Action mechanisms of transcranial direct current stimulation in Alzheimer’s disease and memory loss

Niels Hansen*

Department of Neurophysiology, Ruhr University Bochum, Bochum, Germany

INTRODUCTION

As the pharmacological treatment of Alzheimer’s disease (AD) is often limited and accompanied by drug side effects. Thus alternative therapeutic strategies such as non-invasive brain stimulation are needed. Few studies have demonstrated that transcranial direct current stimulation (tDCS), a method of neuromodulation with consecutive robust excitability changes within the stimulated cortex area, is beneficial in AD. There is also evidence that tDCS enhances memory function in cognitive rehabilitation in depressive patients, Parkinson’s disease, and stroke. tDCS improves working and visual recognition memory in humans and object-recognition learning in the elderly. AD’s neurobiological mechanisms comprise changes in neuronal activity and the cerebral blood flow (CBF) caused by altered microvasculature, synaptic dysregulation from β-amyloid peptide accumulation, altered neuromodulation via degenerated modulatory amine transmitter systems, altered brain oscillations, and changes in network connectivity. tDCS alters (i) neuronal activity and (ii) human CBF, (iii) has synaptic and non-synaptic after-effects (iv), can modify neurotransmitters polarity-dependently, (v) and alter oscillatory brain activity and (vi) functional connectivity patterns in the brain. It thus is reasonable to use tDCS as a therapeutic instrument in AD as it improves cognitive function in manner based on a disease mechanism. Moreover, it could prove valuable in other types of dementia. Future large-scale clinical and mechanism-oriented studies may enable us to identify its therapeutic validity in other types of demential disorders.

The pharmacological treatment of Alzheimer’s disease (AD) is often limited and accompanied by drug side effects. Thus alternative therapeutic strategies such as non-invasive brain stimulation are needed. Few studies have demonstrated that transcranial direct current stimulation (tDCS), a method of neuromodulation with consecutive robust excitability changes within the stimulated cortex area, is beneficial in AD. There is also evidence that tDCS enhances memory function in cognitive rehabilitation in depressive patients, Parkinson’s disease, and stroke. tDCS improves working and visual recognition memory in humans and object-recognition learning in the elderly. AD’s neurobiological mechanisms comprise changes in neuronal activity and the cerebral blood flow (CBF) caused by altered microvasculature, synaptic dysregulation from β-amyloid peptide accumulation, altered neuromodulation via degenerated modulatory amine transmitter systems, altered brain oscillations, and changes in network connectivity. tDCS alters (i) neuronal activity and (ii) human CBF, (iii) has synaptic and non-synaptic after-effects (iv), can modify neurotransmitters polarity-dependently, (v) and alter oscillatory brain activity and (vi) functional connectivity patterns in the brain. It thus is reasonable to use tDCS as a therapeutic instrument in AD as it improves cognitive function in manner based on a disease mechanism. Moreover, it could prove valuable in other types of dementia. Future large-scale clinical and mechanism-oriented studies may enable us to identify its therapeutic validity in other types of demential disorders.

METHODOLOGICAL ASPECTS

The review section about the action mechanisms of tDCS in AD is based on a non-systematic approach, whereas the review section on clinical studies with tDCS in AD and memory is based on a somewhat systematic approach based on the PubMed database. A literature search for original and review articles on tDCS in demential disorders was performed through December 2011 seeking clinical studies on tDCS in AD and memory. The keywords were used in combination with “Alzheimer disease” AND “tDCS,” “dementia” AND “tDCS” as well as “memory” AND “tDCS.” The studies were published between 2004 and 12/2011. The exclusion criteria of articles in the article titles searched were only “brain stimulation,” “depression,” only “memory” or “Alzheimer disease,” or “demential disorder” without “tDCS,” “motor learning,” and only “tDCS” without “memory” or “Alzheimer disease” or “demential disorder.” Thirty-eight papers were screened from 75 articles according to the aforementioned criteria and 33
Table 1 | Clinical studies of tDCS in dementia.

| Study            | Design     | n  | Age (years) | Disease diagnosis | MMSE | Medication | Parameters | Brain target | Effect                              |
|------------------|------------|----|-------------|-------------------|------|------------|------------|--------------|-------------------------------------|
| **ALZHEIMER’S DISEASE** |            |    |             |                   |      |            |            |              |                                     |
| Boggio et al. (2009) | Cross over, sham controlled | 10 | 79 ± 9 | NINCDS, ADRAVA | 17 ± 5 | AChEIs + others | Anodal/sham, 2 mA, 30 min | Left DLPFC | Improved visual recognition memory after atDCS |
| Boggio et al. (2011) | Sham controlled | 15 | 78 ± 7, 81 ± 10 | Adas-Cog, VRT, VAT, ADAS | 21 ± 3, 19 ± 3 | No data | Anodal, sham, 2 mA, 30 min | TC bilateral | Improved visual recognition memory after atDCS |
| Ferrucci et al. (2008a) | Cross over, sham controlled | 10 | 75 ± 7 | DSM-IV, NINCDS-ADRAVA | 23 ± 2 | AChEI | Anodal/ cathodal/sham, 1.5 mA, 15 min | Left/right TPC | Accuracy of the word-recognition memory increased after atDCS |
| **FRONTOTEMPORAL DEMENTIA** |            |    |             |                   |      |            |            |              |                                     |
| Huey et al. (2007) | Double-blind, sham controlled | 10 | 61 (46–80) | Criteria Lund/ Manchester 1994 MDRS | No data | AChEI + memantine | Active/sham, 2 mA, 20 min | FC | No improvement in verbal fluency after active tDCS |

AChEI, acetylcholine esterase inhibitors; Adas-Cog, Alzheimer’s disease assessment scale-cognitive sub scale; ADAS, Alzheimer’s disease assessment scale; DLPFC, dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); FC, frontal cortex; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; NINCDS-ADRAVA, National Institute of Neurological Communicative Disorders and Stroke-Alzheimer disease and Related Disorders Association; TC, temporal cortex; TPC, temporoparietal cortex; VAT, visual attention task; VRT, visual recognition task.

Table: Clinical studies of tDCS in dementia.

- **Study**: Boggio et al. (2009)
  - **Design**: Cross over, sham controlled
  - **n**: 10
  - **Age (years)**: 79 ± 9
  - **Disease diagnosis**: NINCDS, ADRAVA
  - **MMSE**: 17 ± 5
  - **Medication**: AChEIs + others
  - **Parameters**: Anodal/sham, 2 mA, 30 min
  - **Brain target**: Left DLPFC
  - **Effect**: Improved visual recognition memory after atDCS

- **Study**: Boggio et al. (2011)
  - **Design**: Sham controlled
  - **n**: 15
  - **Age (years)**: 78 ± 7, 81 ± 10
  - **Disease diagnosis**: Adas-Cog, VRT, VAT, ADAS
  - **MMSE**: 21 ± 3, 19 ± 3
  - **Medication**: No data
  - **Parameters**: Anodal, sham, 2 mA, 30 min
  - **Brain target**: TC bilateral
  - **Effect**: Improved visual recognition memory after atDCS

- **Study**: Ferrucci et al. (2008a)
  - **Design**: Cross over, sham controlled
  - **n**: 10
  - **Age (years)**: 75 ± 7
  - **Disease diagnosis**: DSM-IV, NINCDS-ADRAVA
  - **MMSE**: 23 ± 2
  - **Medication**: AChEI
  - **Parameters**: Anodal/cathodal/sham, 1.5 mA, 15 min
  - **Brain target**: Left/right TPC
  - **Effect**: Accuracy of the word-recognition memory increased after atDCS

- **Study**: Huey et al. (2007)
  - **Design**: Double-blind, sham controlled
  - **n**: 10
  - **Age (years)**: 61 (46–80)
  - **Disease criteria**: Lund/Manchester 1994 MDRS
  - **MMSE**: No data
  - **Medication**: AChEI + memantine
  - **Parameters**: Active/sham, 2 mA, 20 min
  - **Brain target**: FC
  - **Effect**: No improvement in verbal fluency after active tDCS

The effect of anodal tDCS (atDCS) over the left temporal cortex (TC) and dorsolateral prefrontal cortex (DLPFC) was investigated on recognition and working memory (WM) in 10 AD patients (Boggio et al., 2009), revealing enhancement in a visual recognition memory task after atDCS of the DLPFC and left TC (Boggio et al., 2009). In another study, an improvement in a word-recognition memory task after atDCS of the DLPFC and left TC (Boggio et al., 2009), revealing enhancement in a visual recognition task (VRT) scores were observed (Boggio et al., 2011).

AChEI, acetylcholine esterase inhibitors; Adas-Cog, Alzheimer’s disease assessment scale-cognitive sub scale; ADAS, Alzheimer’s disease assessment scale; DLPFC, dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); FC, frontal cortex; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; NINCDS-ADRAVA, National Institute of Neurological Communicative Disorders and Stroke-Alzheimer disease and Related Disorders Association; TC, temporal cortex; TPC, temporoparietal cortex; VAT, visual attention task; VRT, visual recognition task.

Table: Clinical studies of tDCS in dementia.

- **Study**: Boggio et al. (2009)
  - **Design**: Cross over, sham controlled
  - **n**: 10
  - **Age (years)**: 79 ± 9
  - **Disease diagnosis**: NINCDS, ADRAVA
  - **MMSE**: 17 ± 5
  - **Medication**: AChEIs + others
  - **Parameters**: Anodal/sham, 2 mA, 30 min
  - **Brain target**: Left DLPFC
  - **Effect**: Improved visual recognition memory after atDCS

- **Study**: Boggio et al. (2011)
  - **Design**: Sham controlled
  - **n**: 15
  - **Age (years)**: 78 ± 7, 81 ± 10
  - **Disease diagnosis**: Adas-Cog, VRT, VAT, ADAS
  - **MMSE**: 21 ± 3, 19 ± 3
  - **Medication**: No data
  - **Parameters**: Anodal, sham, 2 mA, 30 min
  - **Brain target**: TC bilateral
  - **Effect**: Improved visual recognition memory after atDCS

- **Study**: Ferrucci et al. (2008a)
  - **Design**: Cross over, sham controlled
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  - **MMSE**: 23 ± 2
  - **Medication**: AChEI
  - **Parameters**: Anodal/cathodal/sham, 1.5 mA, 15 min
  - **Brain target**: Left/right TPC
  - **Effect**: Accuracy of the word-recognition memory increased after atDCS

- **Study**: Huey et al. (2007)
  - **Design**: Double-blind, sham controlled
  - **n**: 10
  - **Age (years)**: 61 (46–80)
  - **Disease criteria**: Lund/Manchester 1994 MDRS
  - **MMSE**: No data
  - **Medication**: AChEI + memantine
  - **Parameters**: Active/sham, 2 mA, 20 min
  - **Brain target**: FC
  - **Effect**: No improvement in verbal fluency after active tDCS

There is evidence that tDCS applied to the scalp over the prefrontal cortex over 20 min does not alter local and global cortical function (Iyer et al., 2005). The current intensity of 1 mA did not result in significant effects on cortical function, whereas verbal fluency increased with 2 mA-atDCS and decreased with 2 mA-cDCS (Iyer et al., 2005). In a systematic review, itching, tingling, headache, burning sensation, and discomfort were the most often reported adverse effects of active tDCS vs. sham tDCS (Brunoni et al., 2011). Skin irritation and skin burning can occur after tDCS application due to the electrochemical products’ skin contact generated by the direct current (Durand et al., 2002; Palm et al., 2008). In addition, magnetic resonance spectroscopy (MRS) in normal subjects failed to detect changes in acetylaspartate, thus showing that atDCS induced no neurotoxic effects (Rango et al., 2008). Furthermore, in motor cortical areas, tDCS induced no relevant changes in serum neuron-specific enolase, a neuronal damage marker, indicating that tDCS induced no harmful effects (Nitsche et al., 2003).

**Safety and side effects of tDCS**

**General observations**

There is evidence that tDCS applied to the scalp over the prefrontal cortex over 20 min does not alter local and global cortical function (Iyer et al., 2005). The current intensity of 1 mA did not result in significant effects on cortical function, whereas verbal fluency increased with 2 mA-atDCS and decreased with 2 mA-cDCS (Iyer et al., 2005). In a systematic review, itching, tingling, headache, burning sensation, and discomfort were the most often reported adverse effects of active tDCS vs. sham tDCS (Brunoni et al., 2011). Skin irritation and skin burning can occur after tDCS application due to the electrochemical products’ skin contact generated by the direct current (Durand et al., 2002; Palm et al., 2008). In addition, magnetic resonance spectroscopy (MRS) in normal subjects failed to detect changes in acetylaspartate, thus showing that atDCS induced no neurotoxic effects (Rango et al., 2008). Furthermore, in motor cortical areas, tDCS induced no relevant changes in serum neuron-specific enolase, a neuronal damage marker, indicating that tDCS induced no harmful effects (Nitsche et al., 2003).

**Observations in AD**

In studies of tDCS in AD, no adverse effects from tDCS application were noted (Boggio et al., 2009). Only an itching sensation, but no side effects were reported in the study of 10 AD patients (Ferrucci et al., 2008a). No adverse effects, nor tDCS effects on the Mini Mental State Examination (MMSE), Alzheimer’s Disease Assessment Scale-Cognitive sub scale (Adas-Cog), or visual attention task (VAT) scores were observed (Boggio et al., 2011).

**Frontotemporal Dementia**

A study demonstrated that active tDCS does not result in a beneficial effect in verbal fluency in 10 patients with frontotemporal dementia presenting mainly behavioral (and in one patient language) symptoms (Huey et al., 2007). The lack of effect may be due to the small current that reaches the frontal cortex due to brain atrophy and neuronal loss with concomitant incapability of the affected cortex to respond to brain polarization (Huey et al., 2007).
Table 2 | Studies of tDCS on cognitive functions.

| Study                        | Healthy subjects/age (age: mean ± standard deviation or range) | Stimulation electrode | Polarity | Duration/intensity | Side effects | Effects                                                                 |
|-----------------------------|---------------------------------------------------------------|-----------------------|----------|-------------------|--------------|-------------------------------------------------------------------------|
| Andrews et al. (2011)       | 10, 20–51 years                                              | Left DLPFC            | Anodal/sham | 10 min, 1 mA     | No           | Improvement in a WM task after atDCS                                   |
| Boggio et al. (2006)        | 18 Patients with PD, 45–71 years                             | M1, left DLPC         | Anodal/sham | 20 min, 1 or 2 mA | No           | Improvement in WM of Parkinson's disease patients after atDCS of the left DLPFC |
| de Vries et al. (2011)      | 38, 23 ± 2 years                                             | Broca’s area          | Anodal/sham | 20 min, 1 mA     | No           | atDCS facilitates the acquisition of grammatical knowledge             |
| Ferrucci et al. (2008b)     | 13, 75 ± 7 years                                             | Cerebellum            | Anodal/cathodal/sham | 15 min, 2 mA | Headache (one patient)        | atDCS and ctDCS impairs practice-dependent proficiency in WM       |
| Fiori et al. (2011)         | 10 Subjects, 3 patients, 45–70 years                        | Wernicke’s area       | Anodal/sham | 20 min, 1 mA     | No           | atDCS improved accuracy on the picture-naming task, both normal and patients had a shorter naming latency during atDCS |
| Fiöl et al. (2008)          | 19, 26 ± 3 years                                             | Cp5                   | Anodal/cathodal/sham | 20 min, 1 mA | No           | Improved recall one week after learning with atDCS                    |
| Fiöl et al. (2011)          | 20, 62 ± 9 years                                             | Right temporo-parietal cortex | Anodal/sham | 20 min, 1 mA     | No           | Efficient learning                                                       |
| Fregni et al. (2005)        | 15, 19–22 years                                              | M1, DLPFC             | Anodal/cathodal/sham | 10 min, 1 mA | No           | atDCS leads to enhancement of WM performance                           |
| Iyer et al. (2005)          | 103, 19–70 years                                             | F3                    | Anodal/cathodal/sham | 20 min, 1 mA | Skin redness | Enhanced verbal fluency by atDCS                                       |
| Javadi and Walsh (2011)     | 32, 23 ± 2 years                                             | Left DLPFC, M1        | Anodal/sham | 20 min, 1 mA     | No           | Enhancement of verbal memorization after atDCS or impairment of verbal memorization after ctDCS |
| Kincses et al. (2004)       | 22, 28 ± 5 years                                             | Fp3                   | Anodal/cathodal | 10 min, 1 mA | No           | atDCS enhanced probabilistic classification learning                   |
| Marshall et al. (2004)      | 13, 19–28 years                                              | F3 and F4             | Anodal/sham | Alternating 15 s off/15 s on over 30 min | No           | atDCS during slow wave sleep improves verbal declarative memory       |
| Marshall et al. (2005)      | 12, 19–27 years                                              | F3 and F4             | Anodal/cathodal | Alternating 15 s off/15 s on over 15 min | No           | Impaired performance in WM task by anodal and ctDCS                   |
| Ohn et al. (2008)           | 15, 27 ± 4 years                                             | F3                    | Anodal/sham | 30 min, 1 mA     | No           | atDCS enhanced performance in a WM task                               |
| Penolazzi et al. (2010)     | 11, 27 ± 5 years                                             | Right F4–C4, Left F3–C3, alternating between atDCS and ctDCS | Anodal/cathodal/sham | 20 min, 1 mA | No           | Right atDCS and left ctDCS facilitated the recall of pleasant images regarding pleasant and neutral images |
| Ross et al. (2011)          | 14, 55–69 years                                              | Both anterior temporal lobes | Anodal/sham | 15 min, 1.5 mA | No           | Numerical improvement in face naming after atDCS                      |
| Sparing et al. (2008)       | 15, 27 ± 4 years                                             | Cp5                   | Anodal/cathodal/sham | 7 min, 2 mA   | No           | Improved picture naming by atDCS                                      |
| Teo et al. (2011)           | 12, 27 ± 9 years                                             | F3 of the DLPFC       | Anodal/sham | 20 min, 1 mA     | No           | Current strength may affect WM performance                             |

(Continued)
WM representations are supported by oscillatory brain activity in healthy subjects (Fregni et al., 2005; Andrews et al., 2011) and increased WM performance in humans (Zaehle et al., 2011). Interestingly, atDCS led to amplified oscillatory EEG activity that in turn improved retention of object-location learning for up to 1 week after learning (Floel et al., 2011). This finding has relevance concerning memory deficits in normal and pathological aging.

### tDCS in Learning and Memory

#### Object-Location Learning in the Elderly

The ability to memorize the location of objects is known to worsen by aging and in neurodegenerative dementia. atDCS over the temporoparietal cortex in 20 elderly healthy subjects resulted in improved retention of object-location learning for up to 1 week after learning (Floel et al., 2011). This finding has relevance concerning memory deficits in normal and pathological aging.

#### Enhancing Declarative Memory by tDCS

Anodal tDCS enhances slow oscillatory EEG activity that in turn can enhance declarative memories (Marshall et al., 2004). As shown in 32 healthy subjects, declarative memory can be improved by anodal and impaired by ctDCS of the DLPFC (Javadi and Walsh, 2011).

#### Enhancing Implicit Memory by tDCS

Both declarative and implicit memory are known to improve via tDCS. For instance, atDCS of Broca’s area enhanced implicit learning of an artificial grammar in 38 healthy subjects (de Vries et al., 2011), an interesting finding supporting tDCS as a potential instrument in the rehabilitation of aphasic patients.

### Modulation of WM by tDCS

#### Enhancing WM by tDCS

Several studies address the physiological effects of tDCS in the WM as a part of declarative memory playing a pivotal role in long-term memory, language, and executive function (Baddeley, 1992).

In 10 patients with cognitive defects after a first-ever stroke, atDCS of the DLPFC led to enhanced WM performance (Jo et al., 2009). In a neurodegenerative disease like Parkinson’s, atDCS of the left DLPFC was also shown to improve WM in 18 patients (Boggio et al., 2006). atDCS to the DLPFC lead to WM enhancement in healthy subjects (Fregni et al., 2005; Andrews et al., 2011) and rats, frontal ctDCS enhanced visual–spatial WM (Dockery et al., 2011). Interestingly, atDCS led to amplified oscillatory activity in theta and alpha electroencephalography (EEG) bands and increased WM performance in humans (Zaehle et al., 2011). WM representations are supported by oscillatory brain activity (Lisman and Idiart, 1995). In particular, theta EEG band activity has been associated with memory encoding and retrieval (Jensen and Tesche, 2002). Thus amplified theta band activity is related to WM’s executive function, indicating the continuous information processing required during WM performance.

As neuroimaging studies revealed a widespread effect in cortical activity by tDCS (Lang et al., 2005), it is likely to imply a tDCS influence on the entire WM system, and not only on the DLPFC. Furthermore, there is some evidence that WM performance can be improved in a manner dependent on current strength in 14 healthy subjects (Teo et al., 2011). No current strength or time-course effect was observed in the accuracy of WM tasks. However, a significant current by time interaction was found in a WM task (Teo et al., 2011). However, the effect-dependence on current intensity of tDCS in memory function is not proven by this single study of one WM task; it requires further examination in healthy subjects and those with diverse cognitive functions.

A time-dependent enhancement of verbal memory resulted after atDCS of the DLPFC (Ohn et al., 2008). Name recall can benefit from atDCS of the anterior temporal lobes (Ross et al., 2011), and word retrieval improved in healthy and non-fluent aphasic patients after atDCS (Fiori et al., 2011).

#### Impairment of WM after tDCS

Bilateral prefrontal ctDCS and atDCS during a memory task can impair neuronal processes related to a WM paradigm (Marshall et al., 2005). Furthermore, cerebellar tDCS of both polarities impaired use-dependent improvement in a WM task (Ferrucci et al., 2008b). WM also revealed impairment by ctDCS to the right parietal lobe (Berryhill et al., 2010).

### Potential Mechanisms of Action of tDCS in AD

#### Effects of tDCS on Neuronal Activity by Altering the Membrane Potential

In an AD mouse model, β-amyloid peptide was shown to disturb the resting membrane potential in muscle fibers (Mukhamedarov et al., 2011). Furthermore, β-amyloid 1–42 peptide caused membrane depolarization leading to hyperexcitability of affected neurons in a human neuronal cell model of AD (Blanchard et al., 2002).

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### Table 2 | Continued

| Study                  | Healthy subjects/age (age: mean ± standard deviation or range) | Stimulation electrode | Polarity                  | Duration/Intensity | Side effects | Effects                                                                 |
|------------------------|---------------------------------------------------------------|-----------------------|---------------------------|--------------------|--------------|------------------------------------------------------------------------|
| Zaehle et al. (2011)   | 10, 25 ± 2 years                                              | Left DLPFC            | Anodal/cathodal           | 15 min, 1 mA       | No           | Increase in WM performance and amplified oscillatory power in theta and alpha bands after atDCS, interference with WM performance after ctDCS |

**Abbreviations for electrode placement according to the 10–20 electrode system (Cp5, Cz, Fp3, C3/4: see Recommendations for the practice of clinical Neurophysiology: guidelines of the International Federation Clinical Neurophysiology. Electroencephalogr. Clin. Neurophysiol. Suppl. 1999;52:1–304), atDCS, anodal transcranial direct current stimulation; min, minutes; ctDCS, cathodal transcranial direct current stimulation, DLPFC, dorsolateral prefrontal cortex; mA, milli Ampere; min, minutes, PD, Parkinson’s disease; TPC, temporoparietal cortex.**
Anodal after-effects are probably mediated in part by gamma-aminobutyric acid (GABA)ergic interneurons as a reduction in synaptic activity in magnetoencephalography; Fernandez et al., 2002).

Motor cortex (Di Lazzaro et al., 2004) and global cortical hyperexcitability is found in AD (Rossini et al., 2007), correlating with cognitive severity in a TMS study (Alagona et al., 2001). As ctDCS led to reduced cortical excitability caused by neuronal hyperpolarization (Nitsche and Paulus, 2000), it might also be beneficial in AD by lowering its somewhat increased cortical excitability.

Non-synaptic mechanisms based on changes in the membrane potential underlying the after-effects of atDCS and ctDCS (Ardolino et al., 2005) might be responsible for modulating cognitive function in AD. The local changes in ionic concentrations could be due to alterations in transmembrane proteins and from changes in H+ ions induced by exposure to a constant electrical field (Ardolino et al., 2005).

**SYNAPTIC AFTER-EFFECTS OF tDCS**

**NMDSA receptor-dependent after-effects**

tDCS induces prolonged after-effects sharing similarities with long-term potentiation (LTP)- and long-term depression (LTD)-like changes in cortical excitability (Paulus, 2004). In an in vitro and in vivo AD mouse model, LTP as the putative mechanism of learning and memory is evidently impaired by β-amyloid peptide (Gengler et al., 2010; Middei et al., 2010). β-amyloid peptide disruption of LTP is N-methyl-D-aspartate (NMDA) receptor-dependent in the mouse hippocampus in vivo and in vitro (Yamin, 2009).

tDCS-induced after-effects are partly NMDSA receptor-dependent (Liebetanz et al., 2002), suggesting that tDCS after-effects may alter NMDSA receptor-dependent cortical plasticity that may be disturbed in AD.

**GABAergic interneurons**

Anodal after-effects are probably mediated in part by gamma-aminobutyric acid (GABA)ergic interneurons as a reduction in short-interval intracortical inhibition and an increase in I-wave facilitation after tDCS intracortical facilitation (Nitsche et al., 2005; Stagg et al., 2009; Stagg and Nitsche, 2011). As in AD, GABAergic cortical inhibitory interneurons play a role in the disease’s early stage (Koliatsos et al., 2006); modulation of these interneurons by tDCS is a possible disease-modifying mechanism. Hippocampus changes in GABA B receptor protein were found in 16 elderly subjects with AD, indicating alterations between the excitatory and inhibitory neurotransmitter systems with consecutively dysfunctional hippocampal circuitry (Iwakiri et al., 2005). A MRS study provides evidence that atDCS causes reduced GABA concentration within the stimulated cortex, whereas ctDCS leads to impaired glutamatergic neuronal activity with a correlated reduction in GABA concentration due to a relationship between these two neurotransmitters (Stagg et al., 2009). Thus tDCS might reduce the disequilibrium between excitatory and inhibitory neurotransmitters systems in AD.

**Gluatamatergic synapses**

In AD, glutamate receptors may be dysregulated by β-amyloid accumulation resulting in the disrupted glutamatergic activity that coincides with cognitive decline (Parameshwaran et al., 2008). The dysregulation of glutamatergic activity might be altered by atDCS, as there is evidence that glutamatergic synapses are involved in anodal after-effects (Stagg et al., 2009; Stagg and Nitsche, 2011), and MRS data support that glutamate and glutamine levels were elevated in the parietal cortex after atDCS (Clark et al., 2011).

Therefore, ctDCS may have the potential to affect cognitive functions in AD by modulating glutamatergic synapses.

**EFFECTS OF tDCS ON HUMAN REGIONAL CEREBRAL BLOOD FLOW**

There is evidence in AD that characteristics of the cerebral microvasculature have changed, leading to altered cerebral blood flow (CBF; van Beek et al., 2012). atDCS induced an increase in regional cerebral blood flow (rCBF), whereas ctDCS resulted in a decrease in rCBF during and after stimulation (Zheng et al., 2011). As tDCS modulates CBF in many cortical and subcortical regions with sustained and widespread changes in neuronal activity (Lang et al., 2005), it is an auspicious instrument in AD.
neurodegenerative dementia (Schmitt, 2005; Fregni et al., 2006). Modulating these neurotransmitter systems via tDCS would therefore seem to be a mechanism-based treatment of AD. Dopaminergic (Nitsche et al., 2006), serotonergic (Nitsche et al., 2009) and cholinergic (Kuo et al., 2007) neuromodulations have been demonstrated by atDCS and ctDCS (Stagg and Nitsche, 2011), indicating another disease-modifying treatment option of tDCS.

There are other mechanisms that determine the response of humans to tDCS, i.e., the BDNF polymorphism (Antal et al., 2004). BDNF modulation is an interesting target in AD, as ß-amyloid processing is involved in the BDNF pathway and (Forero et al., 2006) the BDNF ValMet 66 polymorphism is a neural risk for AD (Voineskos et al., 2011), suggesting BDNF as a factor shaping the cortical excitability response to tDCS in AD patients.

LIMITATIONS OF CURRENT KNOWLEDGE OF tDCS IN DEMENTIAL DISORDERS

There are few studies on the effects of tDCS in demential disorders (AD and frontotemporal dementia, see Table 1). The efficacy of tDCS in other demential disorders (for instance vascular dementia or Lewy body dementia) has thus not yet been proven. Furthermore, only a small battery of cognitive functions, i.e., selective attention, WM, visual and word-recognition memory, instruction remembering and word recall has been evaluated so far (see tDCS in Demential Disorders). tDCS effects on other cognitive functions like calculating, cognitive flexibility, language, orientation, short- and long-term memory, and writing will have to be evaluated in studies with larger cohorts and longer control periods. The tDCS effects studied thus far are short-lived (maximum up to 1 month; Boggio et al., 2011) and there are no observations regarding longer-duration interventions. Nor have the long-term side effects of tDCS been assessed. This is particularly important, as tDCS applied over longer periods might interact with mechanisms involved in neurodegeneration with either beneficial (delayed deterioration of cognition) or harmful effects (accelerated cognitive deterioration). The interaction of tDCS with pharmacological treatment has not yet been addressed systematically in studies. However, current data indicate there is no significant interaction between medication outcome and its interaction with tDCS (Boggio et al., 2011).

PERSPECTIVES OF tDCS IN AD

tDCS may enhance our understanding of the neurobiological substrates underlying the cognitive decline in AD. Factors such as cognitive reserve, genetic variants, learning capacity, volumetric studies of cortical thinning and white matter volume, and integrity will have to be thoroughly and systematically investigated in future studies of tDCS on cortical functions in AD. The therapeutic efficacy of tDCS must be examined by outcome scales commonly used in trials of pharmacological agents such as the ADAS-Cog (Freitas et al., 2011). Moreover, multiple target tDCS or tDCS targeting new brain areas must be developed to overcome multiple cognitive deficits in AD. A multi-electrode stimulation set-up was recently demonstrated that increased focality and intensity at the brain target (Dmochowska et al., 2011).

CONCLUSIONS

tDCS is an easy to perform and non-invasive alternative therapeutic tool for neurodegenerative diseases such as AD. Its effects comprise the enhancement of cognitive functions in explicit and implicit memory. The mechanisms of tDCS are based on changes in membrane polarization, cerebral blood flow, functional connectivity, and brain oscillatory activity that may be altered in AD and other demential disorders.

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