acquisition of a novel lexicon is referred to as episodic memory (Table 1; (Casaletto et al., 2017) and is highly connected to age-related decline (Reuter-Lorenz & Park, 2010). Therefore, studying changes in episodic memory is suitable to gain insight into differences in memory performance and ageing (Antonenko, Faxel, Grittner, Lavidor, & Flöel, 2016; Breitenstein & Knecht, 2002).

Learning a novel lexicon contributes by the activation of brain areas such as the left HPC, the left fusiform gyrus and left inferior parietal lobule (IPL; (Breitenstein et al., 2005). For

encoding and storage, stimuli are received through primary sensory areas and are first processed in the HPC. Through patterned network activity in the HPC-entorhinal axis (such as travelling waves during sleep), the information is thought to be stored in the neocortex via transformation (Dudai, Karni, & Born, 2015; Squire & Alvarez, 1995). Elsewhere, the HPC receives information that is already stored in neocortical areas (Kitamura et al., 2017). The integration of new information into prior knowledge affects the likelihood that novel information will be stored (Gilboa & Marlatte, 2017). According to the transformation hypothesis, as long as a memory trace persists in the HPC, episodic details (time and place) remain intact. However, after transfer to the neocortex, these details get lost. To maintain and strengthen the memory traces, they need to be reactivated through attentional refreshing or articular rehearsal (Cowan, 1992). During retrieval, this HPC-neocortex connection must be reactivated using a cue.

Table 1 Long-term memory; adapted from Squire (2004)

Memory types	Function
Declarative (explicit)	Semantic (facts, concepts) Episodic (events, experiences)
Non-declarative (implicit)	Procedural skills (e.g. motor, perceptual, cognitive) Priming (perceptual, semantic) Conditioning Non-associative learning (habituation, sensitization)

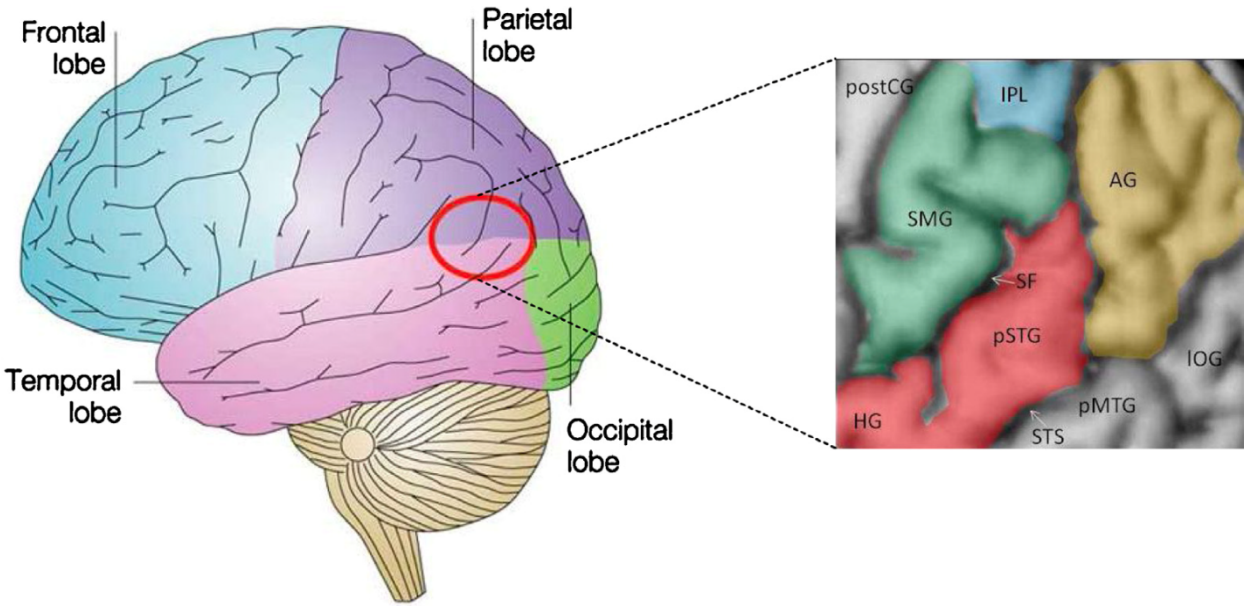
Long-term memory consists of declarative (semantic and episodic) and non-declarative (procedural skills, priming, conditioning and non-associative learning) memory.

In the default mode network (DMN), which participates modestly in the retrieval of episodic memory, the HPC processes network information (Kim, 2016) and has been referred to as a hub for regions dealing with episodic memory (Moscovitch, Cabeza, Winocur, & Nadel, 2016). In a review, Andrews-Hanna et al. (2010), using functional connectivity and graph theory, describe the DMN as a heterogenous and interacting large-scale brain network with a midline core (posterior cingulate cortex and anterior medial PFC) and two subsystems: the dorsal medial PFC (dmPFC) subsystem and the medial temporal lobe (MTL) subsystem. The HPC and the posterior IPL, as part of the MTL subsystem, and the angular gyrus (AG; part of temporo-parietal junction [TPJ]), as part of the dmPFC subsystem, are thought to be involved in episodic memory processing and in familiarity and recollection signals (Rugg & Vilberg, 2013). Moreover, it is widely

believed that the functional connectivity of the DMN decreases with ageing (Tatti, Rossi, Innocenti, Rossi, & Santarnecchi, 2016). However, some parts of the DMN exhibit stronger functional connectivity in older adults (perirhinal cortex and PFC) without a superior cognitive performance to older adults with weaker functional connectivity. This is in contrast to other parts (HPC and parietal cortex), which display a stronger connectivity in younger adults with a superior recollective ability (C. L. Grady & Ryan, 2017).

A greater connectivity among regions, such as the PFC, ventral parietal cortex (VPC) and caudate nucleus, is associated with better cognitive performance in memory retrieval (Geib, Stanley, Dennis, Woldorff, & Cabeza, 2017), of which the interactions are co-ordinated by the left HPC (Geib et al., 2017). Interestingly, processing episodic and semantic learning is possible without involvement of the HPC, but is greatly improved by its use. This illustrates possibilities for compensation in the brain (Stern, 2009).

Figure 2 Location and gyri constituting the temporo-parietal junction (TPJ; (Donaldson, Rinehart, & Enticott, 2015).



Postcentral gyrus (postCG), inferior parietal lobule (IPL), supramarginal gyrus (SMG), angular gyrus (AG), sylvian fissure (SF), posterior part of the superior temporal gyrus (pSTG), Heschl's gyri (HG), superior temporal sulcus (STS), posterior middle temporal gyrus (pMTG), inferior occipital gyrus (IOG).

Another brain area associated with encoding, storage and retrieval of language (episodic memory) is the TPJ of the language-dominant hemisphere. The term TPJ refers to parts of the left posterior superior temporal cortex, IPL, lateral occipital cortex and posterior end of the superior temporal sulcus (Figure 2). Among other roles, it is important for attentional and memory functions, and it is relevant for the integration of different types of audio-

visual information (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Friederici, 2011; Krall et al., 2015).

The integration of information includes functional and topographical connection to the ventral and dorsal pathways, which are involved in language processes such as differentiation of speech and non-speech, comprehension of language, tonal pitch, semantics and syntactic processing (Friederici, 2011). The connection between visual and auditory inputs on the one hand and language (word form) processing on the other is thought to occur in the Wernicke's area (Brodmann area 22, located at the posterior part of the superior temporal gyrus).

The superior posterior temporal lobe also responds to familiarity of auditory spectral patterns, the maintenance phase of phonological WM and the perception of hearing speech (Price, 2012). The TPJ is part of resting state networks such as the DMN, the frontoparietal control network (FCN) and the cingulo-opercular network (CON; (Igelstrom & Graziano, 2017).

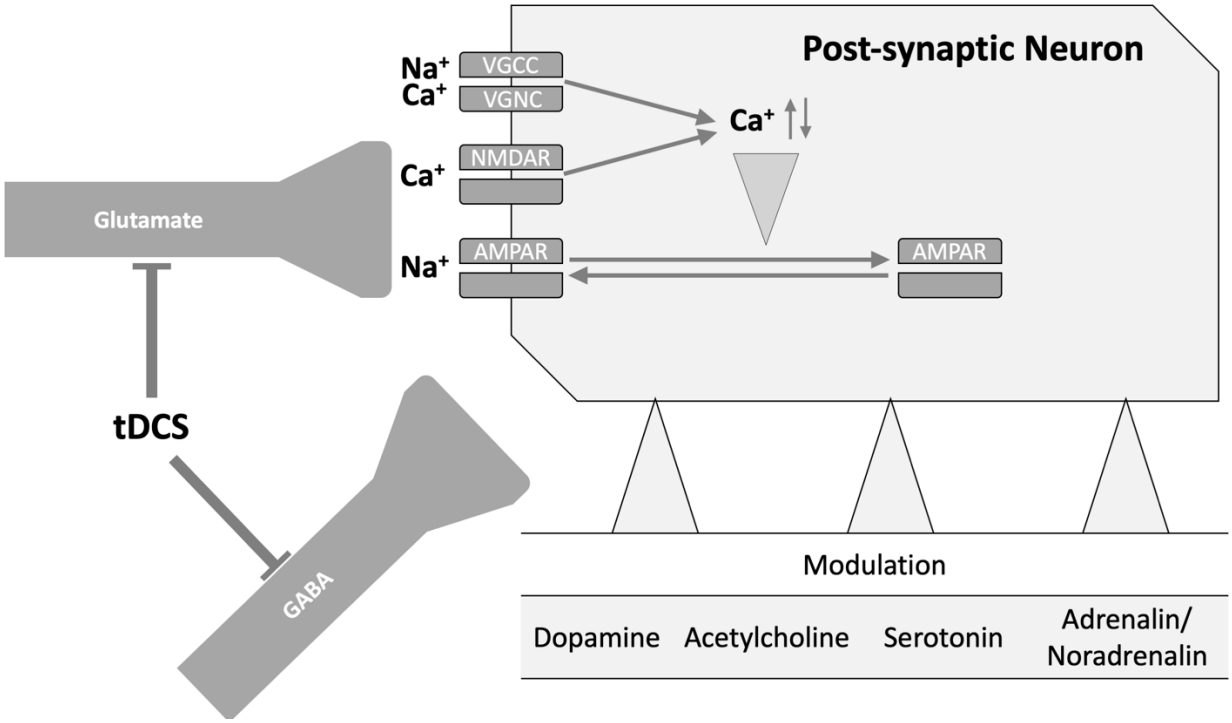
1.3 Modulation of cortical excitability by transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation (NIBS) that was first used during the 1980s in animal experiments and increased in popularity for human subjects around 2000. In an influential study, Nitsche and Paulus (2000) observed a modulation of excitability in neurons of the motor cortex using anodal and cathodal tDCS. These findings were confirmed by several studies modulating motor learning via the primary motor cortex, as well as measuring cognitive performance during and after tDCS (Nitsche, Schauenburg, et al., 2003; Perceval, Flöel, & Meinzer, 2016).

To clarify how tDCS-induced changes work at a cellular level, it should be noted that the electrical potential at the neuronal membrane is essentially thought to be modulated. The activity is naturally determined by voltage-gated and ligand-gated ion channels; however, when an electronic field via direct current is induced, the membrane potential of a cell changes. When using anodal tDCS (atDCS), the resting membrane potential is modulated, and less afferent activity is needed to create an action potential. This means that, in contrast to transcranial magnetic stimulation or deep brain stimulation, neither action potentials nor neuronal activity is directly induced (Polania, Nitsche, & Ruff, 2018; Stagg et al., 2018; Woods et al., 2016).

When atDCS is properly applied, it is thought to induce synaptic plasticity in the form of long-term depression and long-term potentiation (Figure 3). These effects are believed to be directly dependent on current intensity. In fact, increasing current does not automatically lead to increased synaptic plasticity and hence better performance, but rather contrary effects (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). Furthermore, the mechanisms of neuronal plasticity during and after stimulation are thought to differ – there are online effects and after-effects (Gomes-Osman et al., 2018). For the latter, NMDA receptors are important, as has been demonstrated by studies using NMDA receptor antagonists, which block tDCS-induced plasticity. This offers insight into the dependency on substances in terms of altering plasticity and chemical synapses (Liebetanz, Nitsche, Tergau, & Paulus, 2002).

Figure 3 TDCS mechanism; adapted from Stagg, Antal, and Nitsche (2018).



Transcranial direct current stimulation (tDCS) induces plasticity of glutaminergic synapses by de- and hyperpolarizing the neuronal membrane, thereby increasing or decreasing calcium influx through NMDA receptors (NMDARs) and voltage-gated calcium channels (VGCCs)*. Intracellular calcium concentration regulates AMPA receptor (AMPAR) expression and therefore the strengthening or weakening of the synaptic connection. These effects are gated by decreased gamma-aminobutyric acid (GABA) activity and modulated by neuromodulators such as dopamine or acetylcholine.* Voltage-gated sodium channels (VGSC).

A source of variation in the effectiveness of tDCS is the orientation and type of neurons beneath the anode and cathode. First, due to brain folding, the orientation of axons and dendrites towards an induced electric field vector varies and therefore can alter excitability and inhibition (Lemaitre et al., 2012). Second, depending on the type of neuron (e.g. interneurons or pyramidal neurons), the induced polarization is different, and these

neurons consequently respond differently to the electric field (Kabakov, Muller, Pascual-Leone, Jensen, & Rotenberg, 2012; Stagg et al., 2018). The induced electric field reaches not only superficial neurons but also deeper brain regions; this is important because ongoing cognitive processes rely on both certain brain areas and a neuronal network: network activity-dependent model (Fertonani & Miniussi, 2016).

1.4 Usage of anodal tDCS for older adults and hypotheses

The number of research groups using tDCS protocols is rising; however, protocols often differ in duration, intensity, electrode size and placement (Klooster et al., 2016). As a result, many methodical and physiological issues, such as understanding the mediating substrates, mechanism of action, application methods, adverse events and safety, focality, after-effects or induced plasticity, must be clarified. A review by Prehn and Flöel (2015) regarding the usage of atDCS in older age, including healthy participants and people suffering from mild cognitive impairment (MCI) or Alzheimer's disease (AD), provides a broad overview of this topic.

As current comprehensive reviews of the entire topic of tDCS are available (Jamil et al., 2017; Matsumoto & Ugawa, 2017; Polania et al., 2018; Woods et al., 2019), this thesis focuses on issues regarding atDCS as an easy-to-apply method to alter brain functionality in older adults and explores open questions in modulating episodic memory using atDCS over the left temporoparietal cortex and a cathode placed over the contralateral supraorbital area. Validating findings from young people (Flöel, Roesser, Michka, Knecht, & Breitenstein, 2008) in older populations is crucial because older adults demonstrate different network activation in several brain areas (Perceval et al., 2016) and perform more poorly than young adults in cognitive tests (Antonenko et al., 2016). Especially when initially low performers are thought to profit from atDCS, high performers do not, as demonstrated by recent studies (Fertonani & Miniussi, 2016; Hsu, Tseng, Liang, Cheng, & Juan, 2014).

1.4.1 Hypotheses

We hypothesize that healthy older adults receiving atDCS display better learning performance as well as immediate and delayed retrieval performance in a picture-word associative learning paradigm, compared to sham tDCS (stDCS):

Hypothesis 1: Participants receiving atDCS over the left temporoparietal cortex display better learning performance compared to stDCS.

$H0_1$: $\mu_{atDCS\_Learning\%correct} = \mu_{stDCS\_Learning\%correct}$

$H1_1$: $\mu_{atDCS\_Learning\%correct} > \mu_{stDCS\_Learning\%correct}$

Hypothesis 2: Participants receiving atDCS over the left temporoparietal cortex display better performance in an immediate retrieval compared to stDCS.

$H0_2$: $\mu_{atDCS\_R1\%correct} = \mu_{stDCS\_R1\%correct}$

$H1_2$: $\mu_{atDCS\_R1\%correct} > \mu_{stDCS\_R1\%correct}$

Hypothesis 3: Participants receiving atDCS over the left temporoparietal cortex display better performance in a delayed retrieval compared to stDCS.

$H0_3$: $\mu_{atDCS\_R2\%correct} = \mu_{stDCS\_R2\%correct}$

$H1_3$: $\mu_{atDCS\_R2\%correct} > \mu_{stDCS\_R2\%correct}$

Additionally, for each hypothesis, both hit and correct-rejection rates as well as no responses are calculated and compared.

To test for the influence of atDCS on reaction times (RTs), the RTs are compared between conditions. Then, to detect changes in mood (positive and negative affect schedule [PANAS]) and WM (Digit Span) between the third and fourth sessions and between conditions, PANAS and Digit Span scores were also compared. Finally, the difficulty of the task and the adverse events are reported.

2. MATERIAL AND METHODS

The study was completed at the facilities of the NeuroCure Clinical Research Center and the Berlin Center for Advanced Neuroimaging, which are both part of the Charité – Universitätsmedizin Berlin. In addition, the Center for Stroke Research was involved in neuroradiological diagnostics. All procedures were standardized and written in standard operating procedure protocols, and the data acquisition and storage followed the Berliner Datenschutzgesetz – BlnDSG. The study was approved by the local ethics commission of the Charité – Universitätsmedizin Berlin: EA 1/117/15 and was conducted in accordance with the Declaration of Helsinki. The participants were recruited from a previous study, using postings in the area of the hospital Charité – Universitätsmedizin Berlin and local newspaper advertisements (e.g. Berliner Zeitung).

To be considered for inclusion, participants had to meet the following criteria: be between 50 and 80 years of age; be right-handed and a native German speaker; and have no

magnetic resonance imaging (MRI) contraindications, such as ferromagnetic implants, claustrophobia, pregnancy, tattoos, permanent makeup or implanted devices such as a pacemaker, an insulin pump or a cochlear implant. Furthermore, care was taken to ensure that no participants with cardiovascular and psychiatric diseases (e.g. depression) or alcohol and drug abuse were included. Importantly, neurological diseases such as previous strokes, transient ischemic attack, epilepsy, subjective cognitive impairment and memory problems in medical history also led to exclusion. All participants submitted written informed consent prior to the study and received 40 € in compensation upon completion. The participants were briefed to attend the sessions well rested, not to consume excessive amounts of alcohol the day before, not to smoke or consume caffeine-containing beverages for at least two hours before assessment and to refrain from sports that are more vigorous than regular daily physical activity , with the aim of having a baseline with stable neuronal excitability.

2.1 **Study design**

All participants underwent a telephone screening regarding health-related issues and MRI contraindications, and when they met these criteria, they were invited to attend four sessions. The first of these involved neuropsychological testing and intravenous blood collection. The neuropsychological testing included a neuropsychological assessment battery (CERAD-Plus, www.memoryclinic.ch), consisting of a broad range of cognitive functions to detect undiagnosed pre-existing conditions. To ensure that participants exhibited a strong right-handedness, the Edinburgh Handedness Inventory – laterality index ≥ 70; Oldfield (1972) – was utilised. Furthermore, the multiple-choice vocabulary intelligence test (German: *Mehrfachwahl Wortschatz Intelligenztest; MWT*) was used to estimate the crystallized intelligence level to detect participants with very low and low intelligence, who have values ≤20 (Lehrl, 2005). Further tests included a short version of the Geriatric Depression Scale (GDS), which is a self-report measure with values ≤5 indicating depression or AD in older adults (Sheikh & Yesavage, 1986), and the Digit Span as a test of short-term memory. Participants who had abnormalities (results below 1.5 SDs according to age- and education-related normative scores) in any of these tests were contacted by our study physician and encouraged to consult their family doctor and book a memory-related consultation hour at the Department of Neurology and Experimental Neurology at the Charité for further counsel. The second session was at the Berlin Center for Advanced Neuroimaging, where an MRI of the brain and a test trial

of the language learning paradigm were conducted (baseline). The test trial was done to minimize the training effect between the two subsequent stimulation sessions (Strobach, Antonenko, Schindler, Flöel, & Schubert, 2016). The study physician also discussed pathological findings in the MRI with the participant. The MRI data were analysed and published by Antonenko, Hayek, Netzband, Grittner, and Flöel (2019).

The third and fourth sessions were almost identical in procedure – the only difference being whether participants received sham or anodal stimulation. After placing the anode and cathode, all participants received written instruction to assure consistent experimental conditions; if questions arose, only word phrases from the previous set of instructions (see Appendix 1) were used. Afterwards, the associative language learning paradigm (Breitenstein et al., 2005; Breitenstein & Knecht, 2002) was conducted. To detect changes in mood and WM, PANAS (Watson, Clark, & Tellegen, 1988) and Digit Span assessments was conducted before and after the associative language learning paradigm. The PANAS consists of 10 positive and 10 negative items on a Likert scale ranging from 1 to 5. The higher the value, the more positive feelings were reported, and vice versa. At the end of the last session, the participants were asked to report adverse side-effects of atDCS retrospectively, for example itching, burning, pain or concentration problems. Moreover, possible problems related to the language learning paradigm, such as difficulty understanding instructions, the level of difficulty of the task, or the employment of different strategies, had to be reported.

2.2 **Behavioural paradigm**

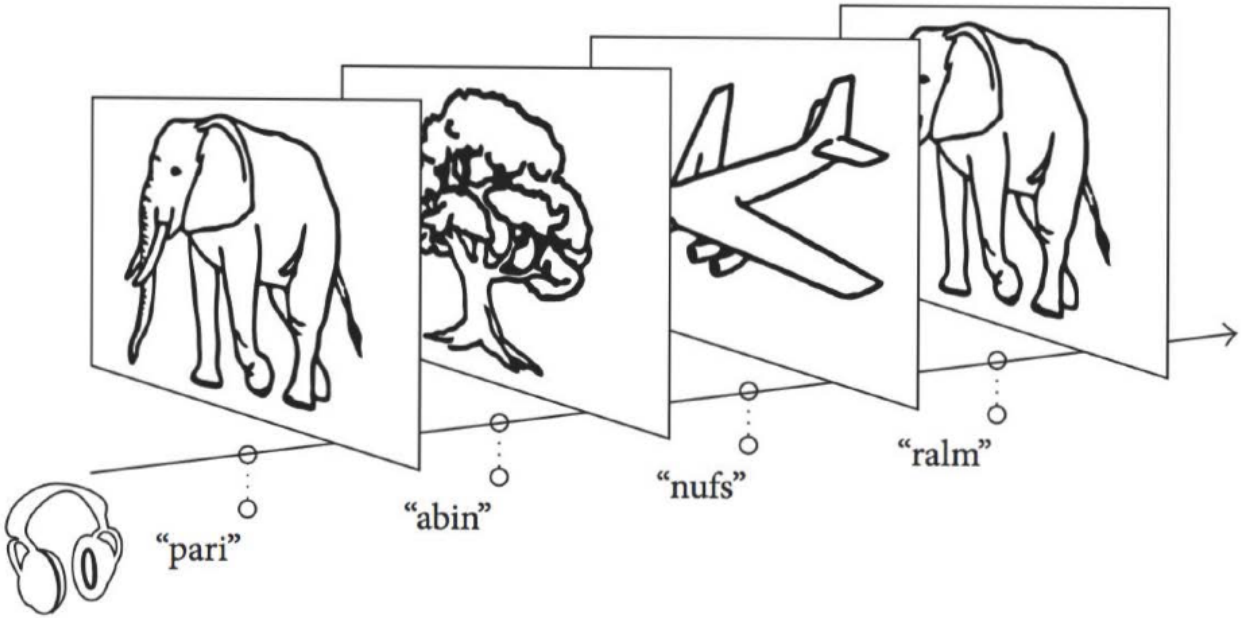
The paradigm utilized in this study is comparable to the acquisition of language in early childhood and was first used by Breitenstein and Knecht (2002). It is believed to infer conclusions about learning in a natural environment through the acquisition of new vocabulary by connecting a novel word to a known object via association. A difficulty-adapted version from previous studies was used to avoid non-compliance and floor effects. The paradigm was presented on a laptop using the software Presentation (Neurobehavioral Systems, http://www.neurobs.com/, version18.1) and headphones in a quiet room.

The participants were instructed to learn object-pseudoword pairs via association (see Appendix 1). For this, we presented 30 common objects such as a picture of an elephant, tree or airplane, originally by Snodgrass and Vanderwart (1980), while hearing a four-

letter pseudoword, such as “pari”, “abin”, “nufs” or “ralm” (Figure 4), read out by a male speaker. These 30 pseudowords were completely new to native German speakers, so a comparable start level was assumed.

Three different sets of stimuli (A, B, C) for each of the 30 novel objects and pseudowords were used in three sessions (baseline, stDCS, atDCS), and the order of the set presentation was balanced across participants. One session consisted of 600 trials divided into five learning blocks (120 trials per block), with short breaks in between. Each pseudoword was shown four times per learning block (L1 to L5), twice with the correct object and twice with an incorrect object. Each incorrect pairing was presented only once during the course of learning (L1–L5; 600 trials). This associative learning phase consisted of correct couplings appearing more frequently than arbitrary incorrect couplings at a ratio of 10:1.

Figure 4 Sequence of a learning block in the language learning paradigm (Antonenko et al., 2016).

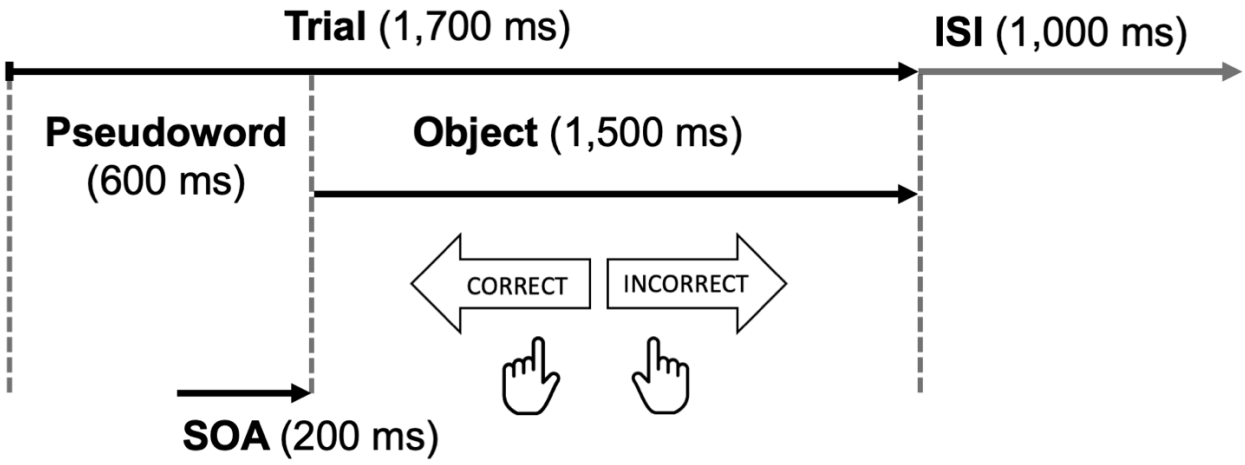


An example of the auditory sample with the subsequent presented visual stimulus.

The order of the trial presentation was randomized, and the participants were unaware of the underlying frequency principle. They were instructed to decide as quickly as possible

whether the pairs matched or not by pressing one of two response buttons, namely, “correct” or “incorrect”, using their left or right index finger (Figure 5).

Figure 5 Time procedure during a trial; adapted by (Antonenko et al., 2016).



Stimulus-onset asynchrony (SOA), interstimulus interval (ISI).

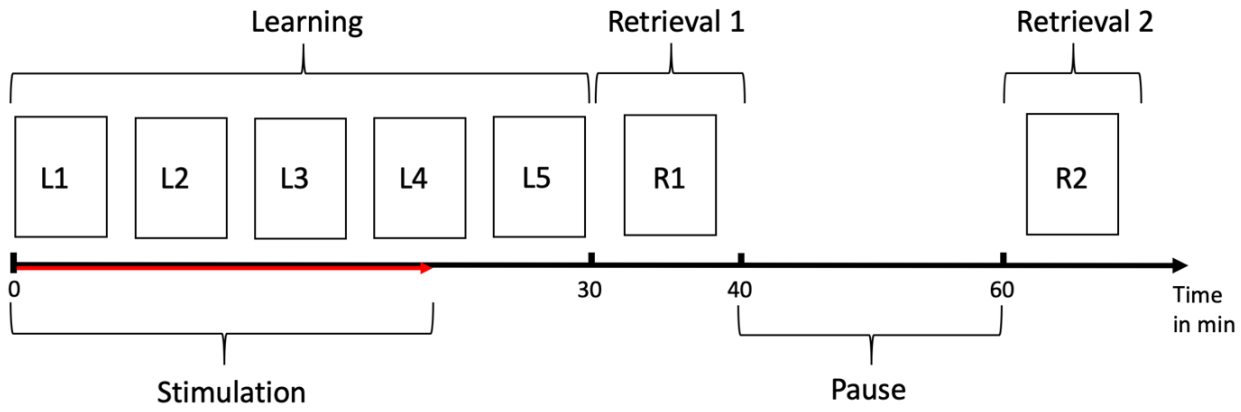
First, the auditory spoken pseudoword was read aloud (delivered over headphones) with a 200-ms delay, and the picture of the object was presented for 1,500 ms. Participants could only reply during the presentation of the object; the short time period was set to prevent the use of mnemonic strategies. If the time span was not adhered to, participants were encouraged to reply faster, and the item was classified as a "no response". The answers were partitioned into five categories pertaining to signal detection theory: hit, correct reject, false alarm, miss and no response (defined in Table 2).

Table 2 Categories according to signal detection theory.

Hit	Pseudoword-object pair **is correct** and has been **answered as correct**.
Correct reject	Pseudoword-object pair **is not correct** and has been **answered as incorrect**.
False alarm	Pseudoword-object pair **is not correct** and has been **answered as correct**.
Miss	Pseudoword-object pair **is correct** and has been **answered as incorrect**.
No response	Participant did **not reply in time**.

After learning, success was measured in a “transfer” task (retrieval blocks; R1 and R2; Figure 6). This section was conducted under the same conditions, but instead of the pictures (objects), the corresponding spoken German words were recited by a male speaker, followed by the pseudoword. The immediate retrieval (R1) was conducted directly after the last learning block (L5), and the delayed retrieval (R2) after a 20-min break. In the baseline session, only an immediate retrieval (R1) was executed. The frequency principle (two “correct” and two “incorrect” per block) and trial timings were identical to those in the learning phase. For further information on the protocol, please see Breitenstein and Knecht (2002).

Figure 6 Timeline: stimulation/performance.



L1 to L5 (Learning blocks 1 to 5); R1 and R2 (Retrieval blocks 1 and 2). The stimulation lasted 20 min (red arrow).

2.2.1 Primary outcome measures

The primary outcome measure for episodic memory performance was the percentage of correct responses during the learning phase (Learning) and the retrieval blocks (R1 and R2).

Learning (Hypothesis 1): For Learning, the correct responses for L1 and L5, consisting of hits and correct rejections, were calculated singularly:

$$L1\%_{correct}\ and\ L5\%_{correct} = \frac{(Number\ of\ hits + Number\ of\ correct\ rejects)}{(Number\ of\ \text{pseudoword}\ object\ \text{pairs})} * 100$$

from which the difference in value was formed and displayed:

$$\text{Learning}\%_{correct} = \text{L5}\%_{correct} - \text{L1}\%_{correct}$$

Immediate and delayed retrieval (Hypotheses 2 and 3): The retrieval was measured immediately (R1) after the learning phase and after a 20-min break (R2). Each retrieval was calculated as follows:

$$R1\%_{correct}\ and\ R2\%_{correct} = \frac{(Number\ of\ hits + Number\ of\ correct\ rejects)}{(Number\ of\ \text{pseudoword}\ object\ \text{pairs})} * 100$$

To determine whether atDCS has an effect on episodic memory performance, the percentage of correct responses were compared. A linear mixed model with a stimulation condition as a within-subject factor was conducted and adjusted for paradigm version, session order, and age.

2.2.2 Secondary outcome measures

For each primary outcome measure, a hit rate was calculated, which sufficiently describes the occurring correct pairs for learning, R1 and R2:

$$Hit\ rate = \frac{Number\ of\ hits}{(Number\ of\ hits + \ Number\ of\ misses)}$$

Moreover, for incorrect pairings, a correct-rejection rate was calculated to describe how sufficiently wrong pairs were discovered (Snodgrass & Corwin, 1988):

$$Correct\ rejection\ rate = \frac{Number\ of\ correct\ rejects}{(Number\ of\ correct\ rejects + \ Number\ of\ false\ alarms)}$$

Lastly, no responses were reported for each primary outcome measure.

Next, to determine whether atDCS had an effect on episodic memory performance, the correct-rejection and hit rates, the no responses and mean RTs were compared. A linear mixed model with a stimulation condition as a within-subject factor was conducted and adjusted for paradigm version, session order, and age.

2.3 **Response bias**

The response bias (RB) is a method to detect strategies in a dichotomous response format (Kulzow et al., 2014) that are not consistent with the instruction (e.g. non-compliance):

$$RB = \frac{(Number\ of\ hits + Number\ of\ false\ alarms)}{(Number\ of\ \text{pseudoword object pairs presented} - Number\ of\ \text{no response})}$$

An RB close to 1 indicates a tendency to answer merely “correct”, and 0 means answering “incorrect” more often, while a value of 0.5 suggests an equal response set. If all items are answered correctly, the RB would be 0.5. For better detection of striking response strategies, a learning curve was created for each participant.

2.4 **Transcranial direct current stimulation**

The participants were stimulated with a battery-driven stimulator (NeuroConn® DC-Stimulator PLUS; neuroCare Group GmbH, Munich, Germany) for 20 min, which covered two-thirds of the learning phase (see Figure 6). The pair of electrodes used were 5 x 7 cm^2 in size and covered in saline-soaked synthetic sponges. The stimulation electrode (anode) was placed over the left temporoparietal cortex (Cp5; 10 - 20 system), while the cathode was placed over the contralateral supraorbital region, and both were fixed in place with a rubber band. This placement has been used in several previous studies (Antonenko et al., 2016; Flöel et al., 2008; Meinzer, Jahnigen, et al., 2014). During the stimulation condition, the direct current was applied with an intensity of 1,000 μA for 1,200 sec (20 min) with an impedance of ≤5 kΩ. The protocol is thought to be well tolerated, without any previously observed safety issues (Nitsche, Schauenburg, et al., 2003). During the sham condition (stDCS), the current was raised linearly to 1,000 μA for 30 sec, which is believed to elicit slight itching or tingling, so the participants were not able to distinguish between the stimulation and sham conditions. These 30 sec are known not to have any functional effects on memory performance (Nitsche, Liebetanz, et al., 2003). In all conditions, a fade in/out for 10 sec was used (Table 3). The stimulation was started concurrently with the beginning of the language paradigm.

Table 3 Stimulation adjustment for atDCS and stDCS.

	atDCS	stDCS
Stimulation mode	Continuous stimulation	
Current intensity	1,000 μA	1,000 μA
Duration	1,200 sec	30 sec
Fade in/out	10 sec	10 sec
Impedance	≤5 kΩ	≤5 kΩ

Anodal transcranial direct current stimulation (atDCS), sham transcranial direct current stimulation (stDCS).

2.5 **Statistical analysis**

Microsoft Excel version 16 (https://products.office.com/excel) was used for organizing the data, and statistical analyses were conducted with IBM SPSS Statistics versions 24 and 26 (https://www.ibm.com/products/spss-statistics). Linear mixed models (random intercept models) for dependent variables were calculated for the primary outcome measures, namely, learning and both immediate and delayed retrievals (R1 and R2), as a measure of task performance, including factor conditions (atDCS, stDCS), session order (third session, fourth session), set (A, B, C) and age. Linear mixed models were also conducted for RTs, no responses and both hit and correct-rejection rates. The significance level was accepted using a two-sided test at α = 0.05. Finally, no adjustment for multiple testing was applied.

3. RESULTS

3.1 **Participants**

Thirty-four participants (16 women and 18 men) aged between 51 and 80 years were recruited for this study (Table 4) and demonstrated normal cognitive test result scores (all values presented as mean ± SD). All participants were naive to the paradigm and right-handed, as determined by the Edinburgh Handedness Inventory (93.5 ± 9.8). Some participants had already had experience with tDCS from a previous study also conducted by our research group; see Antonenko et al. (2017). The duration of education participants received was 15.1 ± 2.5 in years, and the GDS was 1.3 ± 1.4, with no values >5, which indicate possible depression. The remembered numbers in the Digit Span forward and backward were 7.5 ± 2.34 and 6.1 ± 1.8, respectively. Moreover, the scores of the MWT were 33.3 ± 2.0. The time span between the sessions was at least one week,

except for four cases where it was six days: there were 7.8 ± 1.6 days between the second and third sessions and 7.4 ± 1.2 days between the third and fourth sessions.

Table 4 Participant characteristics.

	Female : Male
Gender	16 : 18
	Mean ± SD
Age, years	63.4 ± 7.6
Education, years	15.1 ± 2.5
Geriatric depression scale	1.3 ± 1.4
Laterality quotient (Edinburgh Handedness Inventory)	93.5 ± 9.8
MWT	33.3 ± 2.0
Digit Span	
Forward (max. 14)	7.5 ± 2.3
Backward (max. 14)	6.1 ± 1.8
Days between sessions	
Second and third	7.8 ± 1.6
Third and fourth	7.4 ± 1.2

N = 34. Multiple-choice vocabulary intelligence test (MWT).

No CERAD test performance was below 1.5 SDs in age- and education-related norms (see Table 5 for summary of test scores).

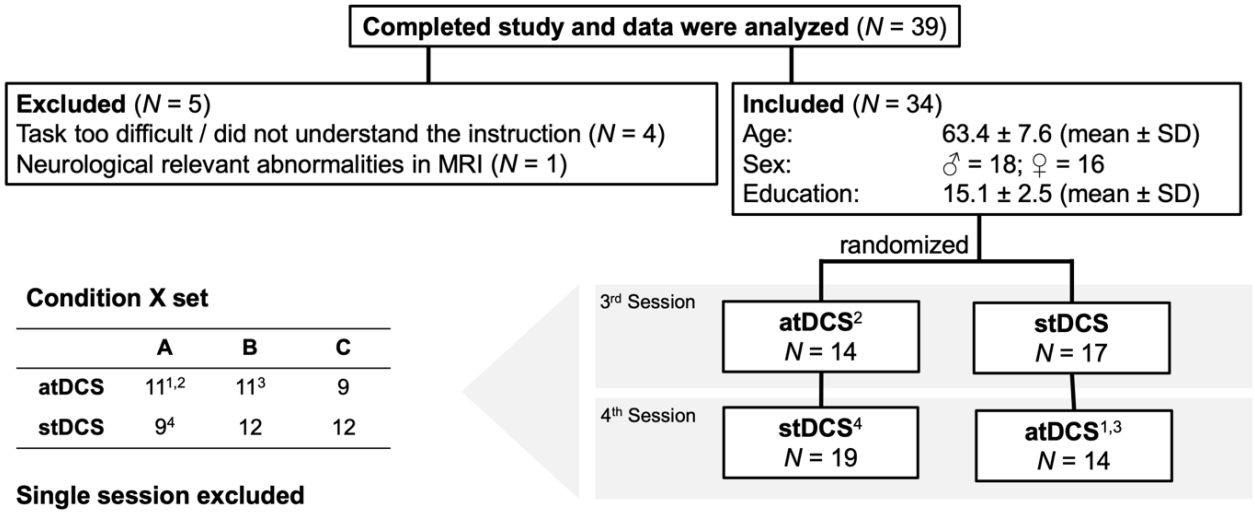
Table 5 CERAD data for the examined population.

	Raw value *Mean ± SD*
Semantic fluency, *N* (in 60 sec)	25.3 ± 6.6
Boston Naming Test, *N* (max. 15)	14.6 ± 0.5
Mini-Mental State (max. 30)	29.4 ± 0.8
Word list learning, *N*	
Total (max. 30)	23.4 ± 3.1
Trial 1 (max. 10)	6.2 ± 1.5
Trial 2 (max. 10)	8.1 ± 1.3
Trial 3 (max. 10)	9.1 ± 1.0
Word list retrieval, *N* (max. 10)	8.3 ± 1.2
Word list intrusions, *N*	0.9 ± 1.9
Figure copying, *N* (max. 11)	11 ± 0.0
Figure retrieval, *N* (max. 11)	10.7 ± 0.7
Phonemic fluency, *N* (in 60 sec)	16.1 ± 4.1
Trail-making test time, sec	
Part A	39.8 ± 11.5
Part B	83.9 ± 32.0
B/A	2.2 ± 0.6

N = 34.

After data analysis and radiology assessment of the MRI findings, five participants were excluded due to difficulty in performing the task, not understanding the description, or neurologically relevant abnormalities in the MRI (see Figure 7). In addition, several sessions were excluded for reasons such as missing values, technical problems, a prominent RB or reported stress during the session .Therefore, there was a slight imbalance in the order of the stimulation condition and paradigm order (see also Figure 7).

Figure 7 Study flow chart on information regarding inclusion and exclusion.



Condition X set

	A	B	C
atDCS	11[1,2]	11[3]	9
stDCS	9[4]	12	12

Single session excluded

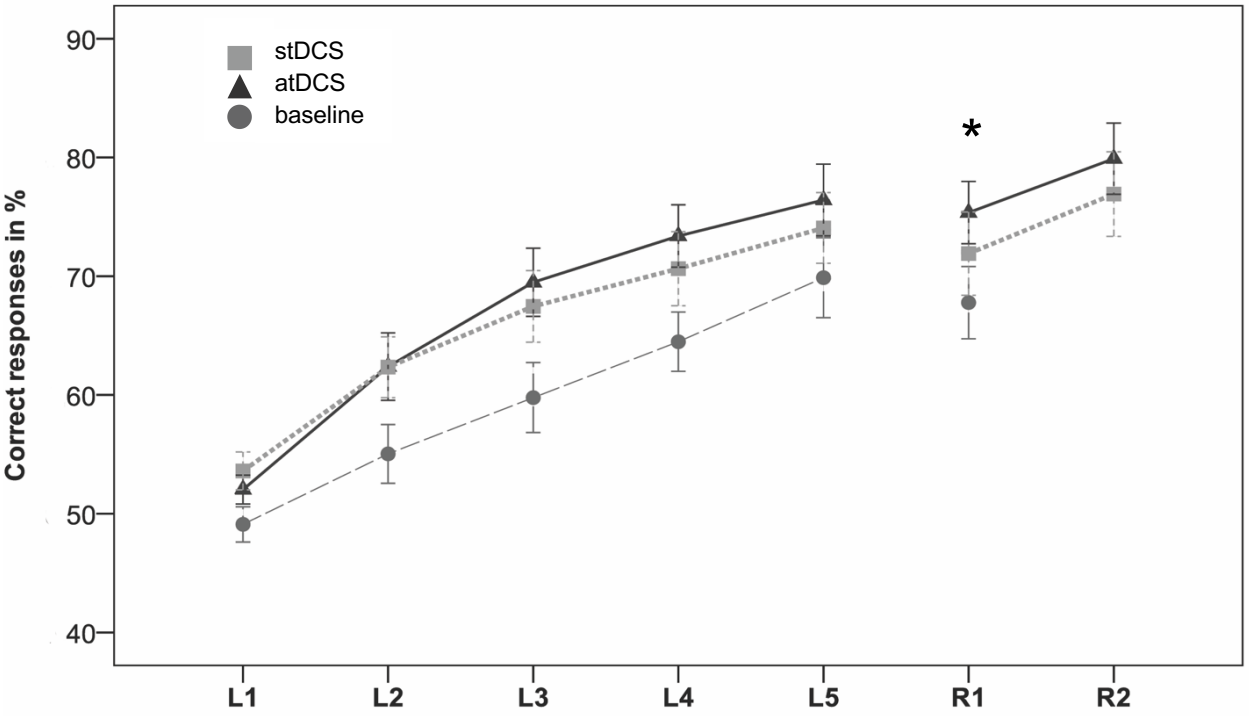
	Session	Condition	Set	Reason
1	4th	atDCS	A	striking values in RB
2	3rd	atDCS	A	Reported Stress
3	4th	atDCS	B	Missing values
4	4th	stDCS	A	Missing values

Condition X set lists the single sessions that were excluded in relation to the set (A, B, C) and the stimulation condition; Single session excluded shows the associated reasons. Response bias (RB), anodal transcranial direct current stimulation (atDCS), sham transcranial direct current stimulation (stDCS).

3.2 Accuracy data: learning and retrieval

A learning curve for the language learning baseline and conditions (stDCS, atDCS) is depicted in Figure 8. The baseline learning curve seems linear, while it appears to be slightly concave for stDCS and especially for atDCS. A reduction in performance from L5 to R1 was observed when the task changed, with a subsequent improvement from R1 to R2.

Figure 8 Percentage of correct responses.

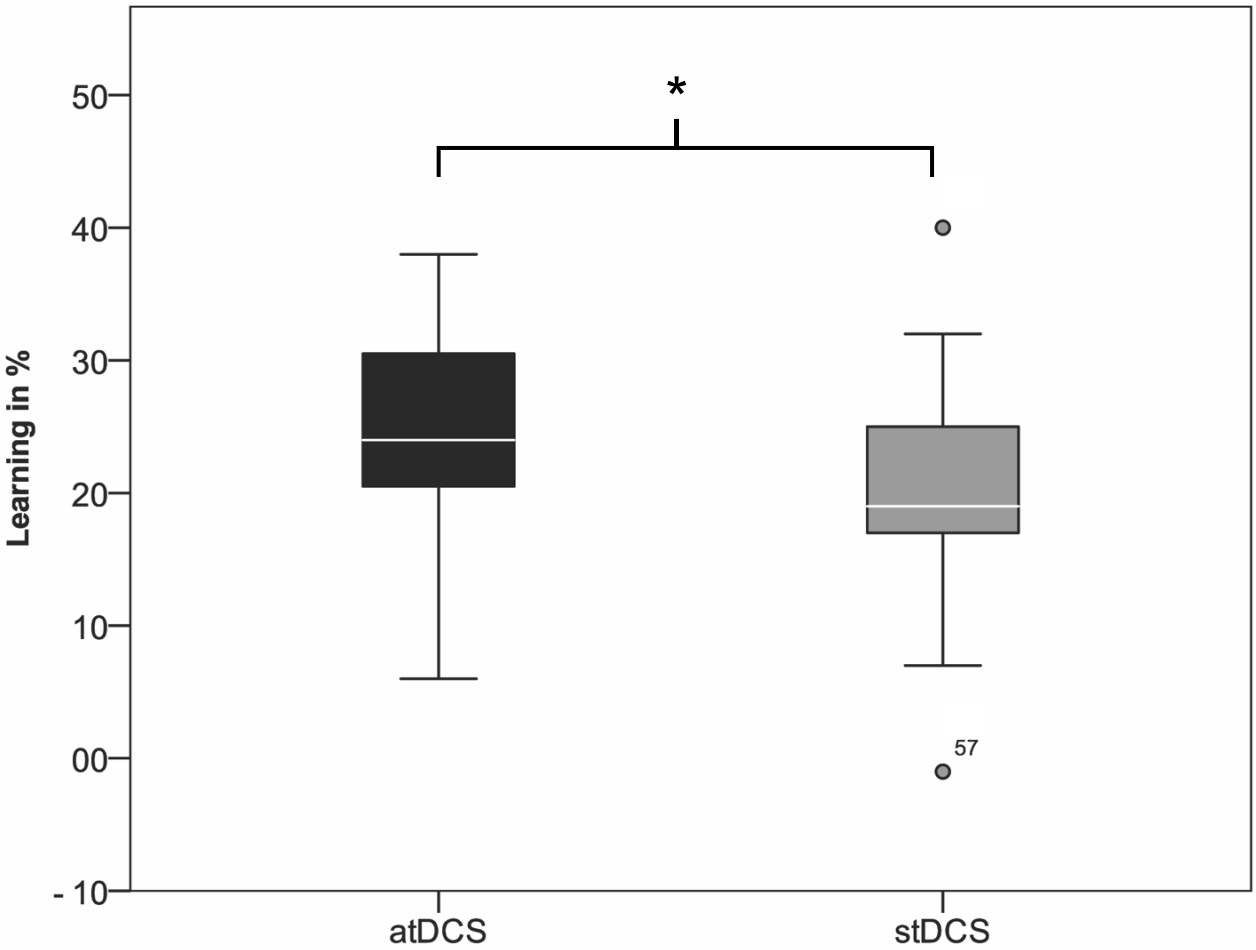


*Means are shown. Vertical bars depict confidence interval: 95%. Significant difference in R1 for conditions * p ≤ 0.05. N = 34. Anodal transcranial direct current stimulation (atDCS), sham transcranial direct current stimulation (stDCS).*

3.2.1 Learning performance (Hypothesis 1)

The parameter for learning (Figure 9) revealed a significant difference in performance between conditions, with a mean difference of 3.8% ($F_{(1,28)} = 5.656$, $p = 0.024$; mean difference [$CI = 95\%$]: 0.038 [0.005, 0.071]; linear mixed models, $N = 34$, 137 data points).

Figure 9 Boxplots for learning.



*Boxplots for learning. The vertical lines inside the box represent the medians. The ends of the box denote the upper and lower quartiles. The two lines outside the box extend to the highest and lowest observations. Dots are outliers. * p ≤ 0.05. N = 34. Anodal transcranial direct current stimulation (atDCS), sham transcranial direct current stimulation (stDCS).*

According to signal detection theory, the rates of stimuli identification did not reveal any significant differences for learning (Table 6).

Table 6 Rates for learning according to signal detection theory.

Single rate	***Result***
Hit rate	$F_{(1,27)} = 0.577$, $p = 0.454$; mean difference [*CI* = 95%]: 0.020 [-0.034, 0.074]
Correct-rejection rate	$F_{(1,28)} = 2.401$, $p = 0.132$; mean difference [*CI* = 95%]: 0.047 [-0.015, 0.110]
No responses	$F_{(1,18)} = 1.175$, $p = 0.893$; mean difference [*CI* = 95%]: - 0.005 [-0.017, 0.006]

N = 34.

3.2.2 Immediate retrieval (Hypothesis 2)

Analyses revealed a significant difference in episodic memory performance in immediate retrieval (R1; Figure 8), with a mean difference of 2.8% between conditions ($F_{(1,89)}$ = 4.815, p = 0.031; mean difference [CI = 95%]: 2.8 [0.4, 5.4]; linear mixed model, N = 34, 127 data points). On average, a better performance of 2.9% was observed in the fourth session regardless of condition ($F_{(1,91)}$ = 9.70, p = 0.002; mean difference [CI = 95%]: 0.029 [1.1, 4.8]). Furthermore, age had no statistically significant effect ($F_{(1,33)}$ = 2.43, p = 0.129; mean difference [CI = 95%]: -0.3 [−0.6, 0.1]). According to signal detection theory, the rates of stimuli identification did not reveal any significant differences for the immediate retrieval (Table 7).

Table 7 Rates for immediate retrieval according to signal detection theory.

Single rate	*Result*
Hit rate	$F_{(1,27)}$ = 1.175, p = 0.288; mean difference [CI = 95%]: 0.019 [-0.017, 0.056]
Correct-rejection rate	$F_{(1,27)}$ = 3.128, p = 0.088; mean difference [CI = 95%]: 0.037 [-0.006, 0.081]
No responses	$F_{(1,28)}$ = 0.209, p = 0.651; mean difference [CI = 95%]: -0.003 [-0.016, 0.010]

N = 34.

3.2.3 Delayed retrieval (Hypothesis 3)

The delayed retrieval (R2) did not yield a significant difference in performance (Figure 8) between stimulation conditions ($F_{(1,27)}$ = 2.317, p = 0.139; mean difference [CI=95]: 0.22 [-0.08, 0.52]; linear mixed models, N = 34, 137 data points). In addition, according to signal detection theory, the rates of stimuli identification did not reveal any significant differences for the delayed retrieval (Table 8).

Table 8 Rates for delayed retrieval according to signal detection theory.

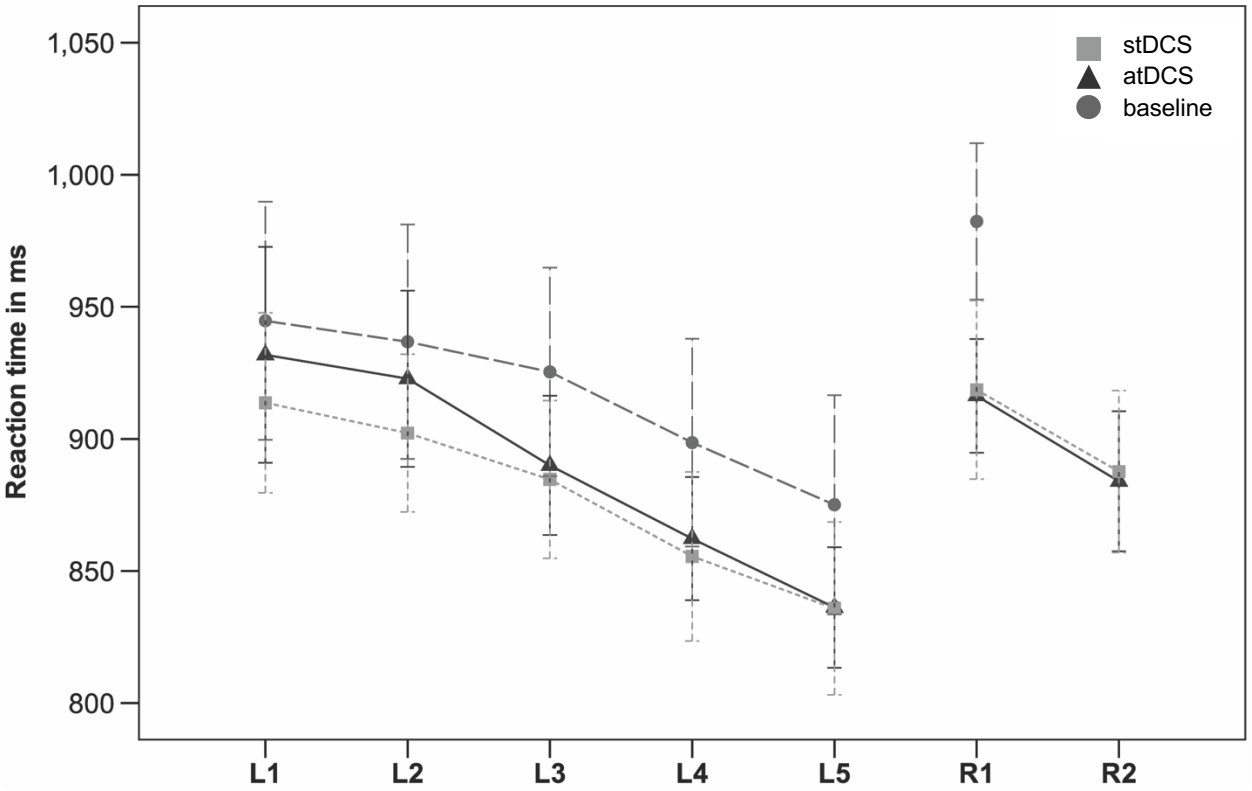
Single rate	***Result***
Hit rate	$F_{(1,27)}$ = 3.504, p = 0.072; mean difference [*CI* = 95%]: 0.046 [-0.004, 0.097]
Correct-rejection rate	$F_{(1,26)}$ = 2.176, p = 0.152; mean difference [*CI* = 95%]: 0.020 [-0.008, 0.048]
No responses	$F_{(1,57)}$ = 0.014, p = 0.908; mean difference [*CI* = 95%]: 0.001 [-0.011, 0.013]

N = 34.

3.3 **Reaction time**

The RT decreased during each session from L1 to L5 as participants became familiar with the task (Figure 10). The immediate retrieval (R1) exhibited an increase due to a change of the task, especially in the baseline condition. In general, the RTs in the delayed retrieval (R2) were shorter than in the immediate retrieval (R1; $F_{(1,88)}$ = 11.05, p = 0.001; mean difference [*CI* = 95%]: -29.6 [−55.2, −4.0]). There were no significant differences in RTs between conditions ($F_{(1,90)}$ = 0.16, p = 0.9; mean difference [*CI* = 95%]: -1.2 [-20.3, 17.9]); however, the RTs in the fourth session were faster than in the third session ($F_{(1,91)}$ = 6.80, p = 0.011; mean difference [*CI* = 95%]: 25.0 [6.0, 44.1]; linear mixed models; N = 34, 136 data points). The observed effects are thus a result of learning but not stimulation.

Figure 10 Reaction time of the memory task.

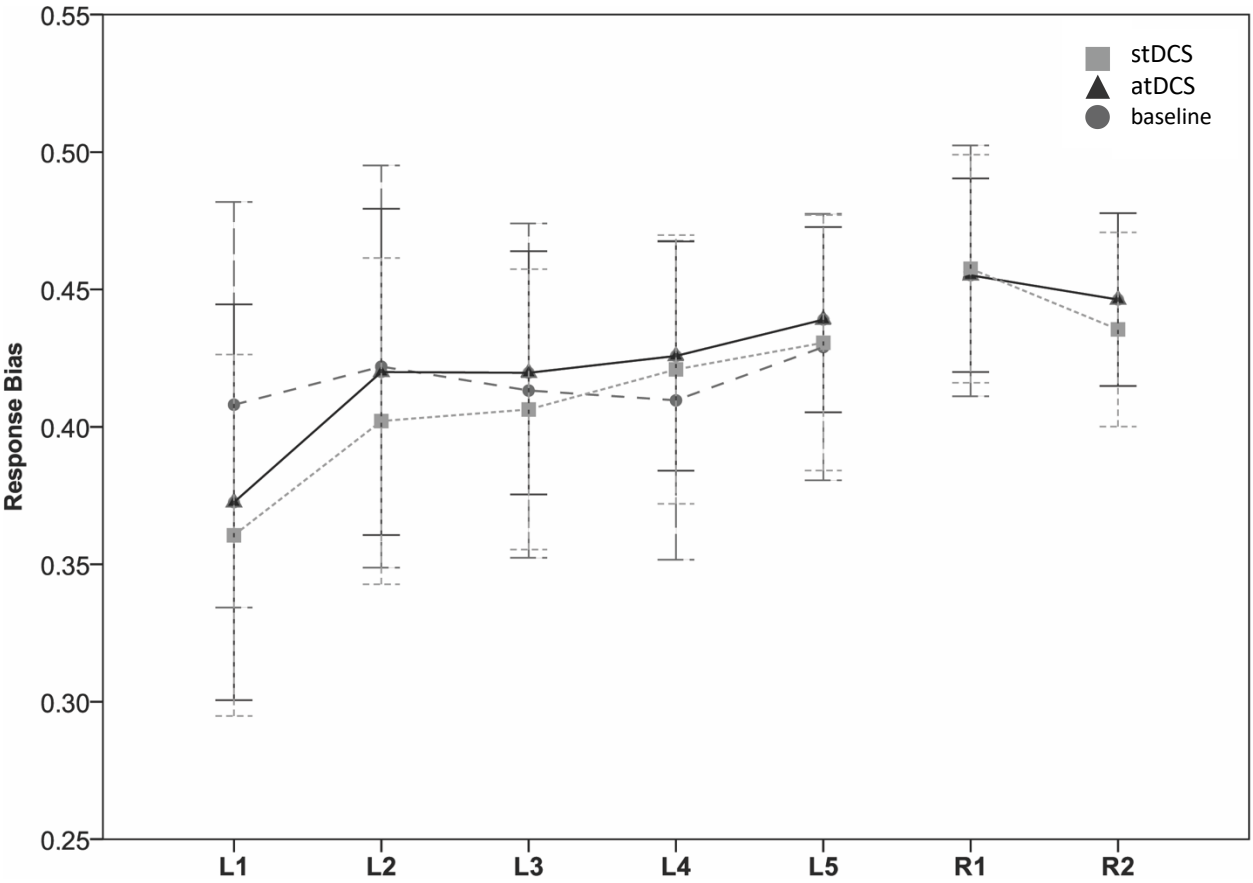


Means are shown. Vertical bars depict confidence interval: 95%. N = 34.

3.4 **Response bias**

In all seven blocks, the participants replied more often with “incorrect”, with a tendency towards 0.5 in later blocks (Figure 11). One participant was detected who had striking values in one session, and the data for this individual and this session were therefore excluded from subsequent analyses. Another participant was completely excluded for not following the instruction correctly, perhaps due to the difficulty of the task (see Figure 7).

Figure 11 Response bias.



Means are shown. Vertical bars depict confidence interval: 95%. N = 34.

3.5 **PANAS**

The analysis of the assessed PANAS (Table 9) did not show significant differences in mood between conditions (positive affect: $F_{(1,100)} = 0.59$, $p = 0.44$; mean difference [*CI* = 95%]: -0.047 [-0.17, 0.08]; negative affect: $F_{(1,101)} = 0.03$, $p = 0.86$; mean difference [*CI* = 95%]: <0.01 [-0.03, 0.04]) nor between the third and fourth sessions (positive affect: $F_{(1,100)} = 2.8$, $p = 0.09$; mean difference [*CI* = 95%]: -0.07 [-0.19, 0.06]; negative affect: $F_{(1,100)} = 0.54$, $p = 0.47$ mean difference [*CI* = 95%]: -0.01 [-0.20, 0.44]; linear mixed models, $N = 34$, 136 data points).

Table 9 Mean and standard deviations of positive and negative mood ratings.

	atDCS		stDCS	
	Pre	Post	Pre	Post
PA	3.31 ± 0.81	3.26 ± 0.80	3.48 ± 0.82	3.30 ± 0.90
NA	1.07 ± 0.10	1.08 ± 0.12	1.08 ± 0.10	1.11 ± 0.15

PA, positive affect; NA, negative affect.

3.6 **Digit span**

The results of the Digit Span task performance (Table 10) revealed no significant difference in stimulation between conditions (forward: $F_{(1,100)} = 0.07$, $p = 0.79$; mean difference [$CI = 95\%$]: 0.06 [−0.38, 0.50]; backward: $F_{(1,100)} = 0.04$, $p = 0.836$; mean difference [$CI = 95\%$]: 0.1 [−0.38, 0.47]) nor between the third and fourth sessions (forward: $F_{(1,100)} = 0.88$, $p = 0.35$; mean difference [$CI = 95\%$]: 0.21 [-0.23, 0.64]; backward: $F_{(1,100)} = 1.08$, $p = 0.3$; mean difference [$CI = 95\%$]: -0.22 [-0.64, 0.20]; linear mixed models; $N = 34$, 136 data points).

Table 10 Mean and standard deviations of digit span.

	atDCS		stDCS	
	Pre	Post	Pre	Post
FWRD	7,85 ± 2,12	7,79 ± 2,26	7,91 ± 2,07	7,59 ± 2,21
BWRD	7,12 ± 2,21	7,24 ± 2,17	7,00 ± 2,30	7,34 ± 2,09

Forward (FWD); backward (BWD). N = 34.

3.7 **Difficulty of the task**

As seen in Table 11, most of the participants had no difficulties in understanding the instructions but felt insecure about carrying them out correctly. The confusion about the paradigm changed from “a little” ($N = 20$) at the beginning to “no” ($N = 26$) at the end. Therefore, we assume that initial difficulties could be reduced through clear instructions and test runs at the beginning of each session. Furthermore, it is interesting that 16 participants used strategies even when they were asked not to.

Table 11 Difficulty of the task reported by the participants in the last session.

Difficulties	Responses		
	No, never	**Sometimes**	**Yes**
Difficulties in understanding the instructions	31	3	0
	No, never	**Mostly**	**Yes, always**
Feelings about carrying out the instructions	3	17	4
	No	**A little**	**Yes**
Confusion at the beginning of the paradigm	7	20	7
Confusion at the end of the paradigm	26	7	1
Instruction could be better	31	NA	3
Understanding the goal of the task	3	NA	31
Use of strategies	17	NA	16
	No	**Don't know**	**Yes**
Better in the third session	14	6	14
Better in the fourth session	16	5	13

Not available (NA). N = 34.

3.8 **Adverse events**

The main adverse event (Table 12) was tingling, which was reported by five participants five times under both stimulations and by six participants only under atDCS. Side-effects such as tingling, itching or burning were mainly observed at the beginning of the stimulation. To control for the occurrence of biases toward the appearance of side-effects, we used a ramp-like stimulation for 30 sec during stDCS (see above). The appearance of a light flash was reported three times under atDCS, but without any visual impairment. The strength of the reported sensations varied from slight to medium; severe side-effects were not reported, and no participant discontinued before completion due to unbearable events.

Table 12 Adverse events reported by participants after stimulation.

Adverse events	Stimulation		
	atDCS	**stDCS**	**Both**
Light flash	3	—	—
Pain	2	—	1
Tingling	6	—	5
Itching	1	—	1
Burning	1	—	1
Fatigue	—	1	2
Nervousness	—	1	3
Loss of concentration	1	—	4
Visual problems	—	—	—
Headache	—	—	—
Discomfort	1	—	—
Something felt different	—	1	1

Anodal transcranial direct current stimulation (atDCS), sham transcranial direct current stimulation (stDCS). N = 34.

4. DISCUSSION

The present thesis explores the effects of atDCS over the left temporoparietal cortex to modulate episodic memory performance in healthy older adults. In the following sections, the findings are discussed with respect to the postulated hypotheses.

4.1 Anodal tDCS improves episodic memory performance

In our randomized, controlled and crossover-designed study, we observed a significant improvement in episodic memory performance in healthy older adults. In addition, steeper learning curves were observed under atDCS compared to stDCS. These results are in line with the findings of other researchers who have also observed that atDCS improves memory performance (Meinzer, Jahnigen, et al., 2014; Perceval, Martin, Copland, Laine, & Meinzer, 2017). In a previous study using the identical task while stimulating the same area, Flöel et al. (2008) already explored the capabilities of atDCS for young adults. It must be stated that the researchers found a significant effect in a learning block similar to L5 (Figure 6). In this thesis, the learning performance was calculated differently (see 2.2.1 Primary outcome measures) to include the whole learning phase.

During an immediate retrieval (R1; Hypothesis 2), the participants could maintain their superior performance even when the task was changed. After a 20-min break, the delayed retrieval revealed no difference between the atDCS and sham conditions (R2; Hypothesis 3).

4.2 Methodological issues

4.2.1 Paradigm

To measure episodic memory, we chose a language learning paradigm for its potential applicability and relevance to older adults and clinical use, as well as its modulation possibilities with atDCS over the left temporoparietal cortex (Breitenstein et al., 2005; Flöel et al., 2008). The paradigm should not be understood to apply to the whole language learning process, but could serve as a model either for the first step in language learning or in the clinical context, reconnecting object and words in aphasia patients (Breitenstein et al., 2005; Breitenstein & Knecht, 2002).

At first glance, it seems that the task used in this study measures semantic memory, but a novel learned word is in fact attached to episodic information (Breitenstein et al., 2005), as the intention of storing this novel word is to employ it again via long-term retrieval. Rather than making only an auditory-visual connection between picture and word, as requested by Breitenstein and Knecht (2002), the subjects in the present study were required to associate the semantic with a novel word, while encoding and storing. Even though our version of the task is close to word acquisition as a child, it in fact involves learning a second language by association in an early stage without grammar. It could also be understood as a cued verbal recall test or a recognition task. This is relevant because a possible effect of atDCS could occur through modulating the cue strength, which is needed for the activation of the correct pseudo-word during retrieval.

4.2.2 Language shaping the brain

Speaking a second language is believed to have an influence on the cognitive reserve in young and older bilinguals by preserving white matter integrity and improved functional network connectivity (Antoniou & Wright, 2017). Altered brain structure was confirmed in a study comparing 30 bilingual individuals (Cantonese-Mandarin/English and monolingual Italian) from 49 to 75 years of age, with an increased grey matter volume in the left and right IPLs for bilingual participants. Additionally, there are differences regarding whether languages were acquired sequentially or simultaneously (Pliatsikas,

2019). For example, in encoding novel words of a second language, participants benefitted from a synchronization between the left HPC, left fusiform gyrus and left IPL. In contrast, using the mother tongue led to an increased activation in the temporal network: bilateral praecuneus/cuneus and the left IPL (Bartolotti, Bradley, Hernandez, & Marian, 2017). Moreover, the effect of bilingualism has been reported to be associated with better structural connectivity (Nissim et al., 2016) and larger cortices in well-educated people (Berryhill & Jones, 2012; Stephens & Berryhill, 2016).

In the case of cognitive decline and its primary and secondary prevention, knowledge of how cognitive abilities and language learning shape the brain and its neuroprotective effects (Pliatsikas, 2019) is important. There are many indications that language knowledge supports the preservation of the cognitive reserve. However, due to methodical issues and publication bias, determining its influence is currently difficult (Antoniou & Wright, 2017).

Multilingualism and skills such as word list retrieval are predictors of increased episodic memory performance in the paradigm used (Breitenstein et al., 2005; Breitenstein & Knecht, 2002). In the current study, one individual with an academic background and degree in linguistics participated, claiming to have experience in four foreign languages (both related and unrelated to German). This person demonstrated superior performance compared to other participants and seemed to benefit from stimulation. This is in accordance with a study stimulating the posterior parietal cortex, where only high performers benefitted from atDCS (Learmonth, Thut, Benwell, & Harvey, 2015). Therefore, using a more demanding task for initial high performers could offer an opportunity to expand the study, especially since low performers seem to benefit more from atDCS (Antonenko et al., 2019; Habich et al., 2017). Furthermore, an increased responsiveness to atDCS correlated with greater grey matter volume was described by Abutalebi, Canini, Della Rosa, Green, and Weekes (2015). According to them, participants' different responsiveness to atDCS requires further examination.

In addition, the question of whether people with a history of language learning or extensive education should be excluded or treated differently than other participants must be addressed. In practice, this could mean using small, simple screening tests to distinguish between participants who have been exposed to a foreign language during childhood or in their educational career and people who speak more than one language in their daily lives.

Intriguingly, different skills trained over one's lifetime, such as playing an instrument or other cognitively demanding abilities, could be investigated. This would be interesting because in an auditory statistical learning online task, musicians with at least 10 years of experience performed better than non-musicians (Mandikal Vasuki, Sharma, Ibrahim, & Arciuli, 2017) and have thicker bilateral superior cortices and lateral frontal lobes, but with no significant differences in areas such as the left IPL or HPC compared to non-musicians (Bermudez, Lerch, Evans, & Zatorre, 2009; de Bot, 2006).

4.2.3 Alternative targets for anodal tDCS

The challenge of where to place the electrodes to modulate episodic memory is difficult to overcome. This is because other areas could be suitable targets for atDCS during learning and retrieval.

The PFC is the focus of ongoing studies, with a view to better understand differences in how atDCS modulates the encoding, consolidation, storage and retrieval of episodic memory (de Lara, Knechtges, Paulus, & Antal, 2017; Manenti et al., 2017). Based on the hemispheric encoding/retrieval asymmetry, the left PFC is more involved in encoding than the right PFC, whereas the right PFC is mainly involved in the retrieval of episodic memory (Habib, Nyberg, & Tulving, 2003). Moreover, the interhemispheric connection between the left and right PFCs is important in episodic memory retrieval performance. This can be seen in research about post-traumatic stress disorder, where a decline in microstructural connectivity of the corpus callosum (connecting the left and right PFCs) has been associated with episodic memory impairment (Saar-Ashkenazy et al., 2014; Saar-Ashkenazy et al., 2016).

Furthermore, the left dlPFC is a suitable target for atDCS because of its contribution to cognitive processes such as WM, semantic processing, executive functions, language comprehension and performance, and as a part of the language network (Tremblay et al., 2014). Manenti, Brambilla, Petesi, Ferrari, and Cotelli (2013) studied episodic memory under the influence of atDCS on the left and right dlPFC (F3 and F4; 10-20 system) as well as the parietal cortex in old and young adults. They observed no effects regarding accuracy in verbal episodic memory performance, which could be due to the shorter stimulation time (6 min) or the chosen moment of stimulation (retrieval).

Other regions of the frontal lobe are also of interest to research groups (Gomes-Osman et al., 2018). To modulate memory networks, regions such as the left ventral inferior

frontal gyrus (IFG) and inferior frontal junction are interesting candidates (Horvath, Forte, & Carter, 2015). In a study using atDCS, where the anode was placed over the left ventral IFG, a significant improvement in semantic word retrieval task after a single session was observed. The authors also reported an atDCS-induced activation pattern of the functional language network in older adults, which is similar to younger ones (Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013).

Another study of the same research group demonstrated that stimulating the primary motor cortex (dual tDCS and atDCS) led to an enhanced word retrieval (Meinzer, Lindenberg, et al., 2014). This is supported by Martin et al. (2017) findings and has been interpreted as overcoming an imbalance in competing networks, including functional reorganization, plus a greater benefit of atDCS for participants with low baseline performance.

It should be highlighted that different electrode placements might influence different parameters, according to signal detection theory. In our data, any of the four possible responses, covered through the hit and correct-rejection rates, were not significant for learning or for immediate and delayed retrieval. Further research could, for example, solve the problem of how different stimulation parameters (stimulated area; duration; current; or external factors, especially age) modulate these rates. It would also be interesting to know whether low baseline performance is a predictor of atDCS responsiveness. To determine that, a marker for task demands could be the deactivation in regions of the DMN, which occurs with more demanding tasks (McKiernan, D'Angelo, Kaufman, & Binder, 2006).

4.2.4 Answer behaviour

Nearly half of the participants in the present study used strategies even if they were asked not to, which could interfere with the results (Zerr et al., 2018). We assume that mnemonic techniques or other creative associations are likely to mediate the outcome of our paradigm. To avoid this, a limited RT frame was set, although the impact of these learning strategies remains unclear. In further studies, a regular reminder could be integrated into the task instructions (possible distractor), or the screening questionnaire could ask about experience with such strategies.

Finally, top-down attention and response control are important because a part of the stimulation effect could be related to changes in those executive functions (Minamoto et

al., 2014). It is particularly unclear when the participants replied incorrectly, during the trials, even if they knew the correct answer. For future studies, it would be interesting to ask participants if they knew how many times they knew the correct answer but replied incorrectly, such that the experiment could be sorted into epochs of perceived success, for example no or a little (0–5), some (5–10) and many (≥15).

4.3 Anodal tDCS and memory processing

In this study, we observed a significant improvement not only in learning episodic memory but also in immediate retrieval. For the delayed retrieval, no significant modulation through atDCS was observed. As a topic of interest, the part of memory processing that atDCS had an effect on remains unclear.

4.3.1 Post-encoding processes

Evidence suggests that atDCS enhances post-encoding processes such as consolidation, storage and retrieval (Jeong, Chung, & Kim, 2015). The retrieval of stored memory is thought to be influenced by cues such as recollection signals (e.g. contextual details) and familiarity signals. During the immediate (R1) and delayed retrieval (R2), the heard German word could be seen as a cue. Therefore, the superior retrieval performance in R1 could be derived from the fact that atDCS enhances familiarity. This is supported by a study in which patients with a VPC lesion profited from cuing in an episodic memory task, resulting in performance equal to that of healthy participants (Berryhill, 2012).

Another possible post-encoding effect could be through atDCS rendering memory less vulnerable to interference. An activated memory is more likely to be interfered with during retrieval than during encoding and storage (C. L. Grady & Ryan, 2017; Winocur & Moscovitch, 2011). This should be considered in future research, especially because older adults seem to lack the ability to suppress distractors (Ikier, Yang, & Hasher, 2008) and use ineffective retrieval strategies (Schacter, Savage, Alpert, Rauch, & Albert, 1996).

4.3.2 Confidence in decision-making and after-effects

Participants in this study were unable to maintain their superior performance after a 20-min break. This could be due to a reduction in confidence or a difference in the after-effects.

Considering how confident the participants were when they made their decision, low confidence decisions may have interfered with the effect of atDCS during the delayed retrieval (R2). Interestingly, a greater activity was observed in the right dlPFC in low confidence judgements (Henson, Rugg, Shallice, & Dolan, 2000). Moreover, an improvement in delayed retrieval was observed during atDCS over the left dlPFC in older adults (Sandrini et al., 2016). This suggests that during learning and retrieval, different areas might be stimulated.

In this study, the stimulation lasted 20 min, while the learning lasted around 30 min with subsequent retrievals. Therefore, the measured effects could be a result of not only online stimulation but also induced after-effects. It is hypothesized that the after-effects of atDCS last from minutes to hours (Jamil et al., 2017), and we can thus attribute the performance in R1 and R2 to after-effects (Figure 6). However, especially in older adults, a delayed reaction after stimulation was observed. For example, a 30-min delayed response was observed in subsequent motor-evoked potentials when atDCS was applied over the left primary motor cortex, while young adults exhibited an increased excitability directly afterwards (Fujiyama et al., 2014).

In summary, there are different reasons why, during the delayed retrieval, the participants were unable to maintain their superior performance. These reasons include a lack of confidence, different after-effects in older adults, or missing repetition.

A focus of future work could be on identifying the factors that modify or stabilize the long-lasting effect of atDCS. For example, researchers could determine whether participants profit most from stimulation during the learning or retrieval phase, or if each process should be stimulated on its own, as Medvedeva et al. (2018) have already tested, albeit with mixed findings. Moreover, the storage of memory during replay-like activation between the HPC and neocortex during a break and its vulnerability to interference should be taken into consideration (Squire, Genzel, Wixted, & Morris, 2015). However, simply prolonging the stimulation duration could lead to an inverse effect of atDCS, as observed in a study involving stimulation longer than 26 min (Paulus, 2011).

4.3.3 Responsiveness in different age groups

Even though there is evidence that atDCS modulates episodic memory performance in different age groups, one cannot generalize conclusions from one group to another (Perceval et al., 2016). In a recent overview, Woods et al. (2019) support the idea that

atDCS responsiveness is age-related and emphasize that in different age groups, cognitive functions are mediated by altered neuronal mechanisms. The reasons older adults maintain responsiveness could be that atDCS improves interhemispheric interaction and lessens the inhibition of the non-dominant hemisphere (Lindenberg, Nachtigall, Meinzer, Sieg, & Flöel, 2013). A similar theory was described by Meinzer et al. (2013), who stimulated the ventral left IFG.

Furthermore, a bihemispheric atDCS stimulation protocol over the left and right IPLs revealed improved verbal learning performance in older adults, but not in young adults (Fiori et al., 2017). A study using transcranial alternating current stimulation also observed an increase in cognitive performance only for older adults (Antonenko et al., 2016). According to Fiori et al. (2017), the task was only challenging for older adults, and adjusting the difficulty for younger adults would thus allow them to benefit from the stimulation as well.

This idea is supported by findings from Kemper and Sumner (2001), who observed a period of rapid decline in linguistic ability around the age of 75. In the current study, participants were of a similar age, with a mean age of 63 and a maximum of almost 80 years (see the Results Section 3.1 Participants above). In this regard, there are reasons to assume that shifting the age group slightly to a younger or older population could affect the stimulation effect and the episodic memory performance.

Uni- and bihemispheric stimulation of the temporoparietal cortex has revealed that older adults profit from both conditions, but bihemispheric stimulation has been shown to be superior to unilateral stimulation (Fiori et al., 2017). This could be in accordance with the suggestion that asynchronous activation, as observed in young adults, is accompanied by better memory performance, as suggested by the HAROLD model. Therefore, during bihemispheric stimulation, an increased difference in activation of the left and right hemispheres leads to better memory performance.

Naveh-Benjamin et al. (2009) noted a difference between the performance of young and older adults through a decrease in hit rates and higher false-alarm rates during an associative test using face-name pairs. We could not observe a significant difference in no responses or in hit and correct-rejection rates. Stimulating the left ventrolateral PFC (F7; 10-20 system) during an intentional memory task, Medvedeva et al. (2018) observed an increased episodic memory performance in young adults. Here, the accuracy used

was calculated differently, using hits minus false alarms; for a comparison, see Section 2.2 Behavioural paradigm in this study. It is interesting that the main effects of the study by Medvedeva et al. (2018) seem to derive from a decreased number of false alarms.

These varying results demonstrate the complexity of memory modulation. According to signal detection theory, the accuracy as calculated in this thesis arises from hits and correct rejections. In other publications, these calculations have been performed differently or are not adequately described. This inconsistency leads to a lack of comparability of results but highlights the importance of selecting proper methods to study episodic memory performance. In general, for studies in this field, analysis of the signal detection theory rates should be conducted.

The reason that some stimulation protocols only work to the advantage of one age group can only be speculated, especially because many papers only include one age group. For future research, different age groups should be included to identify factors that maintain cognitive abilities in older age.

4.3.4 Networks

Since atDCS modulates the interaction between brain regions and affects whole networks rather than a specific area (Manenti et al., 2017), a better understanding is of importance.

For encoding novel words of a second language, participants benefit from a synchronization between the left HPC, left fusiform gyrus and left IPL (Bartolotti et al., 2017). The coupling of the left HPC and the left temporoparietal area has been associated with atDCS-induced improvement in episodic memory performance (Antonenko et al., 2019). Hordacre et al. (2017) identified the strength of functional connectivity as a prime predictor of the effectiveness of atDCS through plasticity induction. This contributes to the assumption that, while stimulating the neocortex at Cp5 (10-20 system), the functional connectivity between the left HPC and the left temporoparietal area is enhanced (Antonenko et al., 2019). This offers credence to the assumption that these areas form process-specific alliances (PSAs), which describe mini networks performing sub-operations, having functional and structural connection to the probed cognitive process. In a recent study, evidence was found for the HPC (recovering memory details) and the AG (processing details) forming a PSA when retrieving episodic memory (Cabeza, Stanley, & Moscovitch, 2018). Further areas crucial for encoding and retrieval are

posterior parts of the HPC; the VPC; and task-specific posterior cortices, including the AG (Moscovitch et al., 2016).

These findings lead to the conclusion that there is no specific area, but rather inter-regional interactions within a network relevant for episodic memory performance. This means that stimulating different areas could lead to the same task improvement because atDCS might modulate the functional connection in PSAs and networks. Therefore, it is necessary to sufficiently define these underlying inter-regional interactions.

4.4 **Medical relevance**

A great deal of research employs NIBS for therapeutic reasons. To date, no protocol for therapeutic application has made it into the treatment of any cognition-related disease (Lefaucheur et al., 2017). A fact in favour of NIBS for future therapy are the difficulty in obtaining high drug levels in the brain due to the blood-brain barrier (Pardridge, 2012), fewer side-effects than many pharmacological treatments (Matsumoto & Ugawa, 2017; Nitsche, Liebetanz, et al., 2003), and its combination with existing treatment as augmentation. In addition, in future hypothetical scenarios, atDCS is thought to be an easy-to-apply method, which could be applied by untrained personnel.

There is evidence that atDCS delays cognitive decline and degeneration of the brain, especially in MCI- and AD-associated parts such as the temporal lobe and temporoparietal regions (Gomes-Osman et al., 2018; Weintraub, Wicklund, & Salmon, 2012). Recent studies claim that older adults diagnosed with MCI benefit from atDCS plus cognitive training in multiple domains (Cruz Gonzalez, Fong, & Brown, 2018), for example through enhanced recognition memory (Manenti, Sandrini, Gobbi, Binetti, & Cotelli, 2018), improved WM performance (Stephens & Berryhill, 2016), improved word retrieval performance and reversed age- and MCI-related abnormalities (Birba et al., 2017; Meinzer et al., 2015). Using atDCS in AD patients also revealed promising results like a modulation in word recognition (Ferrucci et al., 2008), improved recognition memory (Boggio et al., 2012), and improvements in single cognitive domains (Bystad, Rasmussen, Gronli, & Aslaksen, 2017). For a summary of the usage of atDCS in AD, see a review by Cai et al. (2019).

In the future, one could imagine an assistive device such as atDCS next to a battery of cognitive exercises at home and possible implementation in a daily/weekly routine (Woods et al., 2018); however, to date, it is unclear whether processes such as memory

(encoding, storage, retrieval) or attentional control can be sufficiently altered in the long term (Prehn & Flöel, 2015). Unfortunately, studies often use single tasks to measure performance, rather than a broad number of training approaches and exercises, which are needed to measure an increase in ADLs and quality of life (Cruz Gonzalez, Fong, Chung, et al., 2018).

Furthermore, tDCS has previously been employed in the treatment of post-stroke aphasia (Fiori et al., 2013; Thiel & Zumbansen, 2016). Researchers have reported improved response accuracy and faster RTs on a naming task (Fiori et al., 2011), more accuracy in noun naming, and better performance in a verb-naming task (Fiori et al., 2013). The authors stated that the participants benefitted from stimulation even when the size and location of their lesions differed, which is due to the susceptibility of areas spared from atDCS and enhanced plasticity.

Moreover, modulating the language network, an approach taken by Darkow, Martin, Wurtz, Flöel, and Meinzer (2017) demonstrated that even when areas are impaired, others might still be operating impeccably or are capable of taking over new functions. This research group promoted an effect of atDCS on multiple levels, such as modulating activity of the cortex as well as language network activation and connectivity. This contribution of atDCS to post-stroke patients who suffer from aphasia is supported by findings from Meinzer, Lindenberg, et al. (2014).

Speculating about the best area to apply atDCS, a promising approach involves identifying highly active areas (Baker, Rorden, & Fridriksson, 2010). Indeed, in terms of aphasia, numerous electrode placements, such as on the IFG, the STG and the left IPL (as featured in this thesis), show promising results but do not overcome many uncertainties that arise within a stroke scenario (Monti et al., 2013).

Post-stroke aphasia, MCI and AD are of great interest as they are highly connected to this fascinating topic through language and memory disabilities. Then, there are reliable results using NIBS – in particular, atDCS – to increase performance in cognitive processes such as implicit, explicit, WM or motor learning (Coffman, Clark, & Parasuraman, 2014). For more information, refer to a recent review by Pruski and Celnik (2019).

5. CONCLUSION AND FUTURE RESEARCH

In this thesis, it is demonstrated that in a single session, atDCS can modulate episodic memory performance in healthy older adults and that the TPJ is a reliable area to which it can be applied. Considering this result, it is reasonable to conclude that episodic memory performance can be modulated in young (Flöel et al., 2008) and older healthy adults. While memory performance declines in advancing years, and vulnerability to neurocognitive diseases is rising, older adults are in need of intervention to master future problems. But to date only a small number of NIBS studies have been conducted with various age groups.

Despite many difficulties, temporarily modulating age-related cognitive decline appears to be possible (Donaldson et al., 2015; Meinzer et al., 2013), even though many questions are not yet fully answered. To reach optimal stimulation effects, tasks should be adapted according to difficulty. Therefore, the number of fluently spoken languages or other pretrained cognitive skills could be checked in standardized tests to provide more information about the possibility of varying responsiveness to atDCS in groups with advanced language skills and higher education. Furthermore, to avoid ceiling effects, a difficulty adjustment referring to the baseline performance should be conducted. Therefore, an optimal difficulty level could be established before commencing with an augmentation with NIBS (Saxena & Hillis, 2017).

Moreover, findings should be verified by different research groups to raise the profile of memory performance-modulating effects over the TPJ for further research and particularly to gain more information for clinical use of this particular area. Other targets for modulating memory performance are areas such as parts of the frontal cortex or PFC (Gomes-Osman et al., 2018), which leads to the idea that, rather than only one area, a network is in charge of processing memory-related information and is modulated by atDCS. Therefore, a better understanding of processing in large-scale brain networks must be achieved, and the DMN with its subsystems, which are thought to be involved in episodic memory processing, familiarity and recollection signals, and task demands, should thus be explored. De Marco et al. (2016) observed increased functional connectivity in neural structures of the DMN in healthy older adults using tasks in multiple cognitive domains (e.g. WM, verbal memory and executive functions) and formulated the hypothesis that those exercises, frequently conducted, could elicit a positive impact on

MCI and AD patients. However, it is still unclear how much direct current reaches deeper brain regions and how it is distributed between the anode and cathode.

Finally, due to an increasing number of NIBS papers, it becomes more challenging for researchers and clinicians to remain abreast of findings. The heterogeneity of paradigms, stimulation protocols, devices and electrode placement is referred to in nearly every paper (Birba et al., 2017). It should also be noted that for further research, as recommended in a review by Polania et al. (2018), sample sizes of at least n > 20 are suggested to reduce the problem of irreproducibility. For further clarification, a suggestion is to report, at the least, the hit and correct-rejection rates, according to signal detection theory.

To overcome this confusion, a central register should be discussed, which would include the previously mentioned main factors and others (e.g. age group, education). This would enable both patients and researchers to maximally benefit from this exciting technology and its many promises.

6. REFERENCES

Abutalebi, J., Canini, M., Della Rosa, P. A., Green, D. W., & Weekes, B. S. (2015). The neuroprotective effects of bilingualism upon the inferior parietal lobule: A Structural Neuroimaging Study in Aging Chinese Bilinguals. *Journal of Neurolinguistics, 33*, 3-13. doi:10.1016/j.jneuroling.2014.09.008

Antonenko, D., Faxel, M., Grittner, U., Lavidor, M., & Flöel, A. (2016). Effects of transcranial alternating current stimulation on cognitive functions in healthy young and older adults. *Neural Plasticity, 2016*, 13. doi:10.1155/2016/4274127

Antonenko, D., Hayek, D., Netzband, J., Grittner, U., & Flöel, A. (2019). tDCS-induced episodic memory enhancement and its association with functional network coupling in older adults. *Sci Rep, 9*(1), 2273. doi:10.1038/s41598-019-38630-7

Antonenko, D., Schubert, F., Bohm, F., Ittermann, B., Aydin, S., Hayek, D., Grittner, U., & Flöel, A. (2017). tDCS-Induced Modulation of GABA Levels and Resting-State Functional Connectivity in Older Adults. *J Neurosci, 37*(15), 4065-4073. doi:10.1523/JNEUROSCI.0079-17.2017

Antoniou, M., & Wright, S. M. (2017). Uncovering the Mechanisms Responsible for Why Language Learning May Promote Healthy Cognitive Aging. *Front Psychol, 8*, 2217. doi:10.3389/fpsyg.2017.02217

Baker, J. M., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke, 41*(6), 1229-1236. doi:10.1161/STROKEAHA.109.576785

Bartolotti, J., Bradley, K., Hernandez, A. E., & Marian, V. (2017). Neural signatures of second language learning and control. *Neuropsychologia, 98*, 130-138. doi:10.1016/j.neuropsychologia.2016.04.007

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol, 591*(7), 1987-2000. doi:10.1113/jphysiol.2012.249730

Bermudez, P., Lerch, J. P., Evans, A. C., & Zatorre, R. J. (2009). Neuroanatomical correlates of musicianship as revealed by cortical thickness and voxel-based morphometry. *Cereb Cortex, 19*(7), 1583-1596. doi:10.1093/cercor/bhn196

Berryhill, M. E. (2012). Insights from neuropsychology: pinpointing the role of the posterior parietal cortex in episodic and working memory. *Front Integr Neurosci, 6*, 31. doi:10.3389/fnint.2012.00031

Berryhill, M. E., & Jones, K. T. (2012). tDCS selectively improves working memory in older adults with more education. *Neuroscience Letters, 521*. doi:10.1016/j.neulet.2012.05.074

Bettio, L. E. B., Rajendran, L., & Gil-Mohapel, J. (2017). The Effects of Aging in the Hippocampus and Cognitive Decline. *Neurosci Biobehav Rev*. doi:10.1016/j.neubiorev.2017.04.030

Birba, A., Ibanez, A., Sedeno, L., Ferrari, J., Garcia, A. M., & Zimerman, M. (2017). Non-Invasive Brain Stimulation: A New Strategy in Mild Cognitive Impairment? *Front Aging Neurosci, 9*, 16. doi:10.3389/fnagi.2017.00016

Boggio, P. S., Ferrucci, R., Mameli, F., Martins, D., Martins, O., Vergari, M., Tadini, L., Scarpini, E., Fregni, F., & Priori, A. (2012). Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. *Brain Stimul, 5*(3), 223-230. doi:10.1016/j.brs.2011.06.006

Breitenstein, C., Jansen, A., Deppe, M., Foerster, A. F., Sommer, J., Wolbers, T., & Knecht, S. (2005). Hippocampus activity differentiates good from poor learners of a novel lexicon. *Neuroimage, 25*(3), 958-968. doi:10.1016/j.neuroimage.2004.12.019

Breitenstein, C., & Knecht, S. (2002). Development and validation of a language learning model for behavioral and functional-imaging studies. *J Neurosci Methods, 114*(2), 173-179. doi:10.1016/s0165-0270(01)00525-8

Buchweitz, A. (2016). Language and reading development in the brain today: neuromarkers and the case for prediction. *J Pediatr (Rio J), 92*(3 Suppl 1), S8-S13. doi:10.1016/j.jped.2016.01.005

Bystad, M., Rasmussen, I. D., Gronli, O., & Aslaksen, P. M. (2017). Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study. *Neurocase, 23*(2), 146-148. doi:10.1080/13554794.2017.1325911

Cabeza, R. (2002). Hemispheric asymmetry reduction in old adults: the HAROLD model. *Psychology and Aging, 17*(1), 85-100. doi:10.1037/0882-7974.17.1.85

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: an attentional account. *Nat Rev Neurosci, 9*(8), 613-625. doi:10.1038/nrn2459

Cabeza, R., Stanley, M. L., & Moscovitch, M. (2018). Process-Specific Alliances (PSAs) in Cognitive Neuroscience. *Trends Cogn Sci, 22*(11), 996-1010. doi:10.1016/j.tics.2018.08.005

Casaletto, K. B., Marx, G., Dutt, S., Neuhaus, J., Saloner, R., Kritikos, L., Miller, B., & Kramer, J. H. (2017). Is "Learning" episodic memory? Distinct cognitive and neuroanatomic correlates of immediate recall during learning trials in neurologically normal aging and neurodegenerative cohorts. *Neuropsychologia, 102*, 19-28. doi:10.1016/j.neuropsychologia.2017.05.021

Coffman, B. A., Clark, V. P., & Parasuraman, R. (2014). Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *Neuroimage, 85 Pt 3*, 895-908. doi:10.1016/j.neuroimage.2013.07.083

Cowan, N. (1992). Verbal Memory Span and the Timing of Spoken Recall. *Journal of memory and language, 31*, 668 - 684.

Cruz Gonzalez, P., Fong, K. N. K., & Brown, T. (2018). The Effects of Transcranial Direct Current Stimulation on the Cognitive Functions in Older Adults with Mild Cognitive Impairment: A Pilot Study. *Behav Neurol, 2018*, 5971385. doi:10.1155/2018/5971385

Cruz Gonzalez, P., Fong, K. N. K., Chung, R. C. K., Ting, K. H., Law, L. L. F., & Brown, T. (2018). Can Transcranial Direct-Current Stimulation Alone or Combined With Cognitive Training Be Used as a Clinical Intervention to Improve Cognitive Functioning in Persons With Mild Cognitive Impairment and Dementia? A Systematic Review and Meta-Analysis. *Front Hum Neurosci, 12*, 416. doi:10.3389/fnhum.2018.00416

Darkow, R., Martin, A., Wurtz, A., Flöel, A., & Meinzer, M. (2017). Transcranial direct current stimulation effects on neural processing in post-stroke aphasia. *Hum Brain Mapp, 38*(3), 1518-1531. doi:10.1002/hbm.23469

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb Cortex, 18*(5), 1201-1209. doi:10.1093/cercor/bhm155

de Bot, K. (2006). The plastic bilingual brain: synaptic pruning or growth? Commentary on Green, et al. *Language Learning, 56*(1), 127–132. doi:10.1111/j.1467-9922.2006.00358.x

de Lara, G. A., Knechtges, P. N., Paulus, W., & Antal, A. (2017). Anodal tDCS Over the Left DLPFC Did Not Affect the Encoding and Retrieval of Verbal Declarative Information. *Front Neurosci, 11*, 452. doi:10.3389/fnins.2017.00452

De Marco, M., Meneghello, F., Duzzi, D., Rigon, J., Pilosio, C., & Venneri, A. (2016). Cognitive stimulation of the default-mode network modulates functional connectivity in healthy aging. *Brain Res Bull, 121*, 26-41. doi:10.1016/j.brainresbull.2015.12.001

Donaldson, P. H., Rinehart, N. J., & Enticott, P. G. (2015). Noninvasive stimulation of the temporoparietal junction: A systematic review. *Neurosci Biobehav Rev, 55*, 547-572. doi:10.1016/j.neubiorev.2015.05.017

Dudai, Y., Karni, A., & Born, J. (2015). The Consolidation and Transformation of Memory. *Neuron, 88*(1), 20-32. doi:10.1016/j.neuron.2015.09.004

Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., Cogiamanian, F., Barbieri, S., Scarpini, E., & Priori, A. (2008). Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology, 71*(7), 493-498. doi:10.1212/01.wnl.0000317060.43722.a3

Fertonani, A., & Miniussi, C. (2016). Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. *Neuroscientist*. doi:10.1177/1073858416631966

Fiori, V., Cipollari, S., Di Paola, M., Razzano, C., Caltagirone, C., & Marangolo, P. (2013). tDCS stimulation segregates words in the brain: evidence from aphasia. *Front Hum Neurosci, 7*, 269. doi:10.3389/fnhum.2013.00269

Fiori, V., Coccia, M., Marinelli, C. V., Vecchi, V., Bonifazi, S., Ceravolo, M. G., Provinciali, L., Tomaiuolo, F., & Marangolo, P. (2011). Transcranial Direct Current Stimulation Improves Word Retrieval in Healthy and Nonfluent Aphasic Subjects. *Journal of Cognitive Neuroscience, 23*(9), 2309-2323.

Fiori, V., Nitsche, M., Iasevoli, L., Cucuzza, G., Caltagirone, C., & Marangolo, P. (2017). Differential effects of bihemispheric and unihemispheric transcranial direct current stimulation in young and elderly adults in verbal learning. *Behav Brain Res, 321*, 170-175. doi:10.1016/j.bbr.2016.12.044

Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., Salat, D. H., Greve, D. N., Fischl, B., Dale, A. M., & Walhovd, K. B. (2009). High consistency of regional cortical thinning in aging across multiple samples. *Cereb Cortex, 19*(9), 2001-2012. doi:10.1093/cercor/bhn232

Flöel, A., Roesser, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience, 10*(8), 1415-1422.

Fotenos, A. F., Snyder, A. Z., Girton, L. E., Morris, J. C., & Buckner, R. L. (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology, 64*(6), 1032-1039. doi:10.1212/01.WNL.0000154530.72969.11

Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiol Rev, 91*(4), 1357-1392. doi:10.1152/physrev.00006.2011

Fujiyama, H., Hyde, J., Hinder, M. R., Kim, S. J., McCormack, G. H., Vickers, J. C., & Summers, J. J. (2014). Delayed plastic responses to anodal tDCS in older adults. *Front Aging Neurosci, 6*, 115. doi:10.3389/fnagi.2014.00115

Geib, B. R., Stanley, M. L., Dennis, N. A., Woldorff, M. G., & Cabeza, R. (2017). From hippocampus to whole-brain: The role of integrative processing in episodic memory retrieval. *Hum Brain Mapp, 38*(4), 2242-2259. doi:10.1002/hbm.23518

Gilboa, A., & Marlatte, H. (2017). Neurobiology of Schemas and Schema-Mediated Memory. *Trends Cogn Sci, 21*(8), 618-631. doi:10.1016/j.tics.2017.04.013

Gomes-Osman, J., Indahlastari, A., Fried, P. J., Cabral, D. L. F., Rice, J., Nissim, N. R., Aksu, S., McLaren, M. E., & Woods, A. J. (2018). Non-invasive Brain Stimulation: Probing Intracortical Circuits and Improving Cognition in the Aging Brain. *Front Aging Neurosci, 10*, 177. doi:10.3389/fnagi.2018.00177

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat Rev Neurosci, 13*(7), 491-505. doi:10.1038/nrn3256

Grady, C. L., Bernstein, L. J., Beig, S., & Siegenthaler, A. L. (2002). The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. *Psychology and Aging, 17*(1), 7-23. doi:10.1037/0882-7974.17.1.7

Grady, C. L., & Ryan, J. D. (2017). Age-Related Differences in the Human Hippocampus: Behavioral, Structural and Functional Measures. . In D. E. Hannula & M. C. Duff (Eds.), *The Hippocampus From Cells To Systems*. Switzerland: Springer International Publishing AG.

Grotz, C., Meillon, C., Amieva, H., Andel, R., Dartigues, J. F., Adam, S., & Letenneur, L. (2018). Occupational social and mental stimulation and cognitive decline with advancing age. *Age Ageing, 47*(1), 101-106. doi:10.1093/ageing/afx101

Gutchess, A. (2014). Plasticity of the aging brain: new directions in cognitive neuroscience. *Science, 346*(6209), 579-582. doi:10.1126/science.1254604

Habib, R., Nyberg, L., & Tulving, E. (2003). Hemispheric asymmetries of memory: the HERA model revisited. *Trends in Cognitive Sciences, 7*(6), 241-245. doi:10.1016/s1364-6613(03)00110-4

Habich, A., Kloppel, S., Abdulkadir, A., Scheller, E., Nissen, C., & Peter, J. (2017). Anodal tDCS Enhances Verbal Episodic Memory in Initially Low Performers. *Front Hum Neurosci, 11*, 542. doi:10.3389/fnhum.2017.00542

Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clin Geriatr Med, 29*(4), 737-752. doi:10.1016/j.cger.2013.07.002

Henson, R. N. A., Rugg, M. D., Shallice, T., & Dolan, R. J. (2000). Confidence in Recognition Memory for Words: Dissociating Right Prefrontal Roles in Episodic Retrieval. *Journal of Cognitive Neuroscience, 12*, 913-923

Hordacre, B., Moezzi, B., Goldsworthy, M. R., Rogasch, N. C., Graetz, L. J., & Ridding, M. C. (2017). Resting state functional connectivity measures correlate with the response to anodal transcranial direct current stimulation. *Eur J Neurosci, 45*(6), 837-845. doi:10.1111/ejn.13508

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimul, 8*(3), 535-550. doi:10.1016/j.brs.2015.01.400

Hsu, T. Y., Tseng, P., Liang, W. K., Cheng, S. K., & Juan, C. H. (2014). Transcranial direct current stimulation over right posterior parietal cortex changes prestimulus alpha oscillation in visual short-term memory task. *Neuroimage, 98*, 306-313. doi:10.1016/j.neuroimage.2014.04.069

Igelstrom, K. M., & Graziano, M. S. A. (2017). The inferior parietal lobule and temporoparietal junction: A network perspective. *Neuropsychologia, 105*, 70-83. doi:10.1016/j.neuropsychologia.2017.01.001

Ikier, S., Yang, L., & Hasher, L. (2008). Implicit Proactive Interference, Age, and Automatic Versus Controlled Retrieval Strategies. *Psychological Science, 19*(5).

Jamil, A., Batsikadze, G., Kuo, H. I., Labruna, L., Hasan, A., Paulus, W., & Nitsche, M. A. (2017). Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *J Physiol, 595*(4), 1273-1288. doi:10.1113/JP272738

Jeong, W., Chung, C. K., & Kim, J. S. (2015). Episodic memory in aspects of large-scale brain networks. *Front Hum Neurosci, 9*, 454. doi:10.3389/fnhum.2015.00454

Ji, L., Pearlson, G. D., Hawkins, K. A., Steffens, D. C., Guo, H., & Wang, L. (2018). A New Measure for Neural Compensation Is Positively Correlated With Working Memory and Gait Speed. *Front Aging Neurosci, 10*, 71. doi:10.3389/fnagi.2018.00071

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. *J Neurophysiol, 107*(7), 1881-1889. doi:10.1152/jn.00715.2011

Kemper, S., & Sumner, A. (2001). The structure of verbal abilities in young and older adults. *Psychology and Aging, 16*(2), 312-322. doi:10.1037/0882-7974.16.2.312

Kim, H. (2016). Default network activation during episodic and semantic memory retrieval: A selective meta-analytic comparison. *Neuropsychologia, 80*, 35-46. doi:10.1016/j.neuropsychologia.2015.11.006

Kitamura, T., Ogawa, S. K., Roy, D. S., Okuyama, T., Morrissey, M. D., Smith, L. M., Redondo, R. L., & Tonegawa, S. (2017). Engrams and Circuits Crucial for Systems Consolidation of a Memory. *Science, 07*(356), 73–78.

Klooster, D. C., de Louw, A. J., Aldenkamp, A. P., Besseling, R. M., Mestrom, R. M., Carrette, S., Zinger, S., Bergmans, J. W., Mess, W. H., Vonck, K., Carrette, E., Breuer, L. E., Bernas, A., Tijhuis, A. G., & Boon, P. (2016). Technical aspects of neurostimulation: Focus on equipment, electric field modeling, and stimulation protocols. *Neurosci Biobehav Rev, 65*, 113-141. doi:10.1016/j.neubiorev.2016.02.016

Krall, S. C., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P. T., Eickhoff, S. B., Fink, G. R., & Konrad, K. (2015). The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. *Brain Struct Funct, 220*(2), 587-604. doi:10.1007/s00429-014-0803-z

Kulzow, N., Kerti, L., Witte, V. A., Kopp, U., Breitenstein, C., & Flöel, A. (2014). An object location memory paradigm for older adults with and without mild cognitive impairment. *J Neurosci Methods, 237*, 16-25. doi:10.1016/j.jneumeth.2014.08.020

Learmonth, G., Thut, G., Benwell, C. S., & Harvey, M. (2015). The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. *Neuropsychologia, 74*, 108-119. doi:10.1016/j.neuropsychologia.2015.01.037

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Ziemann, U., Garcia-Larrea, L., & Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol, 128*(1), 56-92. doi:10.1016/j.clinph.2016.10.087

Lehrl, S. (2005). *Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B [Multiple Choice Vocabulary Test, version B]*. Balingen, Germany: Spitta Verlag.

Lemaitre, H., Goldman, A. L., Sambataro, F., Verchinski, B. A., Meyer-Lindenberg, A., Weinberger, D. R., & Mattay, V. S. (2012). Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? *Neurobiol Aging, 33*(3), 617 e611-619. doi:10.1016/j.neurobiolaging.2010.07.013

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, 125*(10), 2238-2247. doi:10.1093/brain/awf238

Lindenberg, R., Nachtigall, L., Meinzer, M., Sieg, M. M., & Flöel, A. (2013). Differential effects of dual and unihemispheric motor cortex stimulation in older adults. *J Neurosci, 33*(21), 9176-9183. doi:10.1523/JNEUROSCI.0055-13.2013

Mandikal Vasuki, P. R., Sharma, M., Ibrahim, R. K., & Arciuli, J. (2017). Musicians' Online Performance during Auditory and Visual Statistical Learning Tasks. *Front Hum Neurosci, 11*, 114. doi:10.3389/fnhum.2017.00114

Manenti, R., Brambilla, M., Petesi, M., Ferrari, C., & Cotelli, M. (2013). Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. *Front Aging Neurosci, 5*, 49. doi:10.3389/fnagi.2013.00049

Manenti, R., Sandrini, M., Gobbi, E., Binetti, G., & Cotelli, M. (2018). Effects of transcranial direct current stimulation on episodic memory in amnestic mild cognitive impairment: A pilot study. *J Gerontol B Psychol Sci Soc Sci*. doi:10.1093/geronb/gby134

Manenti, R., Sandrini, M., Gobbi, E., Cobelli, C., Brambilla, M., Binetti, G., & Cotelli, M. (2017). Strengthening of Existing Episodic Memories Through Non-invasive Stimulation of Prefrontal Cortex in Older Adults with Subjective Memory Complaints. *Front Aging Neurosci, 9*, 401. doi:10.3389/fnagi.2017.00401

Martin, A. K., Meinzer, M., Lindenberg, R., Sieg, M. M., Nachtigall, L., & Flöel, A. (2017). Effects of Transcranial Direct Current Stimulation on Neural Networks in Young and Older Adults. *J Cogn Neurosci, 29*(11), 1817-1828. doi:10.1162/jocn_a_01166

Martins, R., Joanette, Y., & Monchi, O. (2015). The implications of age-related neurofunctional compensatory mechanisms in executive function and language processing including the new Temporal Hypothesis for Compensation. *Front Hum Neurosci, 9*, 221. doi:10.3389/fnhum.2015.00221

Matsumoto, H., & Ugawa, Y. (2017). Adverse events of tDCS and tACS: A review. *Clin Neurophysiol Pract, 2*, 19-25. doi:10.1016/j.cnp.2016.12.003

McGarrigle, L., Irving, K., van Boxtel, M. P. J., & Boran, L. (2019). Cognitive Reserve Capacity: Exploring and Validating a Theoretical Model in Healthy Ageing. *J Int Neuropsychol Soc*, 1-15. doi:10.1017/S1355617719000250

McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N., & Binder, J. R. (2006). Interrupting the “stream of consciousness”: An fMRI investigation. *Neuroimage, 29*(4), 1185 - 1191.

Medvedeva, A., Materassi, M., Neacsu, V., Beresford-Webb, J., Hussin, A., Khan, N., Newton, F., & Galli, G. (2018). Effects of Anodal Transcranial Direct Current Stimulation Over the Ventrolateral Prefrontal Cortex on Episodic Memory Formation and Retrieval. *Cereb Cortex*. doi:10.1093/cercor/bhx347

Meinzer, M., Jahnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., Rodriguez, A. D., Lindenberg, R., & Flöel, A. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex, 50*, 137-147. doi:10.1016/j.cortex.2013.07.013

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Flöel, A. (2013). Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. *The Journal of Neuroscience, 33*(30), 12470-12478. doi:10.1523/JNEUROSCI.5743-12.2013

Meinzer, M., Lindenberg, R., Phan, M. T., Ulm, L., Volk, C., & Flöel, A. (2015). Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. *Alzheimers Dement, 11*(9), 1032-1040. doi:10.1016/j.jalz.2014.07.159

Meinzer, M., Lindenberg, R., Sieg, M. M., Nachtigall, L., Ulm, L., & Flöel, A. (2014). Transcranial direct current stimulation of the primary motor cortex improves word-retrieval in older adults. *Front Aging Neurosci, 6*, 253. doi:10.3389/fnagi.2014.00253

Minamoto, T., Azuma, M., Yaoi, K., Ashizuka, A., Mima, T., Osaka, M., Fukuyama, H., & Osaka, N. (2014). The anodal tDCS over the left posterior parietal cortex enhances attention toward a focus word in a sentence. *Front Hum Neurosci, 8*, 992. doi:10.3389/fnhum.2014.00992

Montagne, A., Barnes, S. R., Sweeney, M. D., Halliday, M. R., Sagare, A. P., Zhao, Z., Toga, A. W., Jacobs, R. E., Liu, C. Y., Amezcua, L., Harrington, M. G., Chui, H. C., Law, M., & Zlokovic, B. V. (2015). Blood-brain barrier breakdown in the aging human hippocampus. *Neuron, 85*(2), 296-302. doi:10.1016/j.neuron.2014.12.032

Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., & Priori, A. (2013). Transcranial direct current stimulation (tDCS) and language. *J Neurol Neurosurg Psychiatry, 84*(8), 832-842. doi:10.1136/jnnp-2012-302825

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic Memory and Beyond: The Hippocampus and Neocortex in Transformation. *Annu Rev Psychol, 67*, 105-134. doi:10.1146/annurev-psych-113011-143733

Naveh-Benjamin, M., Shing, Y. L., Kilb, A., Werkle-Bergner, M., Lindenberger, U., & Li, S. C. (2009). Adult age differences in memory for name-face associations: The effects of intentional and incidental learning. *Memory, 17*(2), 220-232. doi:10.1080/09658210802222183

Nissim, N. R., O'Shea, A. M., Bryant, V., Porges, E. C., Cohen, R., & Woods, A. J. (2016). Frontal Structural Neural Correlates of Working Memory Performance in Older Adults. *Front Aging Neurosci, 8*, 328. doi:10.3389/fnagi.2016.00328

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

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

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003). Facilitation of Implicit Motor Learning by Weak Transcranial Direct Current Stimulation of the Primary Motor Cortex in the Human. *Journal of Cognitive Neuroscience, 15*(4), 619-626.

Oldfield, R. C. (1972). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*.

Pardridge, W. M. (2012). Drug transport across the blood-brain barrier. *J Cereb Blood Flow Metab, 32*(11), 1959-1972. doi:10.1038/jcbfm.2012.126

Paulus, W. (2011). Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychol Rehabil, 21*(5), 602-617. doi:10.1080/09602011.2011.557292

Perceval, G., Flöel, A., & Meinzer, M. (2016). Can transcranial direct current stimulation counteract age-associated functional impairment? *Neurosci Biobehav Rev, 65*, 157-172. doi:10.1016/j.neubiorev.2016.03.028

Perceval, G., Martin, A. K., Copland, D. A., Laine, M., & Meinzer, M. (2017). High-definition tDCS of the temporo-parietal cortex enhances access to newly learned words. *Sci Rep, 7*(1), 17023. doi:10.1038/s41598-017-17279-0

Pliatsikas, C. (2019). Understanding structural plasticity in the bilingual brain: The Dynamic Restructuring Model. *Bilingualism: Language and Cognition*, 1-13. doi:10.1017/s1366728919000130

Polania, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci, 21*(2), 174-187. doi:10.1038/s41593-017-0054-4

Prehn, K., & Flöel, A. (2015). Potentials and limits to enhance cognitive functions in healthy and pathological aging by tDCS. *Frontiers in Cellular Neuroscience, 9*(355). doi:10.3389/fncel.2015.00355

Price, C. J. (2000). The anatomy of language: contributions from functional neuroimaging. *Journal of Anatomy, 97*, 335-359.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage, 62*(2), 816-847. doi:10.1016/j.neuroimage.2012.04.062

Pruski, A., & Celnik, P. (2019). The use of non-invasive brain Stimulation (NIBS), specifically transcranial direct current stimulation (tDCS) after stroke. *American Journal of Physical Medicine & Rehabilitation, Publish Ahead of Print*. doi:10.1097/phm.0000000000001209

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science, 17*, 177 - 182. doi:10.1111/j.1467-8721.2008.00570.x

Reuter-Lorenz, P. A., & Park, D. C. (2010). Human neuroscience and the aging mind: a new look at old problems. *J Gerontol B Psychol Sci Soc Sci, 65*(4), 405-415. doi:10.1093/geronb/gbq035

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol, 23*(2), 255-260. doi:10.1016/j.conb.2012.11.005

Saar-Ashkenazy, R., Cohen, J. E., Guez, J., Gasho, C., Shelef, I., Friedman, A., & Shalev, H. (2014). Reduced corpus-callosum volume in posttraumatic stress disorder highlights the importance of interhemispheric connectivity for associative memory. *J Trauma Stress, 27*(1), 18-26. doi:10.1002/jts.21887

Saar-Ashkenazy, R., Veksler, R., Guez, J., Jacob, Y., Shelef, I., Shalev, H., Friedman, A., & Cohen, J. E. (2016). Breakdown of Inter-Hemispheric Connectivity Is Associated with Posttraumatic Symptomatology and Memory Impairment. *PLoS One, 11*(2), e0144766. doi:10.1371/journal.pone.0144766

Sandrini, M., Manenti, R., Brambilla, M., Cobelli, C., Cohen, L. G., & Cotelli, M. (2016). Older adults get episodic memory boosting from noninvasive stimulation of prefrontal cortex during learning. *Neurobiol Aging, 39*, 210-216. doi:10.1016/j.neurobiolaging.2015.12.010

Saxena, S., & Hillis, A. E. (2017). An update on medications and noninvasive brain stimulation to augment language rehabilitation in post-stroke aphasia. *Expert Rev Neurother, 17*(11), 1091-1107. doi:10.1080/14737175.2017.1373020

Schacter, D. L., Savage, C. R., Alpert, N. M., Rauch, S. L., & Albert, M. S. (1996). The role of hippocampus and frontal cortex in age-related memory changes: A PET study. *Neuroreport, 7*, 1165 - 1169.

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS). *Clinical Gerontologist, 5*(1/2), 165-173. doi:10.1300/J018v05n01_09

Snodgrass, J. G., & Corwin, J. (1988). Pragmatics of Measuring Recognition Memory: Applications to Dementia and Amnesia. *Journal of Experimental Psychology: General, 117*(1), 34 - 50.

Snodgrass, J. G., & Vanderwart, M. (1980). A Standardized Set of 260 Pictures: Norms for Name Agreement, Image Agreement, Familiarity, and Visual Complexity. *Journal of Experimental Psychology: Human Learning and Memory, 6*(2), 174-215.

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem, 82*(3), 171-177. doi:10.1016/j.nlm.2004.06.005

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology, 5*, 169 - 177

Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. *Cold Spring Harb Perspect Biol, 7*(8), a021766. doi:10.1101/cshperspect.a021766

Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of Transcranial Direct Current Stimulation. *J ECT, 34*(3), 144-152. doi:10.1097/YCT.0000000000000510

Stephens, J. A., & Berryhill, M. E. (2016). Older Adults Improve on Everyday Tasks after Working Memory Training and Neurostimulation. *Brain Stimul, 9*(4), 553-559. doi:10.1016/j.brs.2016.04.001

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028. doi:10.1016/j.neuropsychologia.2009.03.004

Strobach, T., Antonenko, D., Schindler, T., Flöel, A., & Schubert, T. (2016). Modulation of Executive Control in the Task Switching Paradigm With Transcranial Direct Current Stimulation (tDCS). *Journal of Psychophysiology, 30*(2), 55-65. doi:10.1027/0269-8803/a000155

Tatti, E., Rossi, S., Innocenti, I., Rossi, A., & Santarnecchi, E. (2016). Non-invasive brain stimulation of the aging brain: State of the art and future perspectives. *Ageing Res Rev, 29*, 66-89. doi:10.1016/j.arr.2016.05.006

Thiel, A., & Zumbansen, A. (2016). The pathophysiology of post-stroke aphasia: A network approach. *Restor Neurol Neurosci, 34*(4), 507-518. doi:10.3233/RNN-150632

Tremblay, S., Lepage, J. F., Latulipe-Loiselle, A., Fregni, F., Pascual-Leone, A., & Theoret, H. (2014). The uncertain outcome of prefrontal tDCS. *Brain Stimul, 7*(6), 773-783. doi:10.1016/j.brs.2014.10.003

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063-1070. doi:10.1037/0022-3514.54.6.1063

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med, 2*(4), a006171. doi:10.1101/cshperspect.a006171

Winocur, G., & Moscovitch, M. (2011). Memory transformation and systems consolidation. *J Int Neuropsychol Soc, 17*(5), 766-780. doi:10.1017/S1355617711000683

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., Cohen, L. G., Fregni, F., Herrmann, C. S., Kappenman, E. S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P. C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., & Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol, 127*(2), 1031-1048. doi:10.1016/j.clinph.2015.11.012

Woods, A. J., Antonenko, D., Flöel, A., Hampstead, B. M., Clark, D., & Knotkova, H. (2019). Transcranial Direct Current Stimulation in Aging Research. In *Practical Guide to Transcranial Direct Current Stimulation* (pp. 569-595).

Woods, A. J., Cohen, R., Marsiske, M., Alexander, G. E., Czaja, S. J., & Wu, S. (2018). Augmenting cognitive training in older adults (The ACT Study): Design and Methods of a Phase III tDCS and cognitive training trial. *Contemp Clin Trials, 65*, 19-32. doi:10.1016/j.cct.2017.11.017

Wortman-Jutt, S., & Edwards, D. J. (2017). Transcranial Direct Current Stimulation in Poststroke Aphasia Recovery. *Stroke, 48*(3), 820-826. doi:10.1161/STROKEAHA.116.015626

Zerr, C. L., Berg, J. J., Nelson, S. M., Fishell, A. K., Savalia, N. K., & McDermott, K. B. (2018). Learning Efficiency: Identifying Individual Differences in Learning Rate and Retention in Healthy Adults. *Psychological Science, 29*(9), 1436-1450.

APPENDIX

Appendix 1 Introduction to the associative learning paradigm.

Instruktion für Kunstsprache

In dieser Untersuchung wollen wir überprüfen, ob Probanden auch ohne Rückmeldung und ohne bewusste Erinnerungsstrategien eine Kunstsprache erlernen können.

Im Folgenden wird Ihnen jeweils ein Kunstwort zusammen mit einem Bild präsentiert. Sie sollen dann jeweils intuitiv entscheiden, ob das Kunstwort korrekt oder inkorrekt mit dem Bild gepaart ist. Wir sind uns darüber im Klaren, dass es Ihnen nicht leichtfallen wird, eine Entscheidung zu treffen. Wir möchten Sie dennoch bitten, jeweils ganz spontan mit “richtig” oder “falsch” zu antworten. Welche Tasten Sie dafür drücken, wird Ihnen zu Beginn der Aufgabe mitgeteilt. Den “richtigen“ und “falschen“ Zuordnungen liegt ein kompliziertes Modell zugrunde, dass wir Ihnen zum jetzigen Zeitpunkt nicht verraten dürfen. Wir möchten Sie deshalb bitten, sich nicht darauf zu konzentrieren das Modell zu verstehen, sondern sich ganz von Ihrem Gefühl leiten zu lassen.

Bitte denken Sie nicht lange über Ihre Entscheidung nach. Die Antwort wird vom Computer nur in dem Zeitintervall gespeichert, in dem das Bild auf dem Monitor dargeboten wird. Alle anderen Durchgänge gehen bei der Auswertung verloren.

Es gibt einen kurzen Übungsdurchgang, nach dem Sie auch eventuelle Fragen mit dem/der Versuchsleiter/-in besprechen können und anschließend 5 aufeinander folgende Durchgänge, bei denen Sie versuchen sollen, so gut und so schnell wie möglich einzuschätzen, ob das Kunstwort „richtig“ zu dem Bild zugeordnet ist. Dies wird ungefähr 35 Minuten dauern.

STATUTORY DECLARATION

“I, Justus Netzband, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic: Using Anodal tDCS in an associative learning paradigm in healthy older adults (Effekte anodaler tDCS bei älteren Erwachsenen in einem assoziativen Lernparadigma), independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts, which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

_____

Date Signature

Declaration of your own contribution to any publications

Justus Netzband contributed the following to the below listed publications:

Publication 1; Antonenko, Daria; Hayek, Dayana; Netzband, Justus; Grittner, Ulrike & Flöel, Agnes. tDCS-induced episodic memory enhancement and its association with functional network coupling in older adults. Scientific Reports. 2019.

Contribution:

- Primary data collection (subject recruitment and scheduling, neuropsychological testing, behavioural- and MRI data collection)
- Behavioural data processing

_____

Signature, date and stamp of first supervising university professor / lecturer

CURRICULUM VITAE

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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