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tDCS in Post-Stroke Aphasia Recovery

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Introduction

Transcranial direct current stimulation (tDCS), a form of non-invasive brain stimulation originally studied for its effect on motor limb physiology[1], has been investigated for its use in the treatment of aphasia since 2008[2–3]. The experimental use of tDCS for aphasia, however, began differently from those paradigms established for post stroke motor recovery, both conceptually and in method. Not only is aphasia research a relative newcomer to the field of tDCS experimentation, it has thus far been somewhat of an outlier in its limited use of tDCS autonomously.

Theoretically understood to be vastly more complex than our intricate motor systems, cortical language representation has most recently been conceptualized as a dual stream, diffuse network[4–6], with language processing subcomponents evolved from non-linguistic primates[7–8]. In the dual stream model, human language functions are lateralized primarily in the left hemisphere, with Broca's area comprising the left complement of a bilateral dorsal stream network devoted to naming and articulation. Conversely, Wernicke's area constitutes the origin of a bilateral ventral stream in which semantic meaning is attached to components of speech sounds[6,9–21]. Additional activation in homologous right hemisphere language areas appears to be determined by lexical necessity, with increased articulatory demands

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activated within the bilateral dorsal stream and the decoding of unfamiliar words activated in the bilateral ventral stream network[9]. Complex as it may be to optimally prime the motor cortex for post-stroke limb rehabilitation using tDCS, it may be considered even more challenging to modulate the cortical plexus which encodes and produces language in all of its richness. The theoretical mechanisms of brain activation during tDCS protocols suggest that tDCS primes the brain for enhanced outcomes in behavioral therapies[22], which may have led to the appeal of combining methods concurrently. The specific mechanisms by which tDCS modulates language networks however, remain equivocal. Recent literature indicates that an aggregate therapeutic impact may be generated when combining motor and cognitive resources concurrently[23–24].

Herein, we will provide a broad overview of tDCS/aphasia research and suggest filling gaps in our understanding of the physiological changes induced by tDCS on language networks.

Aphasia

Aphasia is a language disorder which occurs in up to 38% of stroke survivors, often leaving them with lifelong residual deficits[25–29]. As such, aphasia negatively impacts stroke survivors' safety and quality of life. People with aphasia often experience social isolation[30–31], unemployment[31–32], marital difficulties[33], mental health issues[34], and financial burdens[26,35]. The presence of aphasia is associated with a longer duration of hospital stay and higher risk of death[35]. Stroke survivors with aphasia are often concomitantly burdened with dysarthria or apraxia of speech, adding yet another level of difficulty to the already effortful task of communicating.

It has been stated that, "…one never recovers *from* aphasia; one recovers *with* aphasia[36]." Similarly, recovery with aphasia is more of a fluid process than originally understood. It is now acknowledged, for example, that patients having one type of aphasia in the acute phase may present with a different form of aphasia weeks or months hence[37]. Many patients with aphasia have symptoms which, in fact, defy textbook categorization[38–39].

Recovering with Aphasia

Prior to the last decade, aphasia literature generally conformed to the belief that recovery was limited to a 3–6-month window[40–41]. More recent studies, however, provide evidence to rethink this assumption[41–43]. In one recent example, Fiori et al. (2013) studied 7 subjects with chronic aphasia who nonetheless demonstrated multiple language improvements, with temporal stimulation improving naming of nouns, and frontal stimulation enhancing verb production[44].

Patients with aphasia, furthermore, are not always ready to participate in rehabilitation within the first 3–6 months due to sensory deficits, agitation, fatigue, side effects of medications[45] and disordered sleep patterns[46]. The reorganization of dendrites following ischemic lesions can be highly variable[4]. Additionally, patients may experience psychosocial issues such as depression and anxiety which make it difficult to participate optimally in speech therapy during the acute phase[38].

Various forms of behavioral aphasia therapy span decades of research and include: Melodic Intonation Therapy ("MIT")[47], Constraint Induced Language Treatment ("CLT")[48], computer avatar programs such as "Aphasia Scripts"[49] and "Speech Entrainment"[50]. Preliminary evidence suggests that increasing the intensity of speech therapy is beneficial to aphasia recovery[51]. This has led to the development of Intensive Comprehensive Aphasia Programs or "ICAPs"[52]. Advances in technology have generated a surge in computerized aphasia "apps" for home practice[53] and have prompted the rise of telerehabilitation[54]; however, in spite of the many therapies available, no gold-standard aphasia treatment exists to-date[55]. What has been established, is that speech therapy to treat aphasia in any format is superior to no treatment at all[43,56] and that the intensity of treatment appears to be an important factor in the extent of recovery[51–52].

Medications

Medications for auxiliary use in the treatment of aphasia have had mixed success[57], with most notable language improvement found with memantine, vasopressin and piracetam, as well as medications that enhance production of acetylcholine[45]. In their review of pharmacological treatment for aphasia, Small & Llano (2009) caution, however, that these medications are known to be helpful only with the addition of behavioral speech treatment and are not intended to replicate the benefits of speech therapy. It is likewise important to discern medications which have adverse effects on aphasia recovery, particularly since those drugs are often prescribed for other stroke related issues such as hypertension, seizures and heart disease[45].

Neuroimaging

Neuroimaging studies are essential to understanding the substructures of language and the physiological impact of tDCS. As noted by Saur et al. (2006)[58] and Geranmayeh et al., (2014)[59], before the advent of fMRIs, language was considered domain specific. The two hypotheses which predominated the literature at that time were the "perilesional hypothesis" and "laterality shift hypothesis." The suggestion that language laterality to the right hemisphere is maladaptive led to the "disinhibition hypothesis," which stated that transcallosal inhibition is responsible for poor recovery[59]. These divergent views of language recovery could be used to justify a particular treatment; or, in the case of tDCS, each view might accompany differing recommendations for montage and polarity. Laska et al., (2011)[60] and Meinzer et al. (2013)[61] recommend caution however, in the interpretation of fMRI language activation measurements. They note that positive changes in functional language ability may not always correlate with neuroimaging data[61].

tDCS for Aphasia Rehabilitation

Experimentation with alternate forms of physiological intervention for aphasia, such as non-invasive brain stimulation, began in the 1980s with transcranial magnetic stimulation (TMS). TMS targets cortical areas via electromagnetic current and has the ability to transiently induce speech arrest, providing opportunities to explore the neural connectivity of language in the brain[62]. Additionally, TMS supplies a method for mapping the brain, which can be used in conjunction with other brain imaging technologies (e.g., EEG, fMRI, etc.) At the turn of this century, a new form of non-invasive brain stimulation emerged in the field of stroke recovery, transcranial direct current stimulation (tDCS).

Unlike TMS, tDCS uses a low-intensity current of 1–2 mA to modulate (excite or inhibit) neuronal activity[63]. It has been explored in stroke rehabilitation as a method for encouraging brain plasticity, with results often lasting beyond the initial period of stimulation[62]. tDCS also has the advantage of being portable, with built-in sham control, making it suitable for clinical experimentation during behavioral therapies.

The first experiments examining the effects of tDCS on the human motor cortex appeared promising[64–65]. Nitche and Paulus extended their exploration of the effects of tDCS on human motor recovery to include adjunctive fine-motor training[65]; however, it was not until 2007 that tDCS was combined outright with physical therapy for stroke[66]. Results suggested that tDCS might prime the brain as an adjuvant to behavioral motor-limb therapies, optimizing recovery. Subsequent neuronavigation using TMS allowed researchers the opportunity to more precisely map specific cortical areas, providing the chance to explore the effects of various tDCS stimulation intensities and polarities (e.g., excitatory or inhibitory stimulation).

In 2008, 2 studies emerged which looked at the effects of tDCS on language abilities, with 1 study experimenting on healthy subjects[2] and 1 on patients with aphasia[3]. In the majority of subsequent tDCS/aphasia studies, tDCS was paired with language training (Figure 1), possibly because stand-alone tDCS treatment was not viewed to provide the same level of consistent language improvement[9]. Aphasia studies regarding other forms of non-invasive brain stimulation such as TMS may have provided further justification for combining tDCS with language training[67]. Of note, while most tDCS/aphasia studies included sham stimulation along with behavioral intervention, sham stimulation, when used in combination with behavioral therapy, cannot tell us what tDCS does autonomously. As a result, we know something about the effects of tDCS on language behavior, but an understanding of the physiological underpinnings of tDCS on language networks remains elusive.

Cipollari and colleagues (2015) in their recent study combining TMS and EEG to measure the physiological effects of tDCS on aphasia treatment, sought to address the limited amount of literature on the neurophysiology of tDCS on language areas[68]. There are several unique elements in this study, including the use of right homologous language areas, the type of therapeutic intervention (MIT) and the severity level of subjects. tDCS was used to increase activity in the right inferior frontal gyrus (IFG) as it is implicated in prosodic aspects of language function. They discovered via TMS-EEG that right-hemisphere anodal stimulation likely enhanced the effects of MIT. Previously, Wirth et al. (2011) had used EEG to measure the effect of anodal tDCS over the left prefrontal cortex of healthy subjects and similarly noted improved naming compared with sham stimulation[69]. In spite of some limitations, these studies have taken a positive step in the direction of exploring the physiological effects of tDCS on language substrates.

tDCS/Aphasia Literature Reviews

Reviews of tDCS/aphasia literature are numerous[35,43,63,70] (Figure 2), yet recent meta analyses provide conflicting evidence of the effectiveness of tDCS for aphasia. One recent meta-analysis found statistically significant improvements in people with aphasia using tDCS[71], while another meta-analysis reported some promise using cathodal stimulation over the contralateral hemisphere, but found no statistical significance regarding the effects of tDCS for aphasia overall[56].

One common critique across tDCS/aphasia literature reviews, is a paucity of functional communication measures. In a Cochrane systematic review, Elsner and colleagues (2013) found that primary functional measures did not provide adequate information about whether tDCS promotes greater functional recovery than speech therapy alone[56]. Measures in recent aphasia/tDCS studies focus on naming as the central measure of language improvement[3,9,37]. Clinicians have experienced first-hand, however, the patient with aphasia who scores poorly on naming tasks, yet passes important functional communication milestones such as ordering a meal in a restaurant, which are difficult to quantify. Future studies may wish to address whether tDCS promotes gains in functional daily communication, as well as naming tasks.

A Motor-Language Connection and tDCS

Prior views of language representation in the brain held to the notion that each subset of language function operates in discrete modules[4,72]. It is now understood that language operations shift fluidly throughout the brain and are tied to many other brain functions[57,72]. Pullvermüller & Berthier, (2008) report that belief in a modular language system encouraged separation of linguistic tasks in speech treatment, so that naming and syntax, for example, would not be addressed together. They note that fMRI studies have changed our view of the modular concept. The authors recommend combining language and action tasks simultaneously, to strengthen language recovery[43]. One example of the additive effects of combined motor-language training were noted in a set of 2 combined studies, using 23 and 40 healthy adults respectively, in which simultaneous training on language-motor tasks had a beneficial effect on both semantic and motor performance[25]. These findings correspond with a 2009 report by Harnish et al. of combined motor and language improvement after arm training exercises in subjects with chronic aphasia[73] as well as the informal observation of Glover et al. (2002) during a study in young children with hemiplegia[74].

Primaßhin et al. (2016) published a recent collection of 4 aphasia case studies which further demonstrated parallel motor-language recovery systems at work. The authors reported that motor and language improvements are additive in stroke recovery, rather than serving to compete for neural resources[24]. In another study which looked at “pantomime” skills in people with aphasia, van Nispen and colleagues (2016) found that semantic deficits associated with aphasia also appear to have a negative impact on the kinesthetic representation of the distinctive features of objects[75]. In their 2012 review, Roby-Brami et al. reported that brain areas which underlie the motion of reaching and grasping are connected

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with visual pathways as part of a "dynamic system" of networks which communicate via mirror neurons with Broca's area[76].

Cumulatively, these recent papers present the possibility that motor and language rehabilitation work well when combined. This presents an intriguing possibility for the direction of future tDCS/aphasia research. Both language and motor functions may be modulated via tDCS, for example, by targeting the supplementary motor area[77] and cerebellum[78]. Supporting the rationale for this view, Hertrich and colleagues (2016), looked at the role of the supplementary motor area (SMA) in language function and noted that the anterior portion of the SMA (or pre-SMA) was important for "context integration" and language processing[77]. Similarly, in a recent proof-of-concept study, Turkeletaub et al. (2016) reported that tDCS modulation of the cerebellum may enhance verbal fluency[78].

Discussion

Speech-language pathologists strive to use evidence-based practices in the treatment of aphasia and rely on experts' findings to justify the integration of new treatment strategies. We know that the study of tDCS for aphasia rehabilitation is safe[79]; and, that when combined with speech-language therapy, it can sometimes be beneficial[80]. We know that we are not stimulating modular language substrates with tDCS, but rather, an interconnected web of language activity[4,43,57]. Additionally, we know that we are far from understanding the mechanisms of what tDCS does physiologically in the brain to promote language recovery[4]. We believe it is therefore crucial to investigate the biological mechanisms of tDCS upon language networks. Like attempted pharmacological treatments for aphasia, tDCS has been reported to produce neurochemical changes, such as changes in N-methyl-D-aspartate (NMDA) receptor activity. Unlike pharmacological treatments however, tDCS has no known serious side effects[79]. tDCS could therefore be beneficial to aphasic patients when concerns arise regarding multiple drug interactions[23].

Inclusion of behavioral training in the majority of tDCS/aphasia studies may inhibit an understanding of what tDCS does autonomously to language functions. It is true that a tDCS/aphasia experiment without language training would divest aphasic subjects of concomitant therapy; but conversely, it might enable scientists to develop improved tDCS paradigms that can later be combined with behavioral treatments. Further, while there are a number of studies which examine the effects of tDCS on healthy motor physiology, its effects on healthy language networks has not been as thoroughly explored (Figure 3).

Scientific literature contains a wealth of substantive reviews on progress within the field of tDCS/aphasia research; however, the number of review papers has been disproportionately high when compared with the number of experimental studies conducted (Figure 2). The number of tDCS/aphasia review papers has even exceeded those in tDCS/motor-limb literature, in spite of its later origin. This suggests that in tDCS/stroke rehabilitation literature as a whole, there is a great deal of important discussion about the merits of tDCS for aphasia, with a correspondingly smaller number of original research studies supporting the debate.

Hauser, Chomsky and Fitch, described the architecture of language as having both sensory-motor functions, found even in primates, and a subsystem which generates an expanding syntax from conceptual representations[81]. According to Hauser and colleagues (2002), this subsystem then grafts grammatical principles onto the phonological system, resulting in meaningful speech. Inter-connectivity of language to other areas of brain function however, continues to be revealed in surprising ways. Language is a dyadic or interactive process[82], which can be seen in the context of social communication, as well as in the synergy of neuronal connections in cortical language areas which extend toward many other physical and mental human functions[24,57,76]. The question of whether similar mechanisms are at work in post-stroke motor recovery and aphasia is not new. For example, in a retrospective analysis of 21 stroke patients with aphasia, Lazar et al. (2010) suggested the possibility that multimodal brain regions could impact recovery for post-stroke limb deficits and aphasia concurrently[83]. tDCS studies have found a relationship between speech and hand recovery[84], as well as implicit motor learning[85]. As noted by Dipper et al. (2015), nonlinguistic components in the rehabilitation of aphasia are increasingly becoming affirmed[84]. Future studies may wish to investigate whether tDCS of shared motor/language areas could provide similar effects, by simultaneously targeting language and motor systems, toward overall improved functional outcomes.

On a final note, in light of the diversity of languages in tDCS/aphasia protocols[63], it is interesting to consider the findings of recent neuro-linguistic studies which contend that language processing is activated in differing brain regions among speakers of languages that are structurally or morphologically dissimilar (e.g., Mandarin or Hebrew, compared with English, for example)[86–88]. Future tDCS-aphasia studies may therefore wish to compare tDCS montage, polarity and outcomes across linguistically disparate languages, as well as in bilingual versus monolingual speakers.

New Opportunities

This broad overview of tDCS-aphasia literature yields considerable promise. From this we see the following plausible opportunities for further experimentation:

- tDCS modulation of
    - diffuse motor areas which are thought to interface with perisylvian language areas (e.g., the cerebellum, supplementary motor area, etc.);
    - cortical language or language-motor areas with adjunctive multidisciplinary paradigms of restorative therapy (physical, occupational and speech);
    - cortical language or language-motor areas using functional language outcome measures (e.g., taking a phone message, ordering in a restaurant, etc.);
    - cortical language or language-motor areas combined with more intensive, circumscribed aphasia treatment; and

– bilingual subjects, especially wherein the languages spoken are linguistically divergent.

Conclusion

In eight short years, aphasia literature has developed information, both theoretical and practical, on methods for combining tDCS with behavioral therapy for post-stroke aphasia. New data suggests a direct connection between neural motor-limb networks and speech-language systems, opening the door to methods for combining physical and cognitive resources in stroke recovery, through both tDCS and behavioral therapies. While the neurophysiological underpinnings of tDCS on language substrates require further exploration, available data support that continued tDCS/aphasia research may assist in the creation of stronger therapies, providing brain recovery from this common debilitating disorder.

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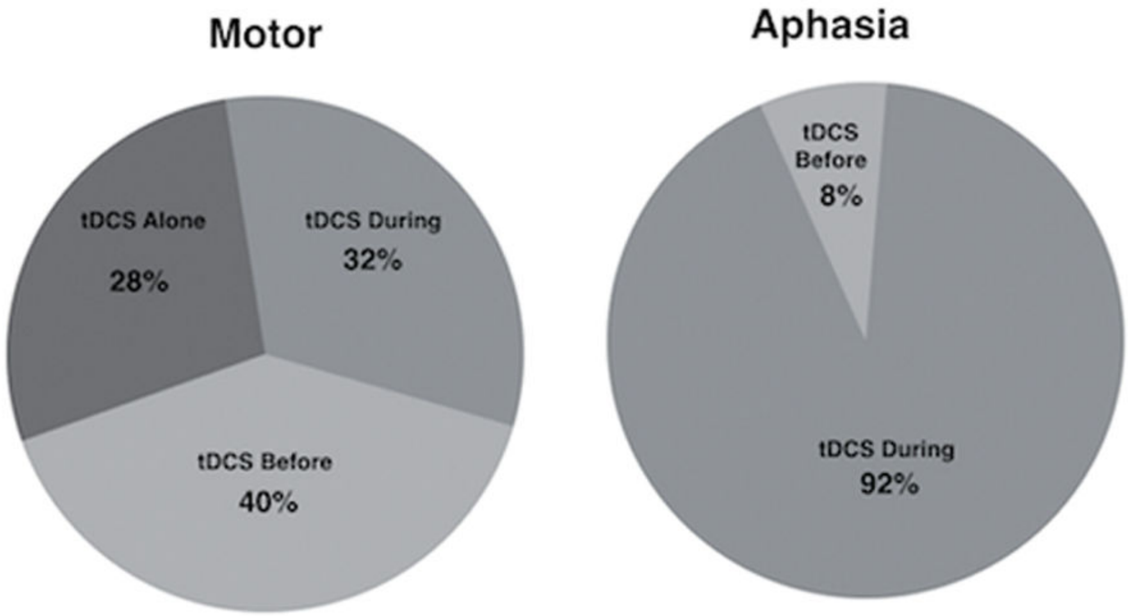

Figure 1. 2014–2015 publications

Differences in use of stand-alone tDCS, as well as timing (before or during therapy), can be seen during post-stroke motor-limb vs. aphasia studies in a recent 2-year period.

Source: PubMed. (Source criteria: tDCS/stroke, tDCS/motor, tDCS/motor/stroke, tDCS/aphasia, tDCS/language)

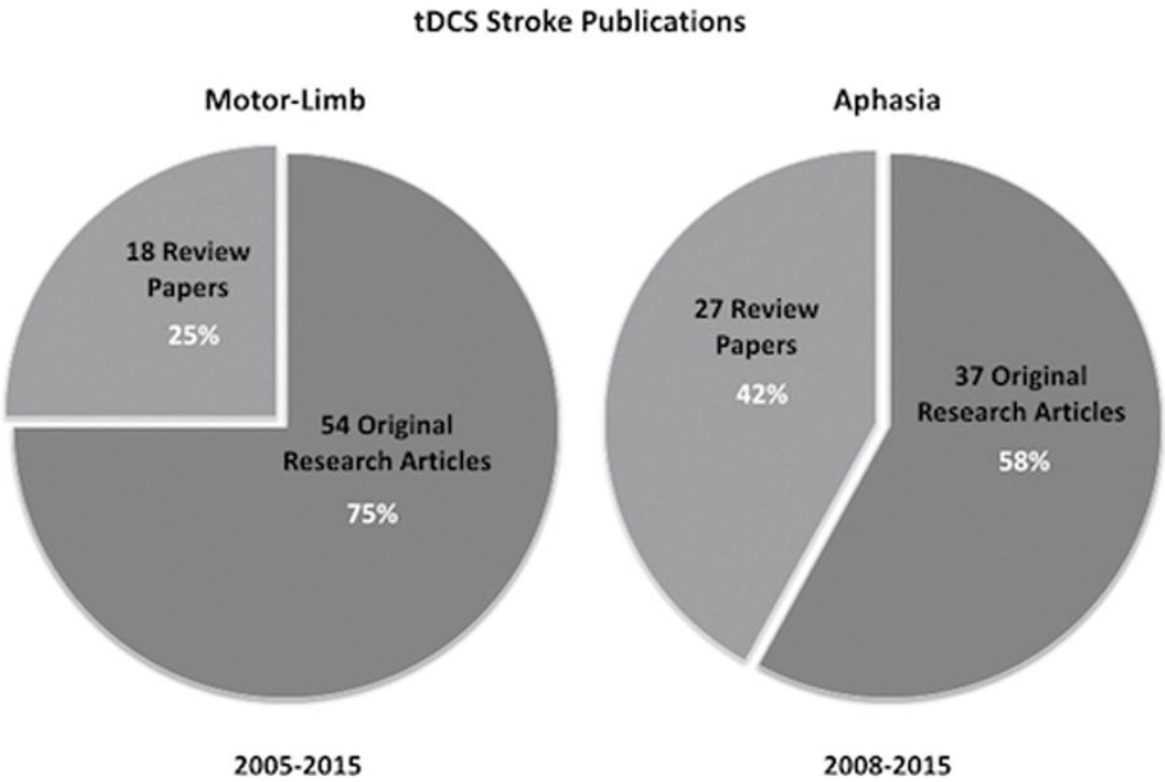

Figure 2. tDCS-Stroke Publications

tDCS Stroke publications by type, for motor-limb and aphasia. Source: PubMed. (Search criteria: tDCS/motor/stroke, tDCS/motor/stroke/review, tDCS/aphasia, tDCS/aphasia/review)

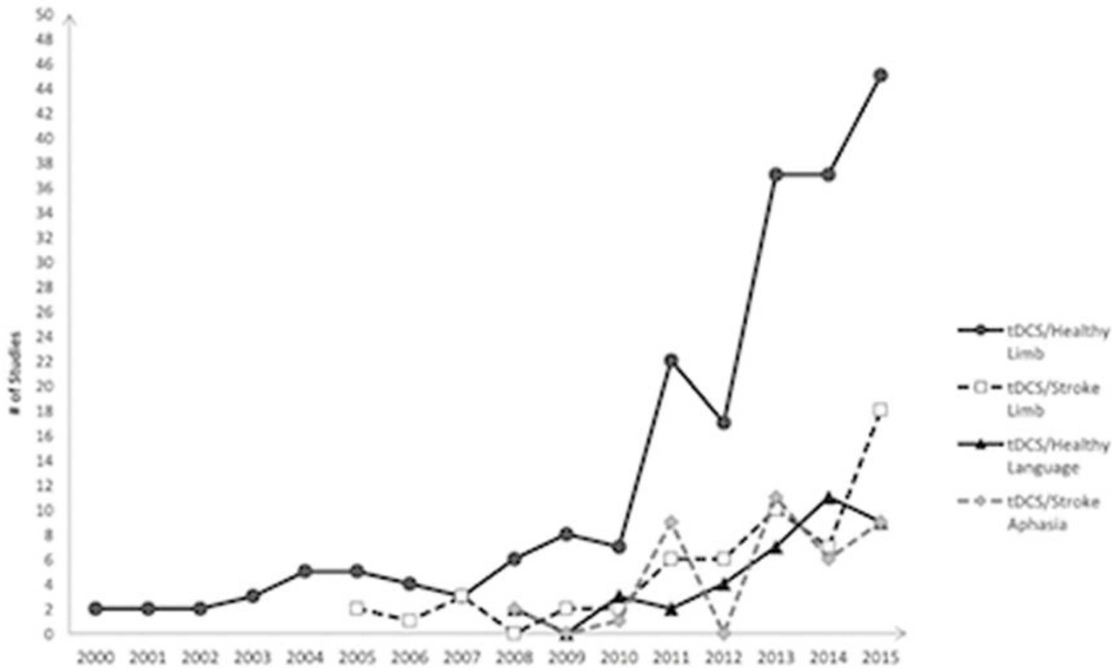

Figure 3. Timeline of tDCS Limb vs. Language Studies

Considerable data has been collected regarding the effects of tDCS on healthy motor physiology vs. the effects of tDCS upon healthy language networks. Source: PubMed. (Search criteria: tDCS/motor, tDCS/motor/stroke, tDCS/aphasia, tDCS/language)