University of Nevada, Reno

The Value of Transcranial Direct Current Stimulation in Improving Working Memory in Neurotypical and Special Populations

A thesis submitted in partial fulfillment
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by

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Abstract

Working memory is a system within the brain which allows one to integrate information from long-term and short-term memories to complete tasks, problem-solve, and achieve goals (Miller *et al*., 1960; Atkinson & Shiffrin, 1968; 1971; Cowan, 1998; 1999). This neural function is critical to daily human existence but declines with age and can be degraded by neurological disorders (Brunoni *et al*., 2013; Shiozawa *et al*., 2014; Jones *et al*., 2015; Moreno *et al*., 2015; Kofler *et al*., 2018). Within the last two decades, it has been of interest to neuroscience researchers to boost working memory performance in neurotypical and special populations by using a noninvasive brain stimulation technique known as transcranial direct current stimulation.

Transcranial direct current stimulation, or tDCS, uses electrodes applied to the scalp to deliver weak electrical currents to underlying cortical neurons to excite or inhibit them (Berryhill, 2017). This neurostimulation technique is both affordable and safe, which makes it an intriguing method to boost cognitive ability. It is for this reason tDCS headsets are now being manufactured by companies for at-home use by the general public to increase cognitive abilities such as intelligence, focus, and memory (NeuroStim, Fischer Wallace, BrainDriver). However, tDCS has been found to produce variable effects in different test groups: while some individuals have benefited from tDCS, others do not respond to stimulation or even experience impairments (Berryhill *et al*., 2014). The purpose of this literature review is to assess the value of tDCS in improving working memory in neurotypical and special populations, such as older adults or clinical patients, based on empirical findings from studies within the past five years. A systematic evaluation of these findings should indicate what is known about tDCS, and what remains to be found before it should be used outside of a controlled laboratory environment.

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Literature Review

<u>Chapter One: Introduction</u>

There is a new claim that the key to unlocked learning and memory potential is simply a headset and a few electrical pulses away. In fact, the application of two electrodes to the head may even be the solution to mental health issues plaguing millions of people around the globe every year. Med-Tech Innovation News asserted in February 2020 that the newest neurostimulation headset can administer electrical stimulation targeting the brain concurrently with behavior therapy to treat depression (Bolland, 2020). Med-Tech Innovation is not an isolated example. Neurostimulation in the form of transcranial direct current stimulation (tDCS) is becoming more popular, and so headset devices are being manufactured by many companies. All these companies claim that tDCS can affordably improve many aspects of cognition: learning, memory, focus, performance, and depression. TDCS is a form of *noninvasive* brain stimulation (NIBS) that is now an intriguing means of augmenting neural activity. This technique is noninvasive because it is applied via the scalp. It is also generally considered safe because the amount of stimulation current devices emit is tiny - measured in milliamps (1/1000 of an Ampere). It is also inexpensive in relation to other methods of neurostimulation, with research devices costing ~$10,000 (NeuroStim) and commercial products costing ~$150 (Fisher Wallace, BrainDriver). During tDCS, electrodes are placed on the scalp to deliver weak electrical currents through the skull to alter neural excitability in the brain. This creates a subtle but widespread neuromodulatory effect in which cortical neurons reached by the current become more or less likely to respond because their membrane potentials are slightly more positive or negative (hyperpolarized or depolarized) (Berryhill *et al*., 2014; Berryhill, 2017). In other words, tDCS appears to be an inexpensive and safe method of improving a person's cognition, and a method which is now being made available outside of a doctor's office in the comfort of one's own home (Fitz & Reiner, 2015).

However, experimental findings reveal major limitations associated with tDCS studies. The evidence of a significant effect of tDCS on cognition has been modest and contested (Horvath *et al.*, 2015; 2016; Medina & Cason, 2017; Nilsson *et al*., 2017). Additionally, the effects of tDCS are not fully understood or completely elucidated. A consumer may experience no benefits or may even find their abilities impaired after an at-home tDCS session (Steenbergen, 2016; Horvath *et al*., 2016). Many factors determine the behavioral outcome, including electrode placement, intensity, duration, task, and individual differences (Berryhill *et al*., 2014). Finally, each participant's cortical morphology and skull shape are unique, and it is difficult to know the cognitive processes occurring in each participant during stimulation (Filmer *et al.*, 2019). A serious challenge in synthesizing the findings across tDCS studies is that methodologies and tDCS parameters differ between laboratories and across studies, making it difficult to understand who can reliably benefit from tDCS, and who's better off looking elsewhere to improve their brain's "intellectual" capability.

Variable results and a lack of efficacy in NIBS treatments keep them from being a reliable means of brain augmentation, especially across a "heterogeneous" population, that is, an array of individuals with key differences, such as brain and skull structure, genetics, and natural ability. This prompts the question: can we predict who will respond to tDCS based on interindividual differences and experimental design? Further, can these findings shed a light on the mechanism through which tDCS alters brain activity?

The purposes of this literature review are as follows: first, to identify key factors that predict whether an individual will benefit from tDCS, and second, to evaluate the merit of tDCS in working memory research. I have accumulated empirical data from previously executed experiments focused on individual differences in terms of response to tDCS in studies of the important cognitive function, working memory, which I will define and discuss further in the next section. Using a tabular format, I will collate evidence from multiple studies and analyze the behavioral or phenotypic underpinnings which may explain how an individual will respond to tDCS. These findings will reveal how researchers can improve tDCS approaches for healthy individuals and for certain patient populations, including older adults and those with behavioral disorders or brain damage, such as Major Depressive Disorder, Schizophrenia, or stroke (Schlaug & Renga, 2008; Brunoni *et al*., 2013; Shiozawa *et al*., 2014; Schwippel *et al*., 2018).

The implications of summarizing a current understanding regarding *who* will respond to tDCS could help future physicians customize treatment plans for each unique patient based on both inherent neural characteristics and tailored protocols. Foregoing other treatments could lower costs of healthcare while simultaneously decreasing risk of care, yielding more beneficial results, and avoiding unwanted side effects (such as impaired performance). Furthermore, my work will synthesize what is currently known about tDCS in working memory, what requires further investigation to maximize beneficial results in working memory-tDCS studies, and if tDCS should be used in clinical or at-home settings at all.

<u>Chapter Two: What is Working Memory? What does a tDCS Experiment in Working Memory look like?</u>

Transcranial direct current stimulation gained popularity in the 2000s, which led to it being the subject of research in most cognitive domains, including working memory. Working memory is considered an executive function. Executive functions allow one to complete tasks, achieve goals, process attended information, or control our impulses (McCabe *et al*., 2010). Working memory, specifically, enables us to hold on to a few pieces of information for a brief period of time. For example, it allows us to add numbers in our head, or reach for something on the counter without looking. Working memory is complex, as people are constantly being bombarded with new information that must be filtered and prioritized throughout time so they can accomplish immediate tasks. It is vital to everyday human life, but still working memory performance degrades as one ages (Jones *et al*., 2015; Passow, Thurm, Li, 2017). For this reason, it is of great interest in research as the general public becomes more and more concerned with increasing their individual intelligence (which will be discussed in further detail later) and maintaining cognitive function in old age.

Working memory may be conceptualized as the "desk" of the human brain. As indicated by its name, working memory is the combined effort of multiple memory systems which enable people to use old and new information to achieve goals, complete tasks, and control behavior (Miller *et al*., 1960; Atkinson & Shiffrin, 1968; 1971). According to the influential Multi-Component Model proposed by Baddeley and Hitch (1974), working memory may be broken down into separate visual and verbal components, both of which are overseen by a "central executive" that modifies and influences working memory, called cognitive control (Baddeley & Hitch, 1974; Baddeley *et al*., 1986; Baddeley, 2000). The central executive may be thought of as the source of volition, allowing an individual to manipulate what they focus on according to perceived importance. The Multi-Component Model predicts little interference between verbal and visual information, but significant within-component interference.

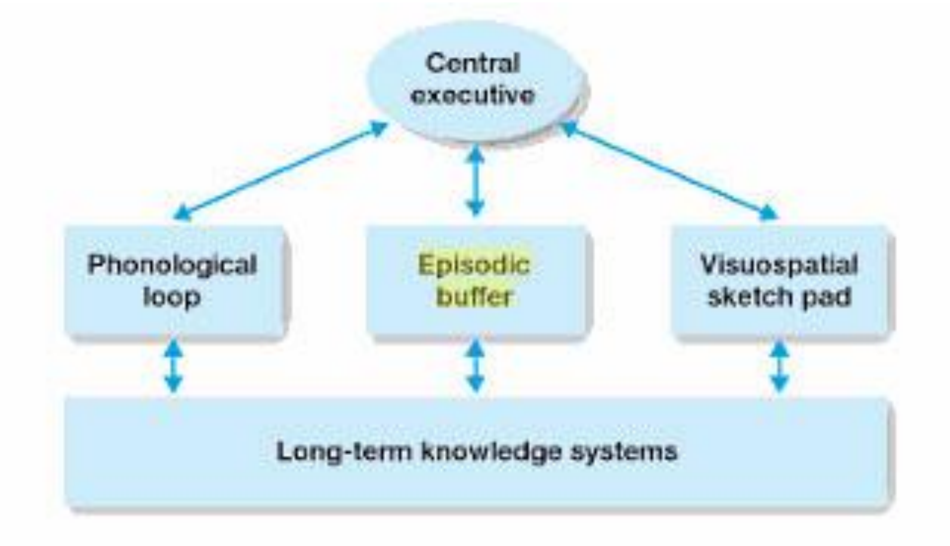

Figure 1. The Multi-Component Model. Baddeley & Hitch proposed that working memory consists of two separate components (based on sensory input), both of which are controlled by a central executive function (1974). This was updated later to include the Episodic Buffer, which represents one's ability to use knowledge from consolidated, long-term memories to complete current tasks (2000). These components work together to create working memory (1974, 2000).

However, there is not a single model of working memory that is generally accepted by the entire scientific community. Many other models of working memory propose different perspectives. For example, the Embedded-Processes Model (Cowan, 1998; 1999) suggests that the mechanism of working memory operates via activating memory within the long-term memory store. Within this activated memory, there is a specific focus of attention that can hold a limited number of items (Cowan, 1999). This is known as working memory capacity (WMC), which is different across individuals and degrades with age (Unsworth & Engle, 2007; Conway *et al.*, 2011). Under the Embedded-Processes Model, working memory is the "working-together" of long-term memory, short-term memory, and attention, all of which are distinct functions which may be controlled by a central executive similar to that proposed by Baddeley & Hitch. This model is widely accepted and supported.

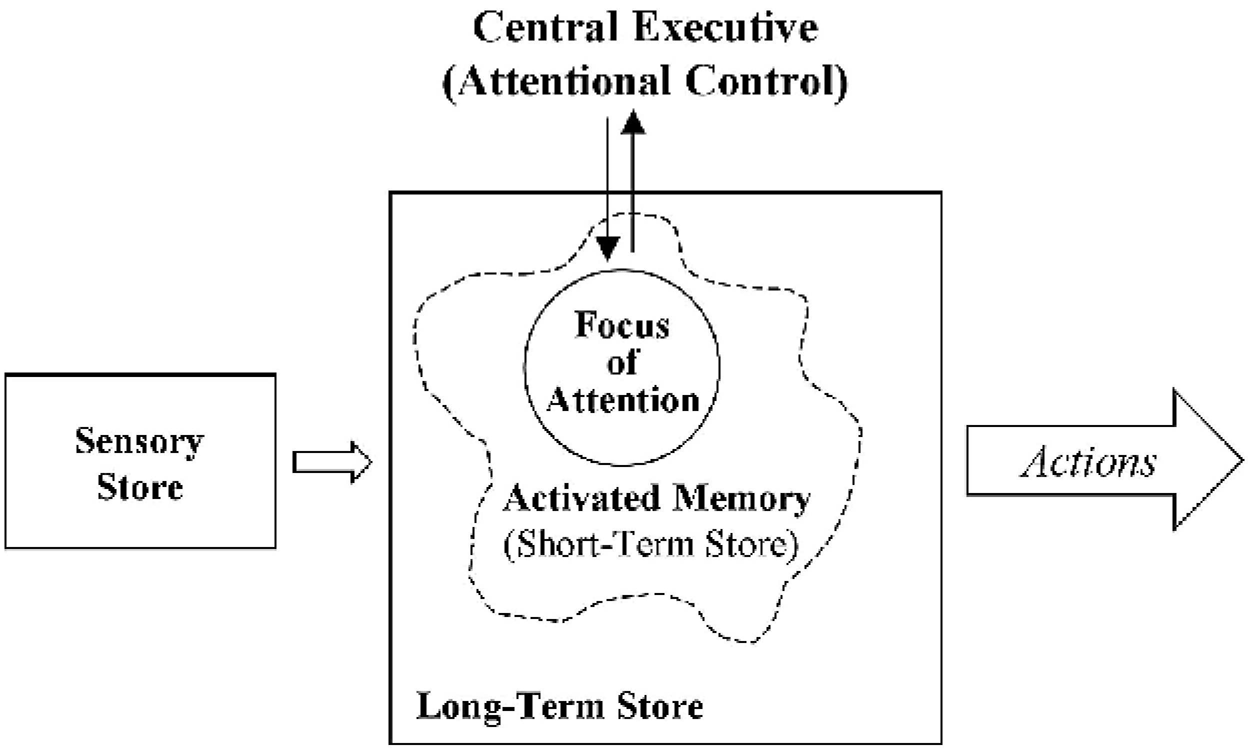

Figure 2. The Embedded-Processes Model. As described by Cowan, this model is a current and supported understanding of how working memory operates in the human brain. It is suggested that focus of attention within a short-term memory store is controlled by a central executive function. Short-term memory which is consolidated may then be incorporated into a long-term memory store (1998).

The disparate models of working memory are alike in that they propose working memory can access and use long-term memory. The difference between working memory and long-term memory is notable, as long-term memory may be held for an indefinite amount of time and includes our ability to recall facts and events, perform skills, or produce instinctual responses (Cowan, 2008; Norris, 2017). It is generally thought to be composed of how people remember events (episodic memory) and facts (semantic memory) (Tulving, 1972). For example, when one recalls their senior prom or the first president of the United States, they are retrieving these memories from the long-term memory store. This interaction between working memory and long-term memory is a contributing factor to what may be called fluid intelligence (Unsworth, Fukuda, Awh, Vogel, 2014). Fluid intelligence refers to our ability to solve problems and identify relationships between elements (as reviewed by: Brown, 2016; Unsworth, Fukuda, Awh, Vogel, 2014).

The distinction between working memory and attention is traditionally less clear, as the two terms are used interchangeably by some researchers and distinguished by others based on practice. According to Cowan, the relationship between attention and working memory may give rise to a person's intellectual ability and aptitude for learning (as reviewed by: Cowan, 2008). Working memory, therefore, is a complex and important system which carries out behavioral processes needed on a day-to-day basis. To reach a full understanding of these behavioral processes, it is just as necessary to understand the neural underpinnings which give rise to these outputs.

The neural correlates of working memory depend on the incoming information. For example, visual working memory relies on visual system inputs such as light cues or image arrays, which are then processed and recalled (Conway *et al*., 2011). The executive function aspect of working memory is associated with the prefrontal cortex of the brain (Müller & Knight, 2006; Funahashi, 2006) and frontoparietal activity, especially in the central executive network (Cole *et al*., 2013; Braunlich *et al*., 2015). Cognitive control is associated with the dorsolateral prefrontal cortex (Müller & Knight, 2006; Mansouri, Tanaka, Buckley, 2009). Lesions to these areas of the brain can result in attention and impulse deficits. Deficits in working memory can lead to serious disorders that decrease a person's quality of life. More specifically, conditions such as Schizophrenia, Major Depressive Disorder, and Attention Deficit Hyperactivity Disorder may be the result of an irregularly small or otherwise compromised prefrontal cortex (Brunoni *et al*., 2013; Shiozawa *et al*., 2014; Moreno *et al*., 2015; Kofler *et al*., 2018; Schwippel *et al*., 2018). Working memory deficits have also been found and researched in Parkinson's patients, Huntington's patients, and patients with mild cognitive impairment (MCI) (Eddy *et al*., 2017; Das *et al*., 2019; Lau *et al*., 2019).

It is understood that working memory may play an important role in how people accomplish goals, problem-solve, and learn. General public interest in improving working memory is high, especially in regard to staving-off working memory degradation due to aging. Training programs that use attentional-tasks to exercise working memory have been promoted to improve intelligence and ward-off unwelcome decreased cognitive performance, such as the well-known "brain-training" program Lumosity (Al-Thaqib *et al*., 2018). tDCS is possibly a new method of increasing cognitive performance because it promotes or inhibits functional connectivity between brain networks. Therefore, it is currently being used in research to modify working memory performance by changing how different working memory neural correlates interact with each other (Berryhill *et al*., 2014; Nejati, Salehinejad, Nitsche, 2018).

In this type of research, tDCS is used as a brain augmenting technique which is meant to elicit a desired behavioral output in a working memory task. For example, a common working memory paradigm is the N-back task, in which a participant is asked to determine if an item is the same as an item presented "N" trials before (Jonides *et al*., 1997; as reviewed by: Rac-Lubashevsky & Kessler, 2016). "N" is an arbitrary number which is chosen by the research team and can make this task easier or more difficult. This paradigm is used frequently in working memory research because it utilizes multiple cognitive processes and multiple brain regions (Jansma *et al*., 2000; Chen *et al*., 2008; as reviewed by: Rac-Lubashevsky & Kessler, 2016). In a study where tDCS is used to augment activity in the prefrontal cortex, researchers may be hopeful that this would boost a participant's performance on the N-back task, that is, they will respond with more accuracy and make less mistakes. This response is the key to such cognitive studies, as a change in brain activity means very little if it does not change how a person behaves. Tasks in working memory are incredibly diverse with the N-back task being a single example among many. As previously stated, neural correlates in working memory are dependent on input, and these inputs are delivered in the form of tasks which can be visual, visuospatial, auditory, verbal.

A basic tDCS study will include two electrodes placed on different locations on the participant's scalp. One electrode is the cathode and delivers hyperpolarizing currents to underlying cortical neurons. In other words, these neurons will be slightly more inhibited. Another electrode, the anode, delivers depolarizing currents to underlying cortical neurons and causes those neurons to be slightly more excited.

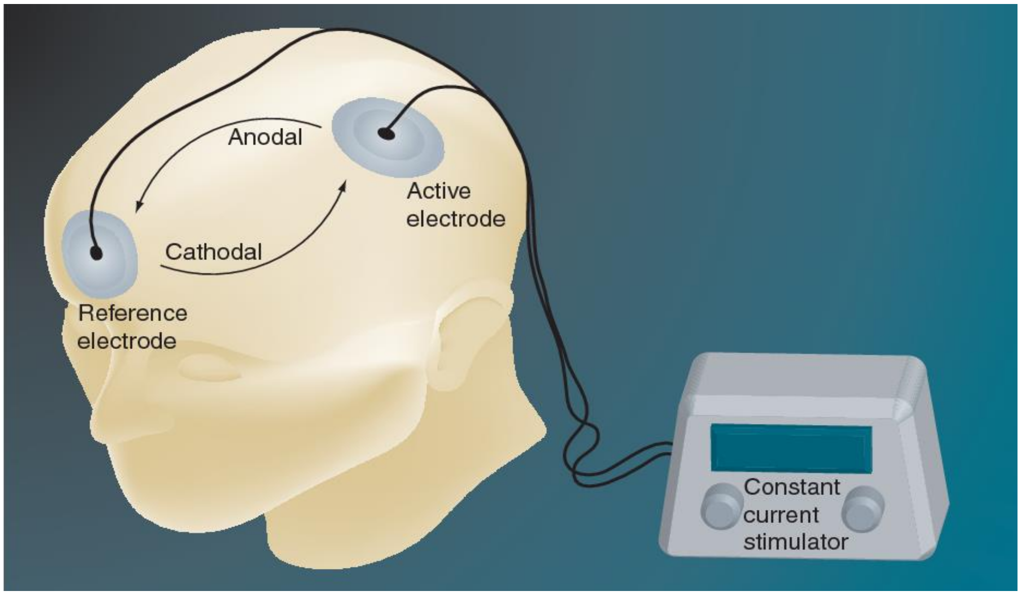

Figure 3. A visual of a tDCS headset. In general, a tDCS headset consists of an active electrode (anode) at one location on the scalp and a reference electrode (cathode) at another location on the scalp (Schlaug, Renga, 2008).

Soaked sponges or gels are used beneath the electrodes to safely conduct current through the scalp and into cortical neurons. These electrodes connect back to a current stimulator.

Sham stimulation is another important component of a tDCS experiment in working memory. Sham stimulation is the application of tDCS electrodes with brief or weak current delivery which should not have a significant effect on underlying neurons. It is used as a control in order to rule out the placebo effect on results, and therefore is used in most tDCS experiments.

tDCS has had contradictory impacts on working memory, with performance showing modest improvements (Tseng *et al*., 2012; Fregni *et al*., 2005; Berryhill & Jones, 2012; Jones & Berryhill, 2012) and impairments (Marshall *et al*., 2005; Berryhill *et al*., 2010; Tanoue *et al*., 2013), as well as non-responders (Nilsson *et al*., 2017; Westwood & Romani, 2018; Luque-Casado *et al*., 2019) who show no significant change in task-related performance after brain stimulation. This is obviously a huge problem, as it is difficult to know if tDCS is valuable in working memory research when effects are so variable. Some researchers believe tDCS has great potential in improving working memory, while others are more skeptical due to variability in tDCS effects across studies (Mancuso *et al*., 2016). The element of mystery surrounding how tDCS will affect one person compared to another makes at-home tDCS headsets particularly risky. Even in a controlled laboratory environment, tDCS is unpredictable, which means that headset manufacturing companies who guarantee boosted performance after an at-home tDCS session are doing so without conclusive evidence from the scientific cohort.

Some of the variability in working memory-tDCS results can be accredited to interindividual differences between people, which are inherent and will never change. However, this does not mean that tDCS cannot be adjusted to accommodate these differences. The missing piece of the puzzle is understanding which montages, experimental procedures, or tDCS techniques have produced success time and time again, if any. Not to mention the unstoppable advancement of science and technology means that newer techniques, such as neuroimaging and

HD-tDCS, offer alternative routes to investigate the impact of tDCS on the human brain and how desired results can be produced (Chen *et al*., 2012).

Chapter Three: Evidence of Inconsistency: The Laboratory to Real-World Problem

There is a dichotomy between what one experiences in a laboratory and what one experiences in the *real-world*. In a laboratory, the goal of researchers is to isolate a specific variable, change something in a highly controlled environment, and observe what results are produced (Jung *et al*., 2018). In working memory research especially, this highly controlled environment struggles to isolate one memory system from another. Along with that fact, the information researchers learn about the human brain in laboratory is limited by the element of control exerted in laboratory setting. Outside of the laboratory, stimuli are diverse, and variables like order of perceived stimuli (order effect), baseline brain state, and emotional state, which are particularly important to working memory-tDCS outcomes, are not controlled in the real world (Bogdanov & Schwabe, 2016).

This issue becomes particularly problematic upon the manufacturing and selling of at-home tDCS headsets. Even in a controlled laboratory, tDCS results are unpredictable and can vary. An individual presumably with no professional scientific experience using tDCS at home is incredibly risky, and desirable results cannot be guaranteed. If researchers can predict how tDCS affects different people with accuracy, then it may be possible one day to calibrate tDCS headsets to accommodate interindividual differences and make them reliable for use at home.

There are techniques which can be used in a working memory experiment to estimate how results can be applied to the real world. For example, transfer tasks may be used to see if the skills an individual learns throughout an experiment may be used in a novel situation. Ke *et al.* (2019) used two similar, but separate, working memory tasks (a verbal N-back task and a shape N-back task) to evaluate if gains made using HD-tDCS on the trained task could be transferred to the untrained shape N-back task. Gains maintained in the untrained task would indicate that tDCS interventions were successfully transferred and were not isolated to the trained task (Ke *et al*., 2019). It is measures like this which may be used to support the value of tDCS in the real world, since novel situations (which could not possibly be trained) arise every day.

Another useful technique is testing for long-term tDCS effects. This usually involves evaluating participants' performance on the experimental task after a long duration of time without any training. The purpose of this is to see if improvements or impairments made in an experiment are long-lasting. Long-lasting effects in tDCS research suggest that augmentation of brain activity can continue throughout an individual's life long after training. Research teams who successfully demonstrate long-lasting effects from tDCS interventions support that tDCS has value in changing brain function, and possibly has value in being pursued as a clinical therapy for those with working memory deficits (Jones *et al*., 2015).

Methodology

In this literature review, I have accumulated data from twenty-four articles which I found on PubMed searching the phrases "working memory", "transcranial direct current stimulation", and "short-term memory". After reviewing these articles, I have tabulated them based on montage, results, and limitations. These tables give a succinct overview of improved versus impaired versus non-responder findings and have revealed patterns throughout tDCS research of what works, and what does not. The articles are organized into two separate tables based on different test populations: neurotypical populations (or healthy young adults) (***Table 1***) and special populations, including individuals with clinical deficits as well as older healthy adults (***Table 2***). This organization should make patterns of improvement versus impairment in specific individuals clearer.

Finally, I have organized what I have learned into a Venn Diagram (***Figure 4***). On the left, I have included what tDCS interventions have worked in neurotypical adults, and on the right, I have included what has worked in special populations. The overlap shows what has worked across various individuals. This is a useful visual which utilizes spatial layout to make valuable experimental procedures easy to discern.

In the Discussion section, I analyzed what these data have shown, and what has still yet to be understood in using tDCS to improve working memory. Further, I discussed the real power of tDCS research, its constraints, and what needs to be fleshed out before tDCS is used by the general public. Using this methodology, I was able to outline a comprehensive overview of recent tDCS research in working memory, what methods have produced desirable results, and what needs to be investigated further to make tDCS a reliable, possibly even therapeutic, means of brain augmentation.

Data

Table 1: tDCS Effects on WM in Neurotypical Healthy Adults

Authors	Montage	Results	Implications & Limitations
Gözenman & Berryhill 2016	***tDCS and HD-tDCS 1.5 mA; 20 min; anodal 2 Test Groups: tDCS A: R or L PPC C: Contralateral Cheek HD-tDCS A: Center of 4 cathodes C: Pz, C4, P8, O2 or Pz, C3, P7, O1 Retro-Cue Task	Low WMC + w/ HD-tDCS - w/ tDCS High WMC - w/ HD-tDCS 0 w/ tDCS	HD-tDCS and tDCS do not produce the same affect Attentional Task which uses WM, but not necessarily a WM task
Ruf, Fallgatter, Plewnia 2017	1 mA; 20 min; anodal A: F3 or F4 C: Contralateral Deltoid Muscle Congruent and Incongruent Spatial vs Verbal Adaptive N-Back Tasks	Congruent + *Successful Task Transfer *Long-lasting Effects (9 m.o.) Incongruent 0	Laterality may affect tDCS training effectiveness Lower pre-training performance correlated with higher improvements Optimal montage must be further investigated
Talsma 2017	1.0 mA; 20 min; anodal A: LDLPFC C: Contralateral Supraorbital Region Updating Task Transfer Task	+ AND -	Improvements only occurred after 1st session, and effects only lasted 24 hours Observed improvements and impairments reiterate that tDCS has still yet to be fully understood
Hill, Rogasch, Fitzgerald, Hoy 2018	***HD-tDCS 1.5mA; 15 min: anodal 2 Test groups: DLPFC A: F3 C: Fp1, Fz, C3, F7 DLPFC+PC A: F3, P3 C: Fp1, Fz, C3, F7, P7, Pz N-Back Task Digit Span Task Corsi Block Tapping Task *** TMS-EEG + EEG recordings	EEG + *Theta and Gamma oscillations increased TMS-EEG + *Increased P60 and N100 amplitude N-Back Task Performance 0	Limited statistical power due to a small sample size Results were more robust for the DLPFC+PC montage These results show no behavioral effects; biological brain activity is not causal of behavioral response

Nikolin, Lauf, Loo, Martin 2018	***HD-tDCS 2 mA; 20 min; anodal HD-tDCS 2 Test Groups: LDLPFC A: F3 C: F5, AF3, F1, FC3 LIPS A: P3 C: P7, Pz, C3, O1 Updating and Maintenance Tasks Verbal Working Memory Task Divided Attention Task	0 *For both groups	Order Effect: the order in which tasks were completed were not randomized and this may have influenced performance HD-tDCS was administered during some tasks, but not all (divided attention task occurred after stimulation) Interindividual differences not accounted for (neuroanatomy, specifically); neuro investigation recommended for future studies
Rabipour, Lacoboni, Davidson, Wu 2018	2.0 mA; 20 min; anodal A: F3 C: Supraorbital Nerve 2 and 3-Back Task Transfer Tasks ***Expectation Analysis	+ *High expectations lead to greater improvement *Those with higher expectations reported a more pleasant experience	Improvements were modest More investigation on the role of expectations needed in the future
Wang, Tian, Hao, Tian, Liu 2018	1.5 mA; 25 min***; anodal vs cathodal (before***) A: RDLPFC C: L supraorbital region Visual N-Back Tasks (0,1, 2)	Cathodal + Anodal -	Effects seen *only* in WM maintenance and *not* WM updating, suggesting the RDLPFC is not the only brain region involved in working memory Cathodal tDCS improved suppression of interference
Westwood & Romani 2018	1.5 mA; 25 min; anodal A: LIFG C: Contralateral Supraorbital Region *Single Session Verbal Fluency Task	0	Low Statistical Power (n=19) Ceiling Effects: tDCS may be more effective in clinical populations
Wörsching 2018	2.0 mA; 20 min; anodal A: F3 C: F4 DWM Task ***fMRI	+ *DWM RT decreased	Only done in males Decreased connectivity in medial part of LPFC Decreased regional brain activity after negative distractor
Abellaneda-Pérez et al. 2019	2.0 mA; 20 min; anodal A: L DLPFC C: R Supraorbital Region	+ *Increased functional connectivity	Stimulation may be able to modify (default-mode network) DMN and transitions between WM and DMN

	Verbal Working Memory Task ***fMRI	0 *No cognitive effects	Low Statistical Power WM task performance and fMRI at baseline were not evaluated
Ikeda et al. 2019	2.0 mA; 13 min; anodal A: F3 C: F4 3-Back Task w/ MEG	0 *Gamma oscillations were induced *Suggested that Gamma must be coupled to theta band phases to be effective	The working memory task could have been too easy; participants not challenged
Ke et al. 2019	***HD-tDCS 1.5 mA; 15 min; anodal HD-tDCS A: F3 C: Fp1, Fz, C3, FT7 Verbal N-Back Task Shape N-Back Task (Transfer Task)	+ *Successful Task Transfer	Lower baseline performance: more improvement with HD-tDCS (in training gains) There was task transfer, but statistical power was low RTs increased Neural Mechanisms for tDCS were not explored.
Luque-Casado, Fogelson, Iglesias-Soler, Fernandez-del-Olmo 2019	1.5 mA; 15 min; anodal A: LDLPFC C: Contralateral Supraorbital Region Digit Span Task *Single Session	0 *Besides small responder group who improved	Low statistical power and ceiling effect could have impacted effectiveness of tDCS Cause of responder group unknown, so further investigation required
Rabipour, Vidjen, Remaud, Davidson, Tremblay 2019	2.0 mA; 20 min; anodal A: Motor Cortex C: Contralateral Supraorbital Region Finger Fitness Task Game-based RT Task * Single Session	0 *Those with higher expectations reported a more pleasant experience	Ceiling Effects: the task may not have been hard enough

*Abbreviations: A, anode; C, cathode; R, right; L, left; min, minutes of tDCS application; mA, strength of current applied in milliamperes; +, results show participants improved with tDCS; -, results show participants experienced impairments with tDCS; 0, results show participants did not respond to tDCS; *, important information regarding results; ***, important information regarding experimental setup; n, number of participants in the study; WM, working memory; WMC, working memory capacity; DWM, delayed-response working memory task; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; PC, parietal cortex; IFG, inferior frontal gyrus; IPS, intraparietal sulcus; m.o., months; DMN, default mode network; RT, reaction time; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; notations such as F3, Fp1, Fz, C3, F7, P7, Pz are electrode positions as described by the international 10-20 EEG system.* ***Table 1*** *is organized chronologically by year and alphabetically by author.*

Table 1 Results: What Trends Are Seen in Working Memory in Neurotypical Healthy Adults Using tDCS?

Empirical data across various tDCS-working memory studies in neurotypical adults in the past four years (***Table 1***) support findings from previous key literature. Of the utmost importance to producing desirable results in tDCS studies is attention to experimental design. First, it is evident that single session tDCS often results in non-responder test groups and is not effective at producing long-lasting effects (Horvath *et al*., 2015; Westwood & Romani, 2018; Luque-Casado *et al*., 2019). Multiple session tDCS more reliably produces responder groups (as reviewed by: Berryhill & Martin, 2018).

In addition to using multiple tDCS sessions, researchers must be meticulous in creating appropriate working memory tasks and the order in which these tasks are performed. Multiple studies have found that tDCS can only boost working memory if the cognitive task is hard enough for the individual. If the task does not challenge the participant, results will plateau in a pattern known as the ceiling effect (Westwood & Romani, 2018; Rabipour *et al*., 2019). This indicates that tDCS may not be able to vastly improve working memory ability, and instead is able to produce modest improvements (Luque-Casado *et al*., 2019; Ke *et al*., 2019). Gözenman and Berryhill, for example, found that tDCS improved performance for individuals with low working memory capacity (WMC), but impaired performance for individuals with high WMC (2016). This could be because the task was not hard enough for high WMC participants, and only low WMC participants were challenged enough to improve (Ikeda *et al*., 2019). In the case of multiple working memory tasks in an experiment, the order in which these tasks are completed may skew tDCS effects or possibly render tDCS ineffective (Nikolin *et al*., 2018). This is known as the order effect. In Nikolin *et al*. (2018), the test group was found to be a non-responder group, possibly due to the order effect since each participant performed the same tasks in the same order for all trials. Nikolin *et al*. (2018) also neglected to account for neuroanatomical differences between participants, which must be considered before tDCS is applied.

Previous tDCS research has evaluated the impact of neuroanatomy, specifically cortical morphology, on tDCS results (Kim *et al*., 2014; Filmer *et al*., 2019). Because tDCS current must travel through the skull and to cortical neurons beneath, the impact of the current depends on variables such as skull thickness and skull shape. The folds and grooves of the cortex are unique from one individual to the next, so once the current makes it to cortical neurons, it is still possible that the exact same brain regions are not being targeted across participants. It is extremely important that differences in neuroanatomy and cortical morphology are accounted for before tDCS is administered, otherwise null effects may be produced in a heterogeneous population (Nikolin *et al*., 2018). In future tDCS studies in working memory, it is vital that researchers use neuroimaging techniques to tailor tDCS to the individual.

Neuroimaging may further the field of tDCS research by giving the cohort a comprehensive understanding of timing, which is another important element in tDCS experiments: tDCS is more effective when applied concurrently with a cognitive (working memory) task (Sathappan *et al*., 2019). This could possibly be due to the strengthening of connectivity between neural networks already activated by the task. Indeed, a canonical tDCS montage would use anodal tDCS since this current is associated with the depolarization, or *excitement*, of underlying neurons. Increased, sustained excitability between neurons can lead to long-term potentiation (LTP), which is the strengthening between neural connections, or synapses. On a larger scale, this LTP can increase connectivity between brain networks, and thus could explain why anodal tDCS is so effective at improving working memory (Purves *et al*., 2001; Stampanoni Bassi *et al*., 2019).

However, there are studies which successfully use cathodal tDCS, which inhibits underlying neurons, to produce working memory improvements. For example, Wang *et al*. (2018) used cathodal tDCS to improve participants' working memory maintenance. It is possible, in this case, that cathodal tDCS contributed to active suppression of salient irrelevant stimuli. Working memory and attention interact closely with one another (although the nature of their relationship is still debated). Recent research indicates that salient stimuli which may distract one from voluntarily attended stimuli are suppressed in a top-down fashion, that is, by an executive function (Feldmann-Wüstefeld *et al*., 2020). This suppression could impact what information from attention is encoded into working memory. If this is the case, this would explain how cathodal tDCS, which has an inhibitory effect on cortical neurons, could improve performance on a working memory task, as less distractor stimuli would be incorporated into working memory (Feldmann-Wüstefeld *et al*., 2020). Use of anodal versus cathodal tDCS, then, is incredibly reliant on the brain regions targeted and affected by the current. The next obstacle, and a direction for future research, would be figuring out how tDCS affects connectivity between cortical networks, and if these networks can be more efficiently targeted once identified. Targeting these brain regions could be done using high-definition tDCS, or HD-tDCS.

HD-tDCS is a recent technique which can be used to target more localized brain regions. Localization in HD-tDCS is achieved by using montages with more than two electrodes, such as a single anode in the center of multiple, equidistant cathodes (4×1 montage) (Turski *et al*., 2017). However, HD-tDCS is easily made ineffective at improving working memory because of this localization: regular tDCS augments brain activity over a large swath of cortical tissue and is thought to modify connectivity between neural networks (Nikolin *et al*., 2018; Hill *et al*., 2018). Localized targeting of brain regions requires in-depth knowledge of how that specific brain region contributes to the entire process of working memory, which may not be fully understood. This does not mean there is no value in HD-tDCS. Research teams like Gözenman and Berryhill (2016) support that HD-tDCS can produce worthwhile effects, as it was used to improve performance on a retro-cue task in low WMC individuals. In this same experiment, regular tDCS impaired performance, suggesting HD-tDCS can produce very different effects than tDCS through a mechanism which is not yet clear.

Hill *et al*. (2018) found that HD-tDCS produced no improvement or impairment in three working memory tasks, but still had neurophysiological effects on the brain. This was seen using neuroimaging, specifically EEG (electroencephalogram) and TMS-EEG (transcranial magnetic stimulation with electroencephalography) recordings. EEG records global brain activity with high temporal resolution to give an inclination of what is happening in the brain at a specific point in time during a task. This tool could be used to probe why timing, as discussed earlier, is so critical in tDCS experiments. Additional studies using neuroimaging techniques such as EEG or functional magnetic resonance imaging (fMRI) set a precedent for tDCS protocols: the combination of imaging and tDCS to understand the mechanism through which tDCS modulates brain activity. fMRI can be used to assess functional connectivity in the brain and how this connectivity is altered by tDCS. Like EEG findings, fMRI data has shown a change in functional connectivity associated with tDCS that *can* produce behavioral changes (Wörsching *et al*., 2018), but does not always do so (Abellaneda-Pérez *et al*., 2019). This is only the tip of the iceberg in neuroimaging investigation in tDCS. Ikeda *et al.* (2019), for example, used magnetoencephalography (MEG) to find valuable information regarding the coordination of theta and gamma oscillations in the brain. Neural oscillations, or brainwaves, are the fluctuations of activity in or across neural populations (Mathalon & Sohal, 2015). These oscillations are categorized based on frequency in Hertz. They may be synchronized across brain regions, and it is studies such as those performed by Ikeda *et al.* and Abellaneda-Pérez *et al*. which indicate that the coordination of specific oscillations during a task may affect how an individual performs in that task. This would require further investigation in future studies.

The role of expectations on tDCS also requires further investigation in the field. It is possible a participant using tDCS will benefit more from stimulation if they have high expectations of improved outcomes (Rabipour *et al*., 2018). This gives more hope to those who use tDCS at home without professional oversight, as their faith in tDCS could possibly boost positive effects. Whether this is due to the placebo effect or not, pre-training expectations could still be a viable option if it will increase the yield of desired results.

Although questions remain regarding tDCS and its effects on working memory, evidence indicates that tDCS can be effective if experiments are tailored to individual needs. The findings explored above importantly provide evidence that tasks must be hard enough for individuals to boost working memory ability after tDCS application. Therefore, it is thought that tDCS can be used to improve working memory in special populations with working memory deficits, such as older adults, who experience natural working memory performance decline, or clinical populations (Westwood & Romani, 2018). The effects of tDCS on working memory in special populations are considered in ***Table 2***.

Table 2: tDCS Effects in WM in Special Populations

Authors	Population	Montage	Results	Implications & Limitations
Jones, Stephens, Alam, Bikson, Berryhill 2015	Older Adults (55-73 y.o.)	1.5 mA; 10 min; anodal PFC, anodal PPC, alternating anodal PFC/PPC A: F3 or P4 C: Contralateral Cheek Visual WM Task Divided Attention Task Transfer Tasks	+ *Successful Task Transfer (Spatial 2-Back) *Long-Lasting Effects (1 m.o.)	TDCS can be used to recover working memory in older adults WM gains can last overtime Transfer for challenging tasks only Neuroanatomical changes underlying long-lasting effects unknown
Arciniega, Gözenman, Jones, Stephens, Berryhill 2018	Older Adults (mean age = 67.72 y.o.)	2.0 mA; 20 min; anodal Bilateral vs Unilateral Bilateral A: R PFC (F6) C: R PPC (P6) Unilateral A: F6 C: F5 Visual LTM Task; Visual WM Task; Recognition Visual WM Task	+ *Improvements only with right unilateral tDCS	Only visual working memory system Montages were only right lateralized Improvements only in low WM older adults The same montage improved WM in young adults with high working memory capacity
Nissim et al. 2019	Older Adults (65-89 y.o.)	2.0 mA; 20 min; anodal A: F4 C: F3 8 Cognitive Tasks ***fMRI	2-Back + *Accuracy and Functional Connectivity 0-Back -	Functional Connectivity between DLPFC-IPL increased with tDCS Fronto-parietal region may support working memory capacity Improvement is effort dependent High dose may yield better results
Eddy, Shapiro, Clouter, Hansen, Rickards 2017	Huntington's	1.5 mA; 15 min; anodal A: LDLPFC C: Contralateral Orbital Area Stroop Task Digit Reordering N-Back Task	+ *In WM capacity - *In Verbal Fluency	Improvements and impairments observed
Van	Adults w/ High-	1.5 mA; 40 min; bifrontal anodal		Bifrontal stimulation produced

Steenburgh, Varvaris, Schretlen, Vannorsdall, Gordon 2017	Functioning Autism	Left Anodal A: F3 C: F4 Right Anodal A: F4 C: F3 Letter & Spatial N-Back Tasks Transfer Task ***fMRI	+ *Successful Task Transfer	improvements + only immediately after stimulation Ceiling Effect Lower baseline performance: more improvement with tDCS due to ceiling effects
Papazova et al. 2018	Schizophrenia	2 Test Groups: 1.0 mA; 21 min; anodal 2.0 mA; 21 min; anodal A: RDLPFC C: L M. Deltoideus Verbal N-Back Task	+ *tDCS improved accuracy *1.0 mA improved more	TDCS can be used to augment brain function in schizophrenics, but dose is likely not significant No found change in RT due to tDCS
Santos et al. 2018	Fibromyalgia	2 mA; 20 min; anodal A: F3 C: Fp2 Dual N-Back Task	+ *Dependent on baseline BDNF (more = less +) *Successful Task Transfer	Level of education showed no significant impact on results Age range = 18-65 y.o. (very broad) Females only Different medications and additional disorders
Schwippel et al. 2018	Schizophrenia	2 Test Groups: 1.0 mA; 21 min; anodal 2.0 mA; 21 min; anodal A: RDLPFC C: L M. Deltoideus Visuospatial N-back Task	+ *2.0 mA test group only → accuracy improved *Greatest improvements in individuals with low cognitive ability and in the most challenging N-back Task	The test group included many smokers, which may have made tDCS less impactful Possible carry-over effect because both sessions were so close together tDCS may be dose specific since only 2.0 mA stimulation worked only
Lau et al. 2019	Parkinson's	2.0 mA; 20 min; A: F3 C: Contralateral Supraorbital Region Go/No-Go Task; Visual WM Task	0	Low statistical power Cognitive tasks and tDCS did not occur concomitantly It is likely results affected by ceiling

		***Single session		effect, as individuals were highly educated.
Das et al. 2019	Mild Cognitive Impairment	2.0 mA; 20 min; anodal A: LIFG C: Contralateral Shoulder Gist-Reasoning Training	- *But increased blood flow to right MFC *Preliminary data indicates tDCS modulates activity across networks	Results may imply that the impact is not directly related to increased blood flow in the brain.

*Abbreviations: A, anode; C, cathode; R, right; L, left; min, minutes of tDCS application; mA, strength of current applied in milliamperes; +, results show participants improved with tDCS; -, results show participants experienced impairments with tDCS; 0, results show participants did not respond to tDCS; *, important information regarding results; ***, important information regarding experimental setup; n, number of participants in the study; WM, working memory; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; PC, parietal cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; y.o., years old; m.o., months; RT, reaction time; BDNF, brain-derived neurotrophic factor; fMRI, functional magnetic resonance imaging; notations such as F3, Fp1, Fz, C3, F7, P7, Pz are electrode positions as described by the international 10-20 EEG system.* ***Table 2*** *is organized chronologically by year and by population.*

Table 2 Results: What Trends Are Seen in Working Memory in Special Populations Using tDCS?

The studies explored in ***Table 2*** suggest that tDCS can be used to improve working memory in special populations, and that these improvements can be maintained over long periods of time (Jones *et al*., 2015). The latter finding is critical in special populations, as long-lasting results implicate tDCS as a long-term treatment for those with working memory deficits. In addition, the above studies demonstrate that improvements made on trained working memory tasks can be transferred to untrained tasks (Van Steenburgh *et al*., 2017; Jones *et al*., 2015; Santos *et al*., 2018). Therefore, tDCS appears to hold great potential and value for therapies in individuals with working memory disorders.

It is just as important that research teams consider individual differences in special populations as it is in neurotypical subjects, if not more so, to produce benefits. Older adults are more likely to be using multiple medications to deal with any ailments. Individuals with psychiatric disorders may have multiple disorders and will also be on medications to modify symptoms. Medications and psychiatric disorders change baseline physiological brain state and thus will affect the impacts of tDCS, which is highly brain state dependent (Brunoni *et al*., 2013; Sathappan, Luber, Lisanby, 2018). Santos *et al.* (2018) found that more baseline brain-derived neurotrophic factor, or BDNF, correlated with less working memory improvements in fibromyalgia patients. High BDNF levels are a characteristic of fibromyalgia, so if tDCS were to be used on this population, it would be prudent to evaluate BDNF prior to treatment (Haas *et al*., 2010). This is just an example of how baseline brain states can impact tDCS results, and thus why it is so important these differences are taken into consideration before using tDCS on clinical populations.

It is also notable that individuals within a special population are still going to have unique cortical morphology, levels of education, and working memory capacity. Like tDCS studies in neurotypical young adults, cognitive tasks in tDCS clinical studies need to be created so tasks are hard enough to challenge participants. If the cognitive tasks are not difficult enough, data from special populations will be skewed by ceiling effects (Van Steenburgh *et al*., 2017; Nissim *et al*., 2019; Lau *et al*., 2019). This may also be the case for transfer tasks, as Jones *et al*. (2015) found that working memory improvements from tDCS in older adults transferred only to more difficult transfer tasks.

Aside from these clear patterns which support evidence found in neurotypical humans, there are still many questions which must be answered before tDCS can reliably be used to improve working memory in special populations. Does dose, or the amount of current applied, change results? Schwippel *et al*. (2018) and Nissim *et al*. (2019) both found evidence that increased current was more effective in improving working memory. However, Papazova *et al*. (2018) found that lower dose (1.0 mA) produced more improvement in schizophrenic participants' accuracy on a task compared to participants who received a higher dose (2.0 mA). How can opposing results in tDCS-working memory research be reconciled? Arciniega *et al*. (2018) provide more evidence in their study which supports that interindividual differences are extremely important in tDCS research, but also reinforce that results can be so unpredictable. Why did the same montage used by this research team to improve working memory in older adults with *low* WMC work in healthy young adults with *high* WMC (Arciniega *et al*., 2018)? It is inconsistencies such as these that future researchers should aim to resolve.

Discussion

Evidence across studies support that tDCS can be used to improve working memory in neurotypical healthy adults, older healthy adults, and clinical patients. However, improvements are entirely reliant on the experimental procedure, which must be designed diligently by researchers to consider interindividual differences. Findings from multiple working memory-tDCS experiments show that this is true whether participants are neurotypical or have working memory deficits. Ultimately, before tDCS can be used safely by the general public, more information regarding neural mechanisms and methods of customization are necessary.

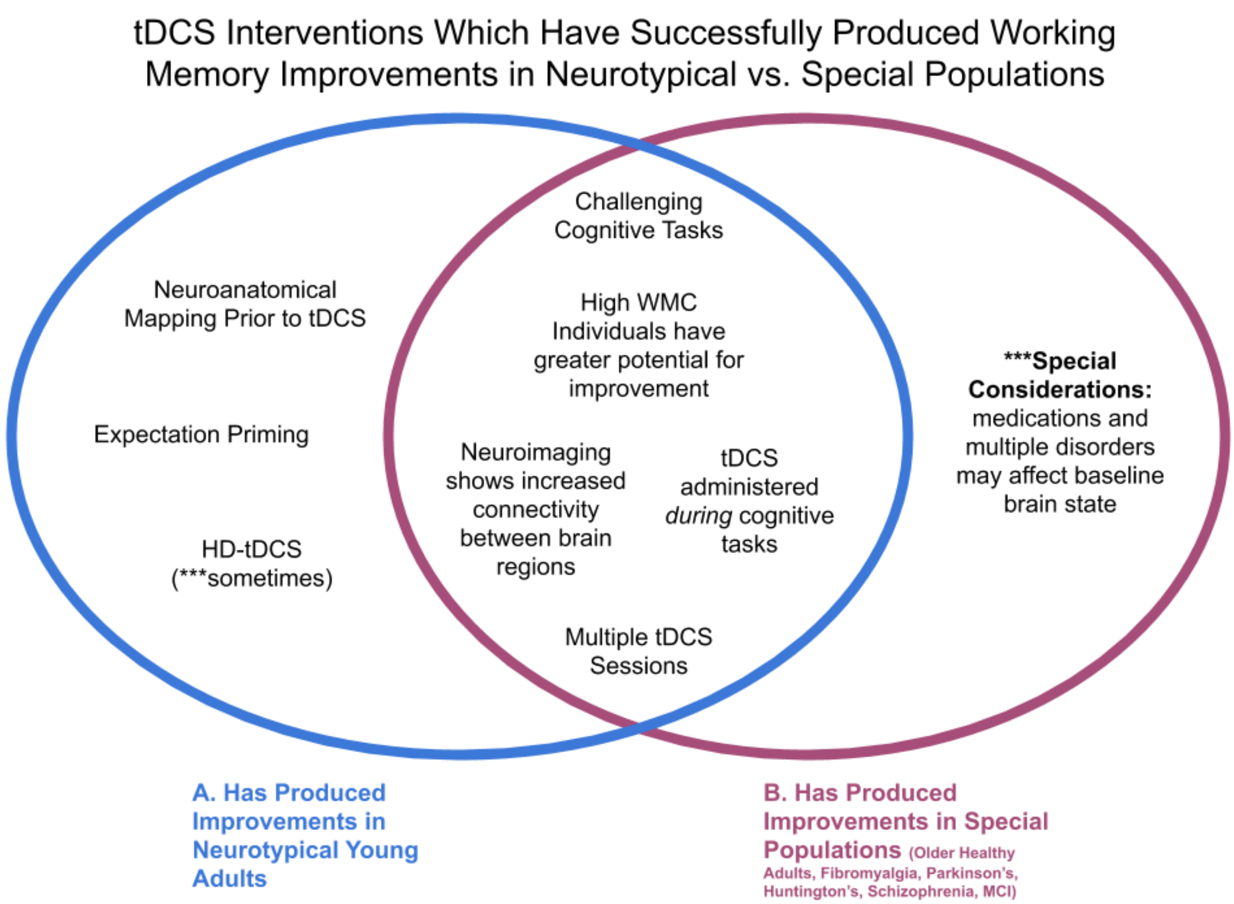

Figure 4. tDCS Interventions Which Have Successfully Produced Working Memory Improvements in Neurotypical vs. Special Populations. A. Phrases in the blue circle reflect tDCS

components which have produced working memory improvements in neurotypical healthy adults. B. Phrases in the purple circle reflect tDCS components which have produced working memory improvements in special populations. Phrases which lie in both circles show tDCS interventions which work in neurotypical *and* special populations. These tDCS methods should always be present in experimental design to increase likelihood of desired results, which are improved cognitive performance.

Across populations, multiple session tDCS has proven more effective than single session tDCS in improving working memory and creating long-lasting effects (Jones *et al*., 2015; Luque-Casado *et al*., 2019; Rabipour *et al*., 2019). Likewise, working memory tasks should occur concurrently with tDCS administration if improvements are to be produced. These elements are the foundation for a successful tDCS experiment in working memory. Scientists can build on this foundation and increase the likelihood of desirable results if they use WMC evaluations to tailor tDCS montages and cognitive tasks to the needs of the individual. This is key to tDCS-working memory research since data show that tDCS is ineffective if cognitive tasks are not challenging enough. Because tDCS appears to produce modest improvements, it is seen in both neurotypical and clinical participants that those with inherently higher WMC have greater potential to benefit from tDCS intervention. Disregard of cortical morphology or skull shape can contribute to null effects as well, so it is strongly suggested that neuroanatomical mapping techniques be incorporated as a staple in *any and every* tDCS experiment.

Beyond physical brain structure, it is also important researchers evaluate the baseline brain and emotional state of their test subjects. This is especially important in clinical populations, as patients with working memory deficits secondary to a disorder, such as Schizophrenia, Huntington's, Parkinson's, or simply old age, use medications or experience symptoms which alter baseline brain activity. Abnormal activity or hormone levels can skew tDCS results, so this may be a future constraint if tDCS were to be used as a clinical treatment. It is up to hereafter studies to see if this constraint could be alleviated through expectation priming or modest current increase, which may be able to slightly boost working memory performance (Papazova *et al*., 2018; Rabipour *et al*., 2018; 2019; Schwippel *et al*., 2018).

To advance tDCS research in working memory, scientists must continue to study the neural mechanisms through which tDCS augments brain activity and connectivity. This may be achieved through the continued use of neuroimaging techniques as tools for further insight. Research within the last five years has found that, while tDCS may have neurophysiological effects (increased connectivity or increased BOLD response), these effects do not necessarily boost working memory (Hill *et al*., 2018; Abellaneda-Pérez *et al*., 2019). Intriguing findings have suggested that cognitive output may be related to synchronized gamma and theta oscillations during a working memory task. This should be pursued more to advance the field in the years to come.

HD-tDCS is a newer stimulation method which could potentially progress the field as well. HD-tDCS provides a more localized delivery of current to underlying cortical neurons, but it is clear this technique is far from being fully understood (Turski *et al*., 2017). Aside from the precision needed to deliver the current to the correct brain region, HD-tDCS appears to affect individuals differently than tDCS, and therefore must be systematically studied (Gözenman & Berryhill, 2016). Like regular tDCS, more knowledge surrounding how to improve working memory time and time again with this stimulation technique must be gained before results can be considered robust enough to be used in daily life.

Companies manufacturing tDCS headsets for at-home use claim that tDCS can safely and affordably boost cognitive performance. Before tDCS is used by the general public in the home, it is important people are aware of the constraints that come with this type of neurostimulation.

There is still too much variability and too many questions regarding tDCS findings in working memory research to guarantee improved working memory performance. However, with the persistent exploration of tDCS/HD-tDCS effects on working memory and advancing neuroimaging techniques, it is possible that the scientific cohort will determine how tDCS affects individuals, and even use this information to create customizable tDCS protocols which can reliably be used for at-home or clinical treatments.

Limitations

Results in this paper are limited mainly to qualitative trends regarding tDCS in working memory. That is, variables such as working memory capacity, cognitive task difficulty, or neuroanatomy are central. This paper does not focus on details of tDCS montages or experimental set-ups, such as optimal electrode placement or laterality of applied current and task stimuli. These elements of tDCS research are still important, especially since some findings indicate that laterality can impact cognitive outcomes (Ruf, Fallgatter, Plewnia, 2017, Arciniega, Gözenman, Jones, Stephens, Berryhill, 2018), but are not explored thoroughly by this project due to a lack of evidence in the articles discussed. This is another limitation of this paper: twenty-four empirical articles were reviewed, which is a small number of studies in all tDCS-working memory research. Thus, results may be affected by low statistical power. Trends seen in data from these twenty-four articles, however, align with previously established concepts in literature reviews of tDCS and working memory, and for this reason are supported by large bodies of evidence.

Conclusion

Transcranial direct current stimulation has the potential to reliably boost working memory in neurotypical and clinical populations. The key in tDCS experiments is to tailor the application technique and cognitive task to the individual. Through the use of new tDCS methods (HD-tDCS) and neuroimaging technology, future research should focus on elucidating the neural mechanism through which tDCS augments brain activity and cognitive behavior. Until tDCS is understood at this level, people should avoid using tDCS at home without professional oversight, as improvements cannot be guaranteed at this time.

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