Neurostimulation for Cognition in Alzheimer’s Dementia and High Risk Populations

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Faculty/Presenter Disclosure

• Received for an investigator-initiated study in-kind equipment support from Newronika, and in-kind research online accounts from Scientific Brain Training Pro.

• Participated in an advisory board for Biogen Canada Inc.
2021 ALZHEIMER’S DISEASE FACTS AND FIGURES

1 IN 3 seniors dies with Alzheimer’s or another dementia

MORE THAN 6 MILLION Americans are living with Alzheimer’s

Alzheimer’s and dementia deaths have increased 16% during the COVID-19 pandemic

OVER 11 MILLION Americans provide unpaid care for people with Alzheimer’s or other dementias

Between 2000 and 2019, deaths from heart disease have DECREASED 7.3% while deaths from Alzheimer’s disease have INCREASED 145%

In 2021, Alzheimer’s and other dementias will cost the nation $355 BILLION.

By 2050, these costs could rise to more than $1.1 TRILLION

50% of Black Americans
42% of Native Americans
34% of Asian Americans
33% of Hispanic Americans
Mild Cognitive Impairment

Roberts et al. Neurology, 2014
Late-Life Depression & Risk of Dementia

Bassuk, 1998
Becker, 2009
Chen, 1999
Chen, 2008 (UK)
Chen, 2008 (Chinese)
Dal Forno, 2005 (Males)
Dal Forno, 2005 (Females)
Devanand, 1996
Fuhrer, 2003
Gatz, 2005
Geerlings, 2000
Geerling, 2008
Goveas, 2011
Hébert, 2000
Irie, 2008
Kim, 2010
Köhler, 2011
Lenoir, 2011
Li, 2001
Lindsay, 2002
Palmer, 2007
Palsson, 1999
Saczynski, 2010
Spira, 2012
Yaffe, 1999

Summary: 1.85 (1.67-2.04)

23 Prospective Studies
Sensory Processing

Cognitive Processing

Sensory Cortices

Association Cortices (e.g. PFC)

Aging

Under-recruitment (decline)

Over-recruitment (compensation)

Dennis & Cabeza, 2008. In Craik & Salthouse (Eds.), Handbook of aging and cognition: Third edition
PACt-MD

Preventing Alzheimer’s dementia with Cognitive remediation plus tDCS in MCI and Depression
Transcranial Direct Current Stimulation (tDCS)
Electrical Stimulation

Egyptian Nile Catfish - *Malapterurus electricus* -2,500 BC → Arthritis

Scribonius Largus used a live torpedo fish to treat a patient with gout and wrote in 46 AD that headaches and gout ... other pains could be cured by standing in shallow water near these electric fish.

The Arabians emphasized the virtues of the sleep, which followed the jolting contact with fish. Haly Abbas referred to the latter as the Pisces dormitans. Avicenna and Averhoses thought it was efficacious when placed on the brow of persons afflicted with migraine, melancholy, or epilepsy.
tDCS

Voltage (mV)

- Threshold
- Stimulus

Action potential

Depolarization

Failed initiations

Repolarization

Resting state

Refractory period

Time (ms)
tDCS to the Motor Cortex

Nitsche & Paulus, Neurology, 2001
tDCS in Alzheimer Dementia

N = 15
Mean Age ~ 79
Number of sessions = 5

Bitemporal Anodal tDCS
(cathode right deltoid)
2 mA

Boggio et al, Brain Stimulation, 2012
tDCS in Major Depression - Cognition

A

Percentage of Hits

Sham  Active

Offline  Online

B

$\delta'$

Sham  Active

Offline  Online

Oliveira et al, Neuroscience Letters, 2013
Cognitive Remediation

tDCS

Threshold

Depolarization

Failed initiations

Refractory period

Action potential

Resting state

Voltage (mV)

Stimulus

Time (ms)
## Principles of Cognitive Remediation

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
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<tbody>
<tr>
<td>Strategic</td>
<td>The development of mental strategies to optimize cognitive performance and task completion</td>
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<tr>
<td>Drill and Practice</td>
<td>The repetition of cognitive exercises over many sessions until performance has improved</td>
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<tr>
<td>Hierarchical</td>
<td>The progression of targeted cognitive abilities from the basic to more complex</td>
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<tr>
<td>Cueing</td>
<td>The use of external aids (usually auditory or visual) to support cognitive performance</td>
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<td>Fading</td>
<td>The gradual removal of cues and external aids in cognitive exercises to increase difficulty</td>
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<td>Adaptive</td>
<td>The adjustment of the difficulty of cognitive exercises so they remain challenging and engaging</td>
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<tr>
<td>Anchoring</td>
<td>The linking of cognitive exercises to &quot;real world&quot; behaviors and areas functioning domains they support</td>
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<tr>
<td>Integration with Other Treatments</td>
<td>The use of additional schizophrenia treatments and supports to maximize the benefits of cognitive remediation</td>
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</table>

Eack SM, 2012
Eligibility criteria for PACt-MD participants with mild cognitive impairment (MCI) or major depressive disorder (MDD)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>MCI group</th>
<th>MDD group with or without MCI</th>
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<tbody>
<tr>
<td></td>
<td>*Age &gt; 60</td>
<td>*Age ≥ 65</td>
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<tr>
<td></td>
<td>*Meets DSM-5 criteria for Mild Neurocognitive Disorder</td>
<td>*Meets DSM-5 criteria for one or more major depressive episode with an offset between 2 months and 5 years or an offset of 5 years or longer if at least one episode was during the participant’s adult life and it received medical attention (e.g., hospitalization; saw a psychiatrist or primary care physician; or treatment with an antidepressant)</td>
</tr>
<tr>
<td>*MADRS score of 10 or below</td>
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Randomized Blind Interventions

**Randomization**
CR + tDCS vs. Sham-Sham

**Induction**
CR + tDCS vs. Sham-Sham (5 days/week) x 8 weeks

4 months

**Consolidation**
Booster CR + tDCS vs. Sham-Sham (5 days/week) x 1 week every 6 months

Assessments and Biomarkers

**To**
(prior to Randomization)
Clinical, Cognitive, Functional Biomarkers
2 days

**T2**
Clinical, Cognitive, Functional
1 day

**T3, T4, etc.**
(every 12 months and prior to booster weeks)
Clinical, Cognitive, Functional
1 day

**Tx**
(at conversion, drop-out, or end of study)
Clinical, Cognitive, Functional Biomarkers
2 days
Hypotheses

Compared to sham + sham, CR + tDCS will:
(1) slow down cognitive decline;
(2) reduce the progression to MCI or dementia;
(3) improve cognition acutely.
Recruitment

Lost to Follow-up (n=59)

Failed Prescreen (n=805)
- Not interested (n=297)
- Did not meet eligibility criteria (n=482)
- Transportation/Mobility Issues (n=19)
- Enrollment period ended (n=5)
- Deceased (n=2)

Total Prescreened (n=1,444)

Consented to (n=486)

Consented but Not Randomized (n=68)
- Time commitment (n=20)
- Failed eligibility criteria (n=28)
- No longer interested (n=7)
- Transportation/Mobility Issues (n=4)
- Lost to Follow-up (n=4)
- Anxiety about study procedures (n=2)
- Moved Away (n=2)
- Enrollment period ended (n=1)

Declined to Consent (n=94)
- Time commitment (n=52)
- Not interested (n=28)
- Other concerns (n=9)
- Transportation/Mobility Issues (n=5)

Randomized (n=418)
- MCI: 224
- Dep+MCI: 90
- Dep-MCI: 104

Did Not Start Intervention (n=43)
- Time commitment (n=13)
- No longer interested (n=3)
- Enrollment period over (n=15)
- Anxiety about study procedures (n=4)
- Progressed to Dementia before starting intervention (n=3)
- Health Issues (n=1)
- Failed eligibility criteria (n=3)
- Lost to follow-up (n=1)

Started Active or Sham Intervention
- MCI: 200
- MDD+MCI=80
- MDD-MCI=95

Rajji et al, J Alzheimer's Disease, 2020
Mindfulness-Based Stress Reduction (MBSR) + tDCS

Total pre-screened (n = 86)

Pre-Screen Fail (n = 34)
- Exclusionary medication or diagnosis (n = 10)
- Contraindication to tDCS (n = 5)
- Did not meet PROMIS Depression and/or Anxiety cut-off (n = 11)
- SBT score too high (n = 2)
- Engages in regular mindfulness (n = 2)
- Dementia diagnosis (n = 4)

Approached for consent (n = 52)

Declined Consent (n = 14)
- Not interested (n = 9)
- Travel issues (n = 1)
- Lost to follow-up (n = 4)

Not enrolled (n = 12)
- Dropped out (n = 6)
- Enrollment window closed (n = 1)
- MoCA too low (n = 1)
- Depression/anxiety scores too low (n = 2)
- Exclusionary medication or diagnosis (n = 2)

Consented (n = 38)

Completed Baseline (n = 38)

Enrolled (n = 26)

Active tDCS (n = 12)

Completed intervention (n = 11)

Completed follow-up (n = 10)

Dropped out due to time commitment (n = 1)

Sham tDCS (n = 14)

Completed intervention (n = 13)

Completed follow-up (n = 13)

Dropped out due to time commitment (n = 1)

Did not complete follow-up assessments (n = 1)
Mindfulness-Based Stress Reduction (MBSR) + tDCS

Brooks, Ajam Oughli et al, Mindfulness, 2021
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