Neurodegenerative Cognitive Disorders

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Neurodegenerative cognitive disorders, also referred to as dementias, affect more than 46 million people worldwide [1]. By 2050, this number is estimated to be more than 131 million. The current costs associated with dementia are estimated to be US $818 billion. To date, there are no interventions to prevent, cure, or even slow down the underlying disease even though some pharmacological treatments could slow down the symptoms or for some of these disorders the underlying risk factors could be modified. Alzheimer's dementia (AD) is the most common form of dementia. Other forms of dementia include vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease dementia, and others.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that can be safely administered to conscious outpatients (i.e., it does not require general anesthesia or surgical implantation of a device). It utilizes low intensity electrical current either to typically increase cortical excitability with an anodal electrode or suppress cortical excitability with a cathodal electrode [2]. Given its ease of use, portability, and high potential of scalability, several studies have tested the effect of tDCS in patients with dementia. Most studies have focused on

patients with AD, and more recently studies have focused on mild cognitive impairment (MCI) or other forms of dementia and cognitive impairments. In this chapter, these studies are reviewed and classified based on the clinical condition they targeted. Specific details and summaries of the clinical and cognitive findings are also presented in Table 20.1.

20.1 Alzheimer's Dementia

In Ferruci et al. [3], 10 participants with Alzheimer's dementia (AD) received 3, 15-min tDCS sessions in a random order and 1 week apart: anodal transcranial direct current stimulation (tDCS), cathodal tDCS, and sham tDCS. Two stimulators were used. For each stimulator, one electrode was placed over the temporoparietal area (left or right) and the other over the right deltoid muscle. Current was 1.5 mA. Cognition was assessed before and 30 min after each session. Anodal tDCS improved word recognition and discrimination by 17% while cathodal tDCS impaired both.

In Boggio et al. [4], 10 participants with AD received 2, 30-min sessions of unilateral anodal tDCS – 1 session to the left dorsolateral prefrontal cortex (DLPFC), another to the left temporal cortex – and a third session of sham tDCS. Cathodal electrode was placed over the right supra-orbital area. Current was 2 mA. Cognition was assessed

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Table 20.1 tDCS studies in neurodegenerative cognitive disorders: basic characteristics and summary of clinical and cognitive effects

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Alzheimer's dementia: tDCS alone							
Ferruci et al. (2008)	Alzheimer's demented	10	75.2 (7.3)	1.5	1	Anode, cathode, or sham over left or right temporoparietal Reference over right deltoid	Anodal stimulation at both sites, improved word recognition, and discrimination Cathodal stimulation impaired both
Boggio et al. (2009)	Alzheimer's dementia	10	70–92	2	1	Anode or sham over left dorsolateral prefrontal cortex or left temporal cortex Cathode over right deltoid	Anodal stimulation at both sites, improved visual recognition memory
Boggio et al. (2012)	Alzheimer's dementia	15	78.9 (8.2)	2	5 consecutive	Anodes over bilateral temporal cortices Cathode over right deltoid	Compared to sham stimulation, active stimulation improved visual recognition memory and these improvements persisted for 4 weeks
Khedr et al. (2014)	Alzheimer's dementia	34	69.7 (4.8)	2	10 consecutive	Anode, cathode, or sham over left DLPFC Reference over supra-orbital region	Anodal and cathodal stimulation improved performance on MMSE immediately and the improvement persisted at 1 and 2 months
Suemoto et al. (2014)	Alzheimer's dementia – focus on apathy	40	80.5 (7.5)	2	6 every other day	Anode over left DLPFC Cathode over right supra-orbital region	tDCS had no impact on apathy
Bystad et al. (2016a)	Alzheimer's dementia	25	~73	2	5 consecutive	Anode over left temporal cortex Cathode over right frontal cortex	tDCS had no impact on verbal memory (primary outcome), global cognition, executive function, or processing speed

Study	Diagnosis	N	Age		Sessions	Electrode placement	Results
Bystad et al. (2016b)	Alzheimer's dementia	1	59	2	12 (twice a day for 6 days)	Anode over left temporal cortex Cathode over right frontal cortex	Participant experienced a clinically significant improvement on verbal memory at 2 months following the last tDCS session
Bystad et al. (2017)	Alzheimer's dementia	1	60	2	Daily over 8 months	Anode over left temporal cortex Cathode over right frontal cortex	39% improvement in verbal immediate recall, 23% improvement in verbal delayed recall, 16% improvement in vocabulary, 10% decline in visuospatial ability, and general stability in other domains
Roncero et al. (2017)	Alzheimer's dementia or frontotemporal dementia	10 (Alzheimer's dementia: 3; frontotemporal dementia: 7)	67.4 (6.3)	2	10 daily sessions followed by 10 sham daily sessions 2 months later (or vice versa)	Anode over left inferior parietal cortex Cathode over right fronto–orbital cortex	Participants improved by 40% on picture naming after active tDCS vs. 19% after sham tDCS
Cespon et al. (2019)	Alzheimer's dementia and healthy older controls	26 Alzheimer's: 12 Healthy: 14	76.0 (5.9)70.2 (5.1)	1.5	1 (anodal, cathodal, or sham, with cross-over design to receive all three types)	Anode or cathode over left DLPFC Reference electrode over right shoulder	Neither anodal nor cathodal stimulation was associated with better working memory performance compared to sham with Alzheimer's and healthy participants analyzed together
Im et al. (2019)	Alzheimer's dementia	20	~73	2	Daily over 6 months	Anode over left DLPFC Cathode over right DLPFC	Active tDCS resulted in better global cognition and language compared to sham tDCS and a trend toward better executive function

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Table 20.1 (continued)

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Gangemi et al. (In Press)	Alzheimer's dementia	2618	~68 ~ 68	22	10 consecutive 10 consecutive per month for 8 months	Anode over left frontotemporal cortex Cathode over right frontal lobe Anode over left frontotemporal cortex Cathode over right frontal lobe	Anodal stimulation was associated with global cognitive stability compared to the sham stimulation which was associated with cognitive decline immediately after the intervention Anodal stimulation was associated with global cognitive stability compared to the sham stimulation which was associated with cognitive decline immediately after the intervention
Liu et al. (In Press)	Alzheimer's dementia or mild cognitive impairment	17 Alzheimer' dementia: 9 mild cognitive impairment: 8	77 (5)	2	Random cross-over design between one session of bitemporal vs. one session of bifrontal (DLPFC), vs, 1 session of sham Sessions separated by 1 week	Bifrontal: Two anodes over left and right DLPFC; cathode over inion Bitemporal: Two anodes over the left and right temporal cortices; cathode over inion	Compared to the performance on the day before stimulation, change on working memory immediately following the one session of bitemporal stimulation (and not bifrontal stimulation) was higher than change following sham stimulation

Alzheimer's dementia: tDCS combined with cognitive enhancement intervention

| Cotelli et al. (2014) | Alzheimer's dementia | 36 | ~77 | 2 | 10 (5 days a week for 2 weeks) | Anode or sham over left DLPFC Both combined with memory or motor training Reference over right deltoid | Memory training improved face-name association and the improvement persisted at 3 months Anodal tDCS did not improve performance beyond memory training |

Study	Condition	N	Age		Montage	Protocol	Results
Penolazzi et al. (2015)	Alzheimer's dementia	1	60	2	Anode over left DLPFC Cathode over right supra-orbital region Each tDCS session was followed by cognitive training Two months later, cognitive training without tDCS	10 consecutive	tDCS combined with cognitive training improved global cognitive function that it persisted for 1 month. No improvement without tDCS
Inagawa et al. (2019)	Alzheimer's dementia or mild cognitive impairment (except for two participants with Lewy body disease)	20	~76	2	Anode over left DLPFC Cathode over right supra-orbital area	Two sessions per day for 5 consecutive days during cognitive training	There were no significant differences between active and sham tDCS on one cognition using the MMSE or the Alzheimer's disease assessment scale – cognition subscale
Mild cognitive impairment: tDCS alone							
Meinzer et al. (2015)	Mild cognitive impairment	18	67.4 (7.3)	1	Anode or sham over left inferior frontal gyrus Cathode over right supra-orbital region	1 during a semantic word-retrieval task	Anodal stimulation normalized performance compared to healthy participants
Yun et al. (2016)	Mild cognitive impairment	16	~74	2	Anode over the left DLPFC Cathode over right DLPFC	3 sessions per week for 3 weeks	Active stimulation resulted in improved subjective memory ability and contentment compared to sham stimulation. No change in objective measures of cognition
Fileccia et al. (2019)	Mild cognitive impairment	34	~71	2	Anode over left DLPFC Cathode over right deltoid	Daily sessions, 5 days per week, for up to 20 sessions	Active stimulation and not sham stimulation was associated with improvement in episodic memory, figure naming, and general cognition, immediately after stimulation

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Table 20.1 (continued)

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Gomes et al. (2019)	Mild cognitive impairment	58	~72	2	10 sessions, twice a week, over 5 weeks	Anode over left DLPFC Cathode over right supra-orbital region	Active stimulation was associated with better executive function, verbal fluency, and memory recall, but with worse visuospatial construction, when compared to sham stimulation
Manenti et al. (In Press)	Mild cognitive impairment	18	75.3 (3.7)	1.5	1 session during re-activation phase of an episodic memory task	Anode over left lateral prefrontal cortex Cathode over right supra-orbital area	Active tDCS was associated with better recognition of words compared to sham tDCS following
Mild cognitive impairment: tDCS combined with cognitive enhancement intervention							
Gonzalez et al. (2018)	Mild cognitive impairment	5	67.0 (6.6)	2	Cognitive stimulation alone (3 daily sessions) followed by sham tDCS + cognitive stimulation (1–5 daily sessions), followed by active tDCS + cognitive stimulation (1–5 daily sessions), followed by cognitive stimulation alone	Anode over left DLPFC Cathode over right deltoid muscle	Active tDCS was associated with shorter completion times on processing speed task
Das et al. (2019)	Mild cognitive impairment	22	62.9 (7.8)	2	1 session prior while watching Planet Earth videos and right before starting a cognitive training session, for a total of 8 sessions over 4 weeks	Anode over left inferior gyrus Cathode over right shoulder	Sham stimulation was associated with better executive function, inhibition, innovation, and episodic memory compared to active stimulation, immediately after the course of stimulation but not 3 months later

Study	Diagnosis	Sample	Age	Intensity	Protocol	Electrode placement	Results
Martin et al. (2019)	Mild cognitive impairment	68	~72	2 mA for 30 min then 0.016 mA for 15 to 30 more min during the remaining of cognitive training Sham: 0.016 mA for 45–60 min	15 sessions of tDCS with cognitive training (3 per week for 5 weeks)	Anode over left DLPFC Cathode over right frontal cortex	Active and not sham stimulation was associated with improvement in verbal memory immediately after the tDCS course. Both were associated with further improvements at 3-month post-treatment
de Souza et al. (2020)	Mild cognitive impairment	16 MCI32 healthy individuals	70 (6)69 (7)	1 mA	3-day visuospatial training combined with active or sham tDCS, followed, 3 months later, with 3-day visuospatial training combined with the opposite stimulation	Anode over right temporoparietal cortex Cathode over left supra-orbital area	Immediately after the training, anodal and not sham stimulation was associated with better training on the visuospatial task among MCI participants and not healthy individuals. The gains experienced by MCI participants under active – and not sham – stimulation were similar to the gains observed for the HC participant No benefits were experienced at 1-month follow-up
Frontotemporal dementia; Lewy body dementia; Parkinson's disease; primary progressive aphasia; vascular dementia							
Benussi et al. (In Press)	Frontotemporal dementia	15 Presymptomatic, 55 Symptomatic	52.5 (9.6)62.0 (7.2)	2	10 sessions (5 daily sessions per week for 2 weeks)	Anode over left DLPFC Cathode over right deltoid	Active stimulation was associated with better global cognition, verbal fluency, processing speed, executive function, emotions recognition, and behavioral symptoms

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Table 20.1 (continued)

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Elder et al. (2015)	Lew body dementia	13 (including 8 with Parkinson's disease dementia)	64.8 (7.7)	2.8	1	Anode over left DLPFC Cathode over right deltoid	Stimulation improved attention
Boggio et al. (2006)	Parkinson's disease	18	61.1	2	1 or 2	Anode over left DLPFC or left motor cortex Cathode over right orbital region	2 mA anodal stimulation improved working memory
Pereira et al. (2013)	Parkinson's disease	16	61.5 (9.9)	2	1	Anode over left DLPFC or left temporoparietal cortex Cathode over right orbital region	Stimulation improved phonemic but not semantic fluency
Doruk et al. (2014)	Parkinson's disease	18	61 (8)	2	10 (5 days a week for 2 weeks)	Anode or sham over left or right DLPFC or left motor cortex Cathode over contralateral supra-orbital region	Both anodal stimulation improved executive function and it persisted for 1 month
Manenti et al. (2016)	Mild cognitive impairment due to Parkinson's disease	20	~69	2	10 sessions (5 sessions per week for 2 weeks) combined with physical therapy	Anode over right or left DLPFC, contralateral to the most affected side Cathode over contralateral supra-orbital region	Active tDCS resulted in better cognition at the end of treatment compared to sham tDCS and this improvement was stable 3 months later Cognitive benefits were observed despite no added benefits in terms of mood or motor symptoms
Elder et al. (2017)	Parkinson's disease dementia	38	66.6 (8.4)	2.8	1 (active or sham, followed by the alternate stimulation after 24 hours)	Anode over left DLPFC Cathode over right deltoid	No difference between active and sham stimulation on cognition

Lau et al. (2019)	Parkinson's disease	10	62.7 (6.6)	2	1 (active or sham, followed by the alternate stimulation after 2 weeks) during the performance of a working memory and an inhibition task	Anode over left prefrontal cortex Cathode over right supra-orbital area	No differences on working memory and inhibition tasks were detected between active and sham stimulation
de Aguiar et al. (2020)	Primary progressive aphasia	30	66.4 (6.7)	2	10–15 sessions of active or sham tDCS delivered during the first 20 min of 45 min naming/spelling therapy sessions After a 2-month washout period, participants received another course of therapy with the alternate tDCS	Anode over left inferior frontal gyrus Cathode over right cheek	Active stimulation was associated with better performance on trained words compared to sham stimulation at the 2-month follow-up and not the 2-week or immediately after therapy assessments
Andre et al. (2016)	Vascular dementia	21	~78	2	4 at-home sessions on 4 consecutive days	Anode over left DLPFC Cathode over right supra-orbital region	Active stimulation was associated with reduced reaction time on working memory and inhibition tasks and increased performance on a picture naming task, compared to sham stimulation, immediately after the tDCS course and not 2 weeks later

DLPFC dorsolateral prefrontal cortex, *MMSE* Mini Mental State Examination, *tDCS* transcranial direct current stimulation

during stimulation. Anodal tDCS at both sites improved performance on a visual recognition memory task by 18% for the DLPFC and 14% for the temporal cortex [4].

The above two studies were followed by others that assessed the impact of a course of tDCS on cognition. In Boggio et al. [5], 15 participants with mild-to-moderate AD received daily consecutively for 5 days, 30-min sessions of bilateral anodal or sham tDCS in a random order. Anodes were placed over the temporal lobes. Cathodal electrode was placed over the right deltoid muscle. Current was 2 mA. Cognition was assessed before the first tDCS session, at the end of treatment on day 5, 1 week later, and then 4 weeks later. Anodal tDCS resulted in improvements in visual recognition memory, and these improvements persisted for 4 weeks following the course of tDCS. The percent change from baseline was about 11%. tDCS was well tolerated by all participants.

In Khedr et al. [6], 34 participants with mild-to-moderate AD were randomized to receive anodal tDCS, cathodal tDCS, or sham tDCS. tDCS was applied to the left DLPFC for 25 min daily for 10 days. The reference electrode was placed over the contralateral supra-orbital region. Current was 2 mA. Follow-up assessments were conducted immediately, and 1 and 2 months following the tDCS course. Other than for a couple of participants experiencing transient itching, headache, and dizziness, tDCS was well tolerated. Both anodal and cathodal tDCS resulted in improvement on Mini-Mental State Examination (MMSE) [7] compared with sham tDCS. The two forms of active tDCS did not differ in efficacy. Improvement on MMSE was by about four points with an initial improvement immediately following tDCS, an additional improvement 1 month later, and persistence of this improvement one additional month later. Such is a change is considered clinically significant.

In Bystad et al. [8], 25 participants with mild-to-moderate AD were randomized to receive anodal tDCS applied to the let temporal cortex with the cathodal electrode over the right frontal cortex or sham tDCS. tDCS was applied for 30 min daily for 5 days. Current was

2 mA. Follow-up assessments were conducted immediately. Other than for itching, transient headaches, and skin irritation, tDCS was well tolerated. Unlike, previous studies to date, active tDCS did not result in better verbal memory (primary outcome), global cognition, executive function, or processing speed compared to sham tDCS.

In a case report by the same group [9], a single participant with mild AD underwent an accelerated tDCS course of 12 sessions, twice a day, over 6 consecutive days. Each session consisted of anodal tDCS applied to the let temporal cortex with the cathodal electrode over the right frontal cortex and lasted for 30 min. Current was 2 mA. This report indicated that the participant experienced a clinically significant improvement in verbal memory recall and tDCS was well tolerated.

In another case report by the same group [10]), another single participant with mild AD received anodal tDCS daily for 8 months. The anode was placed over the left temporal cortex and the cathode over the right frontal cortex. Current was also 2 mA. tDCS was well tolerated. The participant experienced at the 8-month assessment 39% improvement in verbal immediate recall, 23% improvement in verbal delayed recall, 16% improvement in vocabulary, 10% decline in visuospatial ability, and general stability in other domains.

In Roncero et al. [11], 10 participants with AD ($N = 3$) or frontotemporal dementia ($N = 7$) were randomized in a cross-over design to active followed by sham tDCS (2 months later or vice versa) for 10 daily sessions. Anode was placed over the left inferior parietal cortex and the cathode over the right fronto-orbital region. Current was 2 mA. Each session was for 30 min. The primary outcome was picture naming. Active tDCS significantly improved picture naming ability by 40% vs. an improvement of 19% following sham tDCS.

In Cespon et al. [12], 12 participants with AD and 14 healthy older participants were randomized to receive anodal, cathodal or sham tDCS for 1 session delivered to the left DLPFC and then crossed over to receive all three types of stimula-

tion with a 5-day interval between 2 consecutive sessions. The reference electrode was placed over the right shoulder. Current was 1.5 mA. Duration of stimulation was 13 min. Before and after each stimulation session, participants underwent a working memory task while undergoing an electroencephalogram (EEG). All participants were analyzed together. There were no differences detected in working memory performance among the three types of stimulation. However, anodal tDCS was associated with increased P200 and P300 amplitudes in healthy participants while cathodal tDCS was associated with increased P200 amplitude and frontal theta activity in AD participants. Further, only in healthy participants improvements in working memory after anodal tDCS were correlated with increased P300.

In Liu et al. [13], 17 participants with mild AD or mild cognitive impairment (MCI; mean age: 77, SD: 5) were randomized in a cross-over design to receive 1 session of bifrontal or bitemporal or sham tDCS, all separated by 1 week. During bifrontal stimulation, two anodes were placed over the left and right DLPFC and the cathode over the inion. During bitemporal stimulation, two anodes were placed over the left and right temporal cortices and the cathode over the inion. Current was 2 mA. Duration of stimulation was 20 min. On the day before each stimulation and immediately after, participants were assessed cognitively including an assessment of working memory which was the primary domain. The authors report that only following bitemporal stimulation the improvement in working memory was significantly higher than the improvement following sham.

A few studies reported on the impact of tDCS on maintaining cognitive stability among patients with AD rather than cognitive improvement.

In Im et al. [14], 20 participants with mild AD were randomized to receive anodal tDCS to the left DLPFC with the cathode over the right DLPFC, or sham tDCS, daily for 6 months, 30 min per day. The first 3 sessions were delivered by a nurse in a hospital setting and the remaining sessions were delivered at home by a caregiver. Current was 2 mA. Active tDCS resulted in better global cognition as measured using the MMSE and better naming compared to sham tDCS at 6 months. Those randomized to active tDCS also experienced a trend toward improvement in executive function while those randomized to sham tDCS experienced a trend toward a decline. Further, those randomized to active tDCS experienced stability on 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) over the left middle/inferior temporal gyrus compared to a significant decline among those randomized to sham tDCS.

In Gangemi et al. [15], two randomized trials were reported. In the first one, 26 participants with mild AD were randomized to active or sham tDCS, for 10 daily consecutive sessions. Each session lasted for 20 min. Current was 2 mA. Anode was placed over the left fronto-temporal cortex and the cathode over the right frontal lobe. Global cognition and a composite measure of cognitive and function were assessed before and immediately after the 10-day course of tDCS. Active stimulation was associated with stability in cognition/function compared to a decline in cognition among those randomized to sham stimulation. In the second one, 18 participants with mild AD were randomized to a similar protocol except that they received the 10 sessions every month for 8 months. At the end of the 8 months, active stimulation was also associated with stability in cognition/function compared to a decline that was associated with sham intervention. The two studies support the beneficial impact of tDCS on maintaining cognition/function among patients with mild AD although it was not clear why there was a significant decline over 10 days among those who were randomized to sham tDCS. In both studies, resting EEG were collected before and after the interventions and there were changes reported within certain frequencies although it was not clear what the specific EEG analyzed variables were.

Patients with AD not only experience cognitive dysfunction, but also significant behavioral and psychological symptoms. One study focused on the effects of tDCS on apathy. In Suemoto et al. [16], 40 participants with moderate AD were randomized to receive anodal or sham tDCS delivered to the left DLPFC for 20 min, every

other day for 6 sessions over 2 weeks. Cathodal electrode was placed over the right orbit. Current was 2 mA. Assessments were conducted at baseline, 1 week into the tDCS course, at the end of the 2-week course, and then 1 week after completing the course. The primary outcome measure was the score on the Apathy Scale [17]. tDCS was well tolerated with minor side effects, mainly scalp burning sensation and tingling. The two groups did not differ on Apathy Scale at any of the time points of assessments, nor did they differ on other secondary measure, including cognitive, mood, and caregiver burden measures.

Thus, studies in AD have had mixed results when assessing for an acute improvement following a short course of tDCS effect. However, and notwithstanding that the number of studies is small, those that assessed for a cognitive stabilization effect seems to have been more positive. A parallel line of research is to investigate whether the pro-cognitive effects of tDCS can optimize performance in response to other cognitive enhancing interventions, or whether they can be augmented through these other interventions.

In Cotelli et al. [18], 36 participants with mild-to-moderate AD were randomized to receive anodal tDCS combined with memory training, sham tDCS combined with memory training, or anodal tDCS combined with motor training. tDCS was applied to left DLPFC for 25 min, 5 days a week, for 2 weeks. The reference electrode was placed on the right deltoid muscle. Current was 2 mA. tDCS was initiated at the beginning of each training session that occurred 5 days a week for 2 weeks. Memory training consisted of training on face-name association task. Assessments were conducted at baseline, after the 2 weeks of tDCS course, and then 3 and 6 months from the start of the tDCS course. Both groups who received memory training experienced improvement in face-name association talk compared with the group who received motor training. The improvement persisted at 3 month follow-up. However, there was no significant generalization to other cognitive tasks beyond what the participants trained on. More importantly, groups who received anodal or sham tDCS, combined with memory training, did not differ in performance.

In Penolazzi et al. [19], one patient with mild AD received one course of anodal tDCS, daily for 20 min for 10 days, over the left DLPFC. Reference electrode was placed over the right supra-orbital area. Current was 2 mA. Each tDCS was followed by 45 min of cognitive training. Two months later, the patient received the same course of cognitive training but with sham tDCS. Following the first course, the patient experienced improvement in global cognitive function and it persisted for 1 month. There was no such improvement following the second course.

In Inagawa et al. [20], 20 participants with AD or MCI except for 2 with Lewy body disease were randomized to receive active or sham tDCS delivered during cognitive training and over 20 min, twice a day, for 5 consecutive days. Current was 2 mA. Anode was placed over the left DLPFC and the cathode over the right supra-orbital region. While active tDCS was well tolerated, it did not improve cognition as measured using the MMSE or the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [21] over sham tDCS.

20.2 Mild Cognitive Impairment

Given the early preliminary positive evidence supporting a pro-cognitive effect of tDCS in patients with AD, it was logical to assess its effects in pre-AD stages of the illness for potentially more impact on the course of illness.

In Meinzer et al. [22], 18 participants with MCI due to AD (11 amnestic MCI and 7 multiple domain MCI) received, in a cross-over design, 1 session of anodal or sham tDCS to the left inferior frontal gyrus for 20 min. The sessions were separated by 1 week. The cathode was placed over the right supra-orbital region. Current was 1 mA. Participants received tDCS while performing a semantic word-retrieval task and undergoing functional magnetic resonance imaging (fMRI). tDCS was well tolerated. During sham tDCS, participants performed worse than healthy control participants. In contrast, during anodal tDCS, their performance normalized to become comparable to that of the healthy control partici-

pants. This normalization was accompanied by normalization of task-related and resting-state brain activity as measured with fMRI.

In Yun et al. [23], 16 participants with MCI were randomized to receive active or sham tDCS for 3 sessions per week for 3 weeks. Anode was placed over the right DLPFC and the cathode over the left DLPFC. Current was 2 mA. Objective and subjective measures of cognition were completed before and after the tDCS course, as well as FDG-PET. tDCS was well tolerated. While there was no impact of active tDCS on objective measures of cognition, it was associated with better subjective measures and with increased cerebral metabolism in several brain regions, including dorsolateral, ventrolateral, and medial prefrontal cortices, the dorsal anterior cingulate, the anterior and posterior insular regions, and the hippocampal and parahippocampal regions.

In Fileccia et al. [24], 34 participants with MCI were randomized to receive active or sham tDCS, 1 session per day, 5 days per week for up to 20 sessions. Each session was 20 min. Current was 2 mA. Cognitive assessment was completed before and after the 20 sessions. The anode was placed over the left DLPFC and the cathode over the right deltoid. Active stimulation and not sham stimulation was associated with improved episodic memory, figure naming, and general cognition.

In Gomes et al. [25], 58 participants with MCI were randomized to active or sham tDCS, 2 sessions per week, each for 30 min, for 5 weeks with cognitive assessments completed before, and immediately and 90 days after the intervention. The anode was placed over the left DLPFC with the cathode over the right supra-orbital area. Current was 2 mA. Active stimulation was associated with better executive function, verbal fluency, and memory recall, but with worse visuospatial construction, when compared to sham stimulation immediately after the 10-session course. No results were reported on 90-day performances.

In Manenti et al. [26], 18 participants with amnestic MCI were randomized to receive 1 session of active or sham tDCS during the reactivation phase of an episodic memory task. The participants were administered the task on the day before. Then, they were tested on free recall and recognition on the day after and 30 days later. Each session was for 15 min. Current was 1.5 mA. The anode was placed over the left lateral prefrontal cortex and the cathode over the right supra-orbital region. Anodal tDCS was found to be associated with better recognition than sham tDCS after the day of stimulation, though it was not clear whether this was on the day after stimulation or 30 days later.

Similar to studies in AD, a few studies in MCI assessed the impact of adding tDCS to another cognitive enhancement intervention.

In Gonzalez et al. [27], 5 participants with MCI were assigned to receive cognitive stimulation for 3 daily sessions, followed by sham tDCS during cognitive stimulation for 1–5 daily sessions, followed by active tDCS during cognitive stimulation also for 1–5 daily sessions, followed by cognitive stimulation alone again. Each session was for 30 min. The anode was placed over the left DLPFC and the cathode over the right deltoid. Current was 2 mA. Each phase of this study was separated from the previous one by 1 week. Compared to cognitive stimulation alone, active tDCS with cognitive stimulation was associated with faster processing speed, attention, and planning.

In Das et al. [28], 22 participants with MCI were randomized to receive active or sham tDCS for 20 min while watching Planet Earth videos and right before starting a cognitive training session for a total of 8 sessions over 4 weeks. The anode was placed over the left inferior frontal gyrus and the cathode over the right shoulder. Current was 2 mA. In this study, sham tDCS was associated with better executive function, inhibition, innovation, and episodic memory even though active tDCS was associated with improved resting state cerebral blood flow in the right middle frontal cortex. These findings suggested that anodal tDCS inhibited any potential gains from the cognitive training program. The authors speculated that tDCS could have activated inhibitory homeostatic response that "blocked" benefit from cognitive training. Alternatively, the repeated stimulation could have increased

"firing" of neuronal networks and, in turn, prevented consolidation of top-down learning strategies acquired during cognitive training. A third speculation the authors provided, suggested by the increase in cerebral blood flow on the right side, that is, the side opposite of stimulation, is that tDCS could have disrupted the allocation of cerebral blood flow, and, in turn, compromised the neuronal processes that support the learning strategies. Of note, tDCS was delivered before and not during the cognitive enhancement intervention, and while being cognitively engaged in watching a stimulating video, which also could have contributed to the "blocking" effect.

In Martin et al. [29], 68 participants with amnestic MCI were randomized to active or sham tDCS that was combined with cognitive training for 15 sessions administered 3 days per week over 5 weeks. Each cognitive training session lasted 45 to 60 min. During the first 30 min of each session, active tDCS at 2 mA was delivered followed by tDCS at 0.016 mA for the remaining of the session, or sham tDCS at 0.016 mA was delivered for the whole session, after ramping up and down for 1.5 min. The anode was placed over the left DLPFC and the cathode over the right frontal cortex. Cognitive assessments with verbal memory being the primary outcome domain were administered at baseline, end of treatment, and 30 days later. While there was no interaction between time and group, the study showed that only those who received active tDCS experienced improvement in verbal memory from baseline at the first follow-up and both groups experienced an improvement at the 30-day follow-up. Concerns regarding the potential active role of low intensity current was raised given the persistent improvement in verbal memory among those who received the sham intervention.

In de Sousa et al. [30], 18 participants with MCI and 32 healthy older control participants were randomized to receive first active or sham tDCS combined with a training session on a visuospatial task for 3 days followed by 3 months later, by the alternate stimulation combined with the 3-day training on the same task. Current was 1 mA. The anode was placed over the right temporoparietal cortex and the cathode over the left

supra-orbital area. Stimulation was for 20 min. Cognitive assessment was completed immediately after the 3-day training and 1 month later. At the first follow-up, only the MCI participants experienced an enhanced training under active tDCS compared to sham tDCS. They also experienced a gain under active tDCS that is similar to what the healthy control participants gained from the training. However, these benefits did not persist at the 1-month follow-up.

Taken together, and notwithstanding that the studies to date need to be replicated in larger samples, there seems to be an advantage of using tDCS during the earlier stages of cognitive impairment including when it is being combined with a cognitive enhancement intervention.

20.3   Frontotemporal Dementia, Lewy Body Dementia, Parkinson's Disease, Primary Progressive Aphasia, and Vascular Dementia

20.3.1 Frontotemporal Dementia

Frontotemporal dementia represents a group of neurodegenerative cognitive disorders that are typically characterized by early impairments in behavior, executive function, and language. Frontotemporal dementia is considered the third most common form of dementia following AD and Lewy body dementia [31]. Patients with frontotemporal dementia are divided into two subtypes depending on their predominant symptoms: behavioral or language subtype. The onset of frontotemporal dementia tends to be at a younger age than AD or Lewy body dementia. In addition to having no current treatments for the cognitive symptoms of frontotemporal dementia, and, in contrast to AD, there is minimal evidence to support treatments for the behavioral and emotional symptoms of this disorder.

In Benussi et al. [32], 55 participants with frontotemporal dementia were randomized to receive active or sham tDCS, 5 days per week for 2 weeks. Each session was for 20 min. Current was 2 mA. The anode was placed over the left

DLPFC and the cathode over the right deltoid. Cognitive and neurophysiological assessments using transcranial magnetic stimulation (TMS) were completed at baseline, and then immediately and 3 and 6 months after the 2-week course of tDCS. TMS measures were also conducted at 1 month after the 2-week course. tDCS was well tolerated. Active stimulation was associated with better global cognition, verbal fluency, processing speed, executive function, emotions' recognition, and behavioral symptoms compared to sham stimulation. Active stimulation was also associated with enhanced intracortical facilitation and enhanced inhibition as indexed using TMS. There was also a correlation between change in intracortical facilitation and change in processing speed and executive function.

20.3.2   Lewy Body Dementia

Lewy body dementia accounts for 3–15% of all dementias [33, 34]. It is typically characterized by fluctuating cognitive impairments, visual hallucinations, and Parkinsonian motor symptoms. It is also considered an umbrella that includes dementia of Lewy body and Parkinson's disease dementia. The diagnosis of dementia with Lewy body is made when the motor symptoms develop within 1 year before or after the onset of cognitive deficits. In contrast, a Parkinson's disease dementia diagnosis is made when the motor symptoms had been present for more than 1 year prior to the cognitive deficits [35]. Cholinesterase inhibitors are recommended for the treatment of Lewy body dementia, though their clinical impact is modest [36, 37].

In contrast to patients with AD, patients with Lewy body disease experience significant impairments in attention, executive function, and visuospatial abilities early on during the illness. These impairments may even precede deficits in learning and memory [38–40].

tDCS has been tested for its effects on Lewy body dementia-associated cognitive deficits. It has also been tested for its effects on cognitive impairment associated with Parkinson's disease per se, that is, without a full manifestation of dementia.

In Boggio et al. [41], 18 participants with Parkinson's disease received 1 session of anodal tDCS delivered to the left DLPFC for 20 min. Reference electrode was placed over the right orbit. They also underwent a session of motor cortex stimulation and sham tDCS to the left DLPFC. Current was 1 mA in one set of experiments and 2 mA in another set. Before and during the last 5 min of each tDCS session, participants were administered a working memory task. All experiments were well tolerated. tDCS at 1 mA did not result in any working memory change, In contrast, at 2 mA, left DLPFC stimulation resulted in more correct responses than motor cortex or sham tDCS. No change in speed of response was found.

In Pereira et al. [42], 16 participants with Parkinson's disease were randomized to receive 1 session of anodal tDCS to the left DLPFC or left temporoparietal cortex in a counterbalanced order, for 20 min. The cathode was placed over the right supra-orbital area. Current was 2 mA. Anodal tDCS to the DLPFC resulted in improved phonemic but not semantic fluency. It also resulted in enhanced functional connectivity and task-related deactivation as measured with fMRI.

In Doruk et al. [43], 18 participants with Parkinson's disease were randomized to receive anodal tDCS delivered to the left or right DLPFC, or sham tDCS for 20 min, daily, 5 days a week, for 2 weeks. The cathode was placed over the contralateral supra-orbital region. Current was 2 mA. Assessments were conducted at baseline, at the end of tDCS course, and 1 month following baseline. Overall, tDCS was well tolerated with reports of tingling, sleepiness, mild headache, neck pain, skin redness, and trouble concentrating. Anodal tDCS, irrespective of laterality, resulted in improved performance on executive function at the end of the tDCS course and that persisted at 1 month of follow-up. Sham tDCS resulted in improvement at the end of tDCS course, but the improvement did not persist. No significant effects were observed on other cognitive functions.

In Elder et al. [44], 13 participants with Lewy body dementia, including 8 with Parkinson's dis-

ease dementia and 5 with dementia with Lewy bodies, received a single session of anodal tDCS delivered to the left DLPFC for 20 min. The cathode was placed over the right deltoid muscle. Current was 2.8 mA. Before and 10 min after the stimulation, attentional and visuospatial cognitive tasks that have been shown to detect Lewy body dementia-specific deficits were administered. Participants experienced improvements on some of the attentional but on none of the visuospatial tasks following tDCS. tDCS was well tolerated.

In Manenti et al. [45], 20 participants with MCI due to Parkinson's disease were randomized to receive active or sham tDCS combined with physical therapy for 25 min per day, 5 days a week for 2 weeks. The anode was placed over the right or left DLPFC, contralaterally to the side of the body with more motor symptoms, for each individual. Current was 2 mA. Motor, mood, and cognitive symptoms were assessed at baseline and immediately and 3 months following the intervention. Despite no improvement over placebo with respect to motor or mood symptoms, participants randomized to active tDCS experienced better improvement in cognition immediately following the intervention and this enhanced improvement was stable at the 3-month assessment.

In Elder et al. [46], 38 participants with Parkinson's disease dementia were randomized to receive a single session of active or sham tDCS for 20 min and then crossed over to receive the alternate stimulation after 24 hours. Current was 2.8 mA. The anode was placed over the left DLPFC and the cathode over the right deltoid. Cognitive assessment was completed following each session. The study did not demonstrate any significant difference in cognition between active and sham tDCS.

In Lau et al. (2019), 10 participants with Parkinson's disease were randomized to 1 session of active or sham tDCS during the performance of a visual working memory and an emotional inhibition task. They were then crossed over to receive the alternate stimulation 2 weeks later. Current was 2 mA. The anode was placed on the left DLPFC and the cathode over the right supra-

orbital area. No differences in performance on the two cognitive tasks were detected between active and sham stimulation.

Overall, the literature on Lewy body dementia is consistent with the literature in AD and MCI. While there is a mixture of positive and negative findings, the less severe the cognitive impairment, the more beneficial tDCS seems, especially when combined with a cognitive enhancement intervention.

20.3.3 Primary Progressive Aphasia

Primary progressive aphasia is a diagnosis used to identify a heterogeneous group of patients who experience localized degeneration of the language-related brain regions. Patients with primary progressive aphasia are typically classified into one of three variants: the no-fluent/agrammatic variant, when the early clinical presentation consists of slow, effortful, and distorted speech; the semantic variant, when the early clinical presentation consists of well-structured sentences but with poor content and significant loss of the vocabulary; and the logopenic variant, when the early clinical presentation consists of word-finding difficulty and lapses during conversations, as well as sound and spelling errors [47, 48]. Primary progressive aphasia is gradually progressive and during the later stages of the illness, the distinction between the different types of language deficits becomes blurred and cognitive domains other than language become affected. No treatments are available to date.

In de Aguiar et al. [49], 30 participants with primary progressive aphasia were randomized to receive active of sham tDCS for 20 min during the first part of 45-min therapy sessions that were delivered for 10–15 sessions in total. Two months later, participants were crossed over to receive another course of therapy with the alternate type of stimulation. Current was 2 mA. Anode was placed over the left inferior frontal gyrus and the cathode over the right cheek. Assessments were conducted at baseline and then immediately, 2 weeks, and 2 months after the end of therapy. Active stimulation was associated with better

performance on trained words at the 2-month and not the previous follow-ups, compared to sham stimulation.

20.3.4 Vascular Dementia

While often in late life, dementias are associated with mixed pathologies, including pathologies of AD, Lewy body disease, and cerebrovascular disease, vascular dementia is diagnosed when the core clinical features are ascertained to be best attributed to vascular changes identified by brain imaging and cerebrovascular risk factors. The brain parenchymal changes can be ischemic or hemorrhagic in origin. Cerebral amyloid angiopathy can also lead to vascular dementia [50].

In Andre et al. [51], 21 participants with mild vascular dementia (mean age ~74) were randomized to receive active or sham tDCS, at home, for 1 session per day consecutively for 4 days. Current was 2 mA. Anode was placed over the left DLPFC and the cathode over the right supraorbital region. A comprehensive cognitive battery was completed at baseline, immediately after the tDCS course and 2 weeks later. Compared to sham tDCS, active tDCS was associated with faster reaction times on a working memory task and an inhibition task. It was associated with better performance on a naming task. However, these measures were few among many other cognitive measures on which there were no differences were detected between active and sham tDCS.

20.4   Conclusions and Future Directions

Overall, the current literature suggests that tDCS is potentially a useful non-surgical neurostimulation modality to improve cognition in patients with neurodegenerative cognitive disorders, especially during the early clinical stages of these disorders and when combined with another intervention that enhances cognition synergistically. However, it is important to note all studies to date are limited by generally small sample sizes and multiple outcome measures that the studies are exploring. In turn, many of the positive studies have not found differences between active and sham stimulation but positive signal of improvement within the group receiving the active stimulation and not within the group receiving sham. Hence, confirmatory and adequately powered studies are urgently needed and some are underway in older healthy adults (e.g., Woods et al. [52]) and older adults with a neurocognitive disorder (e.g., Rajji et al. [53]).

The literature suggests that if tDCS is to be effective with a persistent impact, it needs to be delivered repetitively, similar to most other interventions for brain disorders. It also suggests that long-term delivery of tDCS, close to a daily frequency, could prevent cognitive decline among older adults with a neurodegenerative cognitive disorder. Studies assessing different durations of tDCS along with different frequencies per week will help characterize the dosing of tDCS. This is especially critical for patients with neurodegenerative disorders who may either need to commute to a center where tDCS is to be delivered or may depend on caregivers and their availabilities to administer it. There is a high need to study the feasibility, tolerability, and acceptability of different remotely delivered tDCS regimens, whether delivered alone or in combination with other cognitive enhancement interventions for patients across the severity spectrum of neurodegenerative disorders [54].

Electrodes placement and current intensity are two other variables that need further studying in various disorders. The current literature supports the use of anodal tDCS in general and 2 mA currents. Further personalization could be supported by modeling studies. Modeling studies predict the flow of current during tDCS [55] and help minimize the impact of morphological variation on tDCS effects. Again, this is highly salient to patients with neurodegenerative disorders who are likely to have experienced cortical shrinkage and tissue loss and using individualized tDCS dosing based on patient's specific morphological characteristics may be necessary in future trials [56].

Combining tDCS with other interventions will add also another level of complexity to be

systematically investigated. tDCS interferes with
neuroplasticity mechanisms [57, 58] as do other
interventions such as cognitive training [59].
Timing of tDCS in relationship with another
intervention will need to consider the potential
interference of one intervention with another at
the level of neuroplasticity mechanisms.

Finally, multidomain studies that combine
different biological assessments, for example,
genetics structural and functional imaging, neu-
rophysiology, within the context of well-powered
clinical trials are needed to better understand
moderators of tDCS impact on cognition or other
symptoms of neurodegenerative disorders, as
well as its mechanisms of action in vivo.

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