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Transcranial Pulsed Current Stimulation: A Scoping Review of the Current Literature on Scope, Nature, Underlying Mechanisms, and Gaps.

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**Impact Statement**

TPCS is a cutting-edge non-invasive brain stimulation method that utilizes pulsatile current to modulate brain oscillations. It shares parameters and effects with other tES techniques like tACS (frequency-dependent) and tDCS (polarity dependent). It is believed to have unique mechanisms for personalized treatment. Despite limited literature, research suggests that tPCS can modulate cortical excitability through entrainment and stochastic resonance. Further studies are recommended to investigate its underlying mechanisms and the effects of different parameters.

**Abstract**

Transcranial pulsed current stimulation (tPCS) is a non-invasive brain stimulation technique that has aroused considerable attention in recent years. This review aims to provide an overview of the existing literature on tPCS, examine the scope and nature of previous research, investigate its underlying mechanisms, and identify gaps in the literature. Searching online databases resulted in 36 published tPCS studies from inception until May 2023. These studies were categorized into three groups: human studies on healthy individuals, patient studies with pathological conditions, and animal studies. The findings suggest that tPCS has the potential to modulate brain excitability by entraining neural oscillations and utilizing stochastic resonance. However, the underlying mechanisms of tPCS are not yet fully understood and require further investigation. Furthermore, the included studies indicate that tPCS may have therapeutic potential for neurological diseases. However, before tPCS can be applied in clinical settings, a better understanding of its mechanisms is crucial. Hence, the tPCS studies were categorized into four types of research: basic, strategic, applied, and experimental research, to identify the nature of the literature and gaps. Analysis of these categories revealed that tPCS, with its diverse parameters, effects, and mechanisms, presents a wide range of research opportunities for future investigations.

**Keywords**

Transcranial pulsed current stimulation, tPCS, transcranial electrical stimulation, tES, Non-invasive brain stimulation, NIBS

**1. Introduction**

Non-invasive brain stimulation (NIBS) refers to a number of techniques that modulate neuronal excitability via transcranial stimulation. In addition to providing a deeper comprehension of brain functionalities, these methods have the potential to serve as supplementary therapies for addressing neurological and neuropsychological conditions (Brunoni et al., 2016).Transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES) are two examples of non-invasive techniques that are utilized for various purposes.

TMS is a neuro-stimulatory technique that induces magnetic pulses to generate action potentials. It can be mainly used as a therapeutic tool in the form of repetitive TMS (rTMS) (Lefaucheur et al., 2014, Rossi et al., 2009) or as an assessment tool using, single or paired-pulse techniques (O’Reardon et al., 2007). On the other hand, tES is a neuro-modulatory technique, which affects neural activity based on modulation of neuronal activity (Nitsche and Paulus, 2000).

TES techniques are classified into four subtypes, depending on their waveform currents. These techniques include transcranial direct current stimulation (tDCS) (Nitsche and Paulus, 2000), transcranial alternating current stimulation (tACS) (Moliadze et al., 2010), transcranial random noise stimulation (tRNS) (Paulus, 2011), and transcranial pulsed current stimulation (tPCS) (Jaberzadeh et al., 2014). These techniques alter the spontaneous firing rates of cortical neurons, which may lead to long-lasting cortical neuroplasticity through spike-timing-dependent plasticity (STDP), which has two main effects: long-term potentiation (LTP) and long-term depression (LTD). The general parameters in different tES techniques are current intensity, duration of application, current density, and electrode montages (Nitsche et al., 2005). Different tES techniques are also accompanied by distinct parameters that serve as the foundation for the induction of neuroplasticity through specialized mechanisms and impacts on cortical neurons (Figure 1).

TDCS is a commonly employed neuromodulatory technique that utilizes two electrodes with opposing charges to apply direct current. The effects of tDCS, which induce depolarization or hyperpolarization of the resting membrane potential of neurons, depend on polarity. Anodal tDCS (a-tDCS) and cathodal tDCS (c-tDCS) are two variations of this technique (Nitsche and Paulus, 2000).These changes in membrane polarization may also lead to LTP and LTD through inhibitory and facilitatory mechanisms (Nitsche et al., 2005).

TACS, unlike tDCS, applies alternating currents and modulates the neural resting membrane potential through the frequency of the applied current. Indeed, tACS synchronizes neuronal networks and entrains spontaneous brain oscillations (Elyamany et al., 2021). The unidirectional flow of direct current in tDCS results in a net direct current component (NDCC) that matches the amplitude of the applied current, leading to tDCS primarily affecting the brain through its static effect (Jaberzadeh et al., 2015, Jaberzadeh et al., 2014) (Figure 1a). On the other hand, in tACS, positive and negative phases of equal size are used, which effectively cancel each other out, resulting in an NDCC of zero, and tACS mainly affects the brain through its dynamic effects (Figure 1b). Like tDCS, tACS also modulates neuroplasticity by STDP mechanism, leading to changes in network connectivity (Brunoni et al., 2016). However, unlike tDCS, tACS induces cross-frequency coupling between exogenous and endogenous brain oscillations (Elyamany et al., 2021).

TPCS, as a novel advancement in neuromodulatory techniques, involves the conversion of direct current into pulses with adjustable parameters such as pulse duration (PD) and inter-pulse interval (IPI) (Jaberzadeh et al., 2015, Jaberzadeh et al., 2014). This innovative approach allows for the modulation of neuronal activity through both static and dynamic effects. For instance, anodal-tPCS (a-tPCS) utilizes monophasic positive rectangular pulses with equal PD and IPI, resulting in a 50% NDCC of the applied current (Figure 1c). However, longer PDs (or shorter IPIs) can yield a higher NDCC, leading to increased static effects (Jaberzadeh et al., 2015). On the other hand, cathodal-tPCS (c-tPCS) applies monophasic stimulation with negative rectangular pulses, producing a combination of dynamic and static effects (Figure 1d) (Dissanayaka et al., 2020a). Additionally, symmetric biphasic rectangular pulses (Figure 1e) result in zero NDCC as the opposite phases of the pulses cancel each other out, like tACS. Remarkably, tPCS offers variable levels of NDCC (Figures 1c and d) that may mitigate potential electrochemical effects caused by acidic and basic reactions under the electrodes, distinguishing it from other neuromodulatory techniques (Jaberzadeh et al., 2015, Jaberzadeh et al., 2014).

**Milliampere (mA)**

**NDCC = 0**

**100% Dynamic effect**

**0% Static effect**

**NDCC = Maximum of amplitude applied current**

**100% Static effect**

**0% Dynamic effect**

**a-tDCS**

**Pulse duration = Inter-pulse interval**

**a**

**+**

**0**

**-**

**Milliampere (mA)**

**Milliampere (mA)**

**Milliampere (mA)**

**Milliampere (mA)**

**b**

**c**

**d**

**e**

**+**

**0**

**-**

**+**

**0**

**-**

**tACS**

**a-tPCS (Monophasic)**

**+**

**0**

**-**

**NDCC = 50% of amplitude applied current**

**50% Static effect**

**50% Dynamic effect**

**NDCC = 50% of amplitude applied current**

**50% Static effect**

**50% Dynamic effect**

**c-tPCS (Monophasic)**

**+**

**0**

**-**

**tPCS (Biphasic)**

**NDCC = 0**

**100% Dynamic effect**

**0% Static effect**

**Figure 1:** Different types of transcranial electric stimulations (tES).

a-tDCS: anodal transcranial direct current component, tACS: transcranial alternating current stimulation, a-tPCS: anodal transcranial pulsed current stimulation, c-tPCS: cathodal transcranial pulsed current stimulation; NDCC: net direct current compone

Therefore, in this scoping review, we aim to comprehensively map out the existing literature on the use of tPCS, its range, and the nature of current studies. Specifically, we aim to explore the underlying mechanisms behind the physiological and therapeutic effects of tPCS. By doing so, we hope to identify the types of research explored in published tPCS studies and determine gaps in the literature and areas that require further investigation.

**2. Method**

This scoping review was conducted based upon the protocol proposed by Peters (Peters et al., 2020) and suggested in the Joanna Briggs Institute (JBI) manual's guideline for evidence synthesis. We completed the evaluation form in the JBI manual to establish the scoping review. The scoping review framework, which consists of population, concept, and context (PCC), was selected to develop the study's eligibility criteria, title, and research questions.

**2.1. Types of participants**

The participants in the studies included in this review involved healthy and patient participants – human and animals – that received tPCS as an intervention. All of the studies possessed relevant ethics committee approval.

**2.2. Concept**

The concept of this study included all the studies in English that applied tPCS, including cathodal and anodal tPCS, monophasic and biphasic tPCS, and bi- or unihemispheric tPCS.

**2.3. Context**

The context of this scoping review was established by health science, including psychology, psychiatry, and physiotherapy.

**2.4. Sources**

The current review considered the following types of studies: experimental study designs, including randomised and non-randomised controlled trials, sham-controlled trials, single- and double-blinded studies, parallel and crossover studies, and pilot and feasibility studies. Nevertheless, unpublished and conference studies, systematic reviews, and meta-analyses were not included in this review. All evidence sources in this study met the following inclusion and exclusion criteria associated with the PCC framework (Table 1).

**Table 1: Framework (PCC)**

|  |  |
| --- | --- |
| **Inclusion criteria** | |
| **Population** | Healthy and patients populations, animals and human population |
| **Concept** | Anodal or cathodal transcranial pulsed current stimulation (tPCS), single session or multiple sessions of tPCS as a stand-alone or a priming technique. |
| **Context** | Physiotherapy, psychology, psychiatry |
| **Types of evidence source** | Randomized control trials, sham-control, crossover or parallel study designs, single and double-blinded studies, pilot studies, feasibility studies |
| **Exclusion criteria** | |
| **Population** | None |
| **Concept** | Transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS) |
| **Context** | Non- English studies |
| **Types of evidence source** | Systematic reviews, meta-analyses, scoping reviews, narrative reviews, books chapters mentioned available studies, and conference/symposiums abstracts |

**2.5. Search Strategy**

In line with the JBI manual, this scoping review has followed a three-step online-based search strategy to find all evidence sources from inception to May 2023. Firstly, a limited search fulfilled MEDLINE and MEDCARE accessed via the Ovid and PubMed platforms. Based on these databases, the MeSH and subject headings have been chosen. The relevant accepted keywords were "Transcranial pulse (d) current stimulation" and "tPCS" after consulting with my supervisor (SJ). Then, the titles and abstracts of retrieved articles were analysed along with the index terms describing them. Secondly, all identified keywords and index terms incorporated across eleven primary databases (MEDLINE, MEDCARE, PsycINFO, Scopus, Web of Science, Wiley online library, PEDro, ScienceDirect, Google Scholar, PubMed, and Ovid). In addition, all the grey literature, which included the keywords in their titles and abstracts, was searched in online secondary databases. These databases included (Google™ and Google Scholar™, ProQuest, Web of Science with conference proceedings, Scopus conference proceedings, Health and Medical collections of Monash library, Health technology assessment (Ovid), AMED: allied and complementary medicine (Ovid), and Access Medicine). Finally, an additional article was found within the included studies' reference list which was also included.

**2.6. Study Selection**

The peer review of electronic search strategies (PRESS) appraised the quality of included studies and the results were exported into the Covidence™ software package. After that, two reviewers independently analysed these titles and abstracts of the studies (MM, AT). The full text of studies were used to determine the studies as ‘relevant’ or ‘irrelevant’ which was then independently evaluated by these two reviewers using a standard form. Finally, all discrepancies were solved by discussions, and there was no need for the decision of the third reviewer.

**2.7. Data Extraction**

The risk of error in the data extraction has been minimized by a form developed to extract outcomes from included studies based on the inclusion criteria, which covers all the current review's aims (Table 2). One reviewer (MM) entered this structured form into Microsoft Excel, and another reviewer (SJ) checked it for accuracy. Finally, extracted information included, publications, study design, participants, tPCS protocols, and the aims of the studies.

**3. Results**

The literature search identified 500 articles, including 498 studies from online databases and two studies (Heidarzadegan et al., 2022, Alon et al., 2011) from searching in the cited references of included studies. In the second stage, 204 articles remained after removing duplicates from the initial search result. Then, 80 articles were excluded after screening the titles and abstract, and 124 studies remained. Finally, after excluding 88 full-text articles due to incompatibility with inclusion criteria, 36 studies were included in this scoping review. All these stages’ processes were analysed using PRISMA-SCR statement (Figure 2).

Records identified through database searching (n = 498)

Additional records identified through other sources (n = 2)

Records found eligible (n =500)

Records excluded after screening of titles and abstracts (n =80)

Full-text articles excluded for not meeting inclusion criteria (n =88)

(n =31) Books and articles just mentioned tPCS as a tES method

(n =8) Book chapters about tPCS which only discussed the available tPCS studies

(n =11) Systematic reviews about tPCS which only discussed the available tPCS studies

(n =8) Dissertation and thesis about tPCS

(n =5) Conferences/symposium abstracts

(n =3) Journal letters to authors about tPCS

(n =21) articles mentioned other tES techniques

(n =1) Non-English language article

Full-text articles assessed for eligibility

(n =124)

Identification

Screening

Eligibility

Records after duplicates removed (n =204)

Included

Included studies (n=36)

**Figure 2:** Flow diagram showing the selection process of articles following PRISMA-SCR guidelines.

**3.1. Extent and nature of the current tPCS studies (aim 1)**

### Main findings from the included studies are summarized in table 2 to outline the extent and nature of the current tPCS literature.

**3.1.1. Description of included studies**

We categorized these studies into three groups based on the diverse populations they represented.

**3.1.1.1. Human studies on healthy participants (2011–2023)**

This category comprises 25 studies that assessed the effects of tPCS on brain oscillations, cortical excitability, and psycho-physiological effects such as heart rate, fatigue, blood test, cognitive and behavioural outcomes.

* Brain oscillations and neural coherency based on electroencephalography (EEG) outcomes.  These studies have demonstrated that different tPCS frequencies can significantly impact resting functional connectivity and brain oscillations. For instance, 4 Hz and 75 Hz frequencies (Dissanayaka et al., 2020b) and random frequencies ranging from 1–5 Hz and 6–10 Hz (Saavedra et al., 2014) increased resting functional connectivity compared to tPCS at 1 or 100 Hz (Morales-Quezada et al., 2015a); however, a low frequency of 0.5 Hz has the opposite effect (Luu et al., 2016). Furthermore, studies on other parameters indicated that 1 and 2 mA intensities could modulate interhemispheric coherence (Morales-Quezada et al., 2014), and tPCS duration had a nonlinear effect on the long-lasting effects of stimulation (Vasquez et al., 2016). On the other hand, tPCS delivered through different montages could have varying effects on cortical brain oscillations (Vasquez et al., 2017). A study on event-related potentials (ERP) found that phase-locked tPCS had no significant effects on learning control or resting EEG of the salience network oscillation (Mansouri et al., 2019).
* Brain coherency and tPCS effects based on functional magnetic resonance imaging (fMRI) outcomes. Three fMRI studies demonstrated that tPCS induces more changes in neural connectivity patterns compared to tDCS (Dissanayaka et al., Sours et al., 2014, Alon et al., 2011). Another study showed that the type of electrode montages influences current flow through superficial and deep structures (Datta et al., 2013).
* Cortical excitability by TMS outcomes.Two studies showed that c-tPCS at both 4 Hz and 75 Hz induced a significant increase in intracortical facilitation (ICF) (Dissanayaka et al., 2020a); however, a-tPCS at 75 Hz had significantly higher CSE changes (Dissanayaka et al., 2022). On the other hand, a low frequency of 0.5 Hz could decrease the size of CSE (Luu et al., 2016). Two studies reported increasing CSE to improve movement disorders (Iddings and others, 2021; 2019). Other studies indicated that a-tPCS with longer PD (Jaberzadeh et al., 2015) and short-IPI increased CSE; however, long-IPI had no significant changes in CSE (Jaberzadeh et al., 2014).
* Physiological and cognitive-behavioural outcomes. Three studies indicated significant effects of tPCS on biochemical (Wu et al., 2022a), mental (Shen et al., 2022), and physical fatigue (Wu et al., 2022b). Although one study demonstrated that tPCS over the somatosensory cortex improves sensory perception (Saito et al., 2019), another study failed to show any effects over the posterior parietal lobe on tactile discrimination (Saito et al., 2022). Similar conflicting results were also reported on the tPCS effects on learning, attention, and heart rate (Morales-Quezada et al., 2016), while a study showed considerable effects on cognitive-physical behaviours (Morales-Quezada et al., 2015b). Finally, a study revealed the long-term tolerability of tPCS with no significant side effects (Paneri et al., 2016).

**3.1.1.2. Human studies on patient populations (2012-2023)**

These studies demonstrated the significant positive effect of tPCS on a number of pathological conditions, including consciousness after brain injury (Barra et al., 2022), spasticity and movement disorders in patients with spinal cord injury (SCI) (Liu et al., 2021, Iddings et al., 2021, Iddings et al., 2019), pain and cognition in fibromyalgia (Castro et al., 2021), cognitive dysfunction in schizophrenia (Singh et al., 2019), spastic cerebral palsy (SCP) (Thibaut et al., 2017b), and balance and movement in Parkinson’s disease (Alon et al., 2012).

**3.1.1.3. Animal studies (2019-2023)**

These studies explored the neurophysiological mechanisms of tPCS. The findings of a study revealed that tPCS, similar to other tES techniques, significantly influenced motor disorders in collagenase-induced intracerebral haemorrhage (Heidarzadegan et al., 2022). Another study suggested that tPCS can enhance the locomotor function of stroke rats by regulating the expression of microtubule-associated protein around the ischemic penumbra (Wang et al., 2021). Finally, a study examined whether the appropriate current intensity of a-tPCS-induced cortical excitability was associated with calcium elevation in astrocytes, which regulate synaptic transmission (Ma et al., 2019).

**3.1.2. Participants of included studies**

The sample size in studies on healthy male and female populations ranged from 5 to 100 individuals between the ages of 18 to 65 old-years-age (Dissanayaka et al., Dissanayaka et al., 2022, Dissanayaka et al., 2020a, Dissanayaka et al., 2020b, Luu et al., 2016, Vasquez et al., 2016, Paneri et al., 2016, Morales-Quezada et al., 2016, Morales-Quezada et al., 2015a, Morales-Quezada et al., 2015b, Jaberzadeh et al., 2015, Jaberzadeh et al., 2014, Alon et al., 2011). However, some studies recruited only male participants because the women's menstrual cycle may affect the size of CSE induced by tPCS (Saito et al., 2022, Shen et al., 2022, Wu et al., 2022a, Wu et al., 2022b, Saito et al., 2019). In studies with patient populations, the sample sizes ranged from 9 to 70 participants between the ages of 2 to 75 (Barra et al., 2022, Liu et al., 2021, Iddings et al., 2021, Castro et al., 2021, Singh et al., 2019, Iddings et al., 2019, Thibaut et al., 2017a, Alon et al., 2011). All these studies recruited both male and female participants, except one, which only recruited females with fibromyalgia (Castro et al., 2021). Furthermore, the participants in all of the included animal studies were rats (Heidarzadegan et al., 2022, Wang et al., 2021, Ma et al., 2019).

**3.1.4. Study design of included studies**

Methodologically, Except for four studies (Ma et al., 2019, Saito et al., 2019, Singh et al., 2019, Luu et al., 2016) that were not mentioned, all other studies employed randomized designs with either single-blinded (Dissanayaka et al., Dissanayaka et al., 2022, Mansouri et al., 2019, Paneri et al., 2016, Jaberzadeh et al., 2015, Jaberzadeh et al., 2014) or double-blinded (Wu et al., 2022a, Wu et al., 2022b, Barra et al., 2022, Shen et al., 2022, Dissanayaka et al., 2022, Liu et al., 2021, Dissanayaka et al., 2020a, Thibaut et al., 2017b, Vasquez et al., 2017, Vasquez et al., 2016, Morales-Quezada et al., 2016, Morales-Quezada et al., 2015a, Morales-Quezada et al., 2015b, Morales-Quezada et al., 2014, Saavedra et al., 2014, Castillo Saavedra et al., 2014). Even though all included studies used sham stimulation as a control, four studies had control groups in which no intervention was administered (Dissanayaka et al., Barra et al., 2022, Iddings et al., 2021, Castro et al., 2021), and two studies did not refer to any control groups at all (Thibaut et al., 2017a, Vasquez et al., 2017). The cross-over design was employed in thirteen studies, although two reported using parallel designs (Castro et al., 2021, Morales-Quezada et al., 2015a). Among the included studies, four were pilot studies (Barra et al., 2022, Dissanayaka et al., 2020a, Thibaut et al., 2017a, Sours et al., 2014); and four were feasibility studies (Barra et al., 2022, Iddings et al., 2019, Luu et al., 2016, Alon et al., 2012).

**Table 2: Categories of tPCS studies in the literature. The design, participants, tPCS stimulation protocol, and the study aim(s) are provided.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number** | **Publications** | **Study design** | | | | | | | **Participants** | **TPCS stimulation protocol** | **Study aim(S)** | | | |
| **Authors, year** | **Randomized** | **Double-blinded** | **Sham- control** | **Crossover** | **Parallel** | **Pilot study** | **Feasibility study** | **Sample size, Age range, gender female/male** | **Sessions number, duration, amplitude, frequency, montage** | **Stimulation type(s)** | **Condition of interest** | **Outcome measures** | **TPCS effect(s)** |
| **Human studies conducted on healthy participants** | | | | | | | | | | | | | | |
| 1 | Wu et al., 2022a |  |  |  |  |  |  |  | 60, m | 15min, 1.5 mA, 60-80 Hz, frontal lobe | tPCS | Biochemical fatigue | HRV, blood test | + effects |
| 2 | Wu et al., 2022b |  |  |  |  |  |  |  | 40, m | 20- 30min, 2 mA, orbitofrontal lobe | tPCS | Physical fatigue | HRV, HbO2 | + effects |
| 3 | Shen et al., 2022 |  |  |  |  |  |  |  | 60, m | 15min, 1.5 mA, 60-80 Hz, forehead | tPCS | Mental fatigue | Behaviour tests | + effects |
| 4 | Dissanayaka et al., 2022a |  |  |  |  |  |  |  | 11, 19-36, f/m | 3, 15 min, 1.5 mA, 75 Hz, M1 | a-tPCS, a-tDCS | rs- FC | fMRI | No change |
| 5 | Dissanayaka et al., 2022b |  |  |  |  |  |  |  | 17,19-30, f/m | 5, 15 min, 1.5 mA, 4 &75 Hz, M1 | a-tPCS | Frequencies | MEPs size |  |
| 6 | Saito et al., 2022 |  |  |  |  |  |  |  | 20, 21-25, m | 8, 10 min, 0.7 mA, P3 & P4 | a-tPCS, tRNS | Tactile discrimination | GOT | No change |
| 7 | Dissanayaka et al., 2020b |  |  |  |  |  |  |  | 17,19-47, f/m | 5, 15 min, 1.5 mA, 4 &75 Hz, M1 | a/c-tPCS | Frequency bands | EEG oscillation |  |
| 8 | Dissanayaka et al., 2020a |  |  |  |  |  |  |  | 15,18-35, f/m | 3, 15 min, 1.5 mA, 4 &75 Hz, M1 | c-tPCS | Frequencies | MEPs size |  |
| 9 | Saito et al., 2019 |  |  |  |  |  |  |  | 17, 21-25, m | 5, 10 min, 0.7 mA, M1 | a-tPCS, a-tDCS, tRNS, tACS | Tactile discrimination | SEP-PPD, GOT |  |
| 10 | Mansouri et al., 2019 |  |  |  |  |  |  |  | 20, above 18 | 4, 2 mA, 4-8 Hz, F4 | tPCS, tACS | EEG oscillation | ERP, EEG power | No change |
| 11 | Vasquez et al., 2017 |  |  |  |  |  |  |  | 20, 18-65 | 1, 20 min, 2 mA, 6-10 Hz, different | tPCS | EEG oscillation | EEG power |  |
| 12 | Thibaut et al., 2017a |  |  |  |  |  |  |  | 48, 18-65, f/m | 1, 20 min, 2 mA, 6-10 Hz, M1 | tPCS, tDCS | Pain, cortical coherence | PPT/EEG power | + effects |
| 13 | Luu et al., 2016 |  |  |  |  |  |  |  | 12, f/m | 5, 17 min, 1.16 mA, 0.5 Hz, computer head modelling | HD a/c-tPCS | LTP/LTD | MEPs size |  |
| 14 | Vasquez et al., 2016 |  |  |  |  |  |  |  | 40, 18-65, f/m | 1,10-20-30 min, 2 mA, 6-10 HZ | tPCS | Different duration | EEG power | No change |
| 15 | Paneri et al., 2016 |  |  |  |  |  |  |  | 100,(18-40), f/m | 18-30, 20 min, 5-7 mA, 7KHz-11KHz, F8-FP2 | MHF-tPCS, tDCS | Long-term tolerability | Side effects | No change |
| 16 | Morales-Quezada et al., 2016 |  |  |  |  |  |  |  | 30, mean 25, f/m | 1, 20 min, 2 mA, 1-5 Hz | bi-tPCS | Attention, learning | PALT, AST, HRV | No change |
| 17 | Morales-Quezada et al., 2015b |  |  |  |  |  |  |  | 30, 18-65, f/m | 1, 20 min, 2 mA, 1-5 HZ | bi-tPCS | Cognition, physical behaviours | BART, stroop, math, HRV | + effects |
| 18 | Morales-Quezada et al., 2015a |  |  |  |  |  |  |  | 40, 18-65, f/m | 1, 20 min, 2 mA, 1-5 & 6-10 & 11-15 Hz | bi-tPCS | Random frequencies | EEG power, coherence |  |
| 19 | Jaberzadeh et al., 2015 |  |  |  |  |  |  |  | 11, 20-51, f/m | 5, 20 min, 1.5 mA, M1 | a-tPCS, a-tDCS | pulse duration | MEPs size |  |
| 20 | Jaberzadeh et al., 2014 |  |  |  |  |  |  |  | 12, 20-51, f/m | 4, 10 min, 1.5 mA, M1 | a-tPCS SIPI, LIPI, tDCS | Inter-pulse interval | MEPs size |  |

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|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number** | **Publications** | **Study design** | | | | | | | **Participants** | **TPCS stimulation protocol** | **Study aim(S)** | | | | |
| **Authors, year** | **Randomized** | **Double-blinded** | **Sham- control** | **Crossover** | **Parallel** | **Pilot study** | **Feasibility study** | **Sample size, Age range, gender female/male(size),** | **Sessions number, duration, amplitude, frequency, montage** | **Stimulation type(s)** | **Condition of interest** | | **Outcome measures** | **TPCS effect(s)** |
| **Human studies conducted on healthy participants** | | | | | | | | | | | | | | | |
| 21 | Morales-Quezada et al., 2014 |  |  |  |  |  |  |  | 40, above 18 | 1, 20 min, 0.2 & 1 & 2 mA, 1-5 Hz | tPCS | intensities | | EEG power, coherence |  |
| 22 | Saavedra et al., 2014 |  |  |  |  |  |  |  | 40, 18-65 | 1, 20 min, 2 mA, 1 & 100 & 1-5 Hz | tPCS | Random frequencies | | EEG power, coherence |  |
| 23 | Sours et al., 2014 |  |  |  |  |  |  |  | 11, above 18, f/m | 1, 15 kHz, 15 bursts per the 60s, M1 | tPCS | rs- FC | | fMRI |  |
| 24 | Datta et al., 2013 | Modelling study, human head model | | | | | | |  |  | CES, tPCS | Different montages | | (Sub)cortical midbrain |  |
| 25 | Alon et al., 2011 |  | | | | | | | 5, 23-27, f(4) | 5, 12 min, 15 kHz ,M1 | tDCS, tPCS | rs- FC | | fMRI |  |
| **Human studies conducted on patients with pathological conditions** | | | | | | | | | | | | | | | |
| 26 | Barra et al., 2022 |  |  |  |  |  |  |  | 12, 18-75 | 1, 20 min, 2 mA, 6-10 Hz, F3 | tPCS, tDCS | Brain injury | consciousness | |  |
| 27 | Iddings et al., 2021 |  |  |  |  |  |  |  | 17, cSCI | 22 min | U-tPCS, Bi-tPCS | cSCI | MEPs size, Motor control | |  |
| 28 | Liu et al., 2021 |  |  |  |  |  |  |  | 63, 2-12 | 60, 20 min, 1mA, 400 HZ, Cz | tPSC +TENS | SCP | limb spasticity | |  |
| 29 | Castro et al., 2021 |  |  |  |  |  |  |  | 70, 30-65, f | 5, 20 min, 6-10 Hz | bi- tPCS | Fibromyalgia | Pain, cognition | | + effects |
| 30 | Singh et al., 2019 |  |  |  |  |  |  |  | 9 | 1, 20 min, 4-8 Hz, occipital lobe | tPCS | Schizophrenia | Cognition | |  |
| 31 | Iddings et al., 2019 |  |  |  |  |  |  |  |  | 20 min, M1 | Bi-tPCS, tDCS | cSCI | MEPs size, Motor control | |  |
| 32 | Thibaut et al., 2017b |  |  |  |  |  |  |  | 6, 18-65 | 5, 20 min, 2 mA, 6-10 Hz | bi- tPCS, tDCS | CVP | EEG coherence | |  |
| 33 | Alon and others 2012 |  |  |  |  |  |  |  | 10 | 20 min, M1 | a-tPCS | Parkinson | Movement gait, balance | |  |
| **Animal studies (rats)** | | | | | | | | | | | | | | | |
| 34 | Heidarzadegan et al., 2022 |  |  |  |  |  |  |  | 56, m | 7, 20 min, 0.2 mA, 30 Hz | tPCS, tDCS, tRNS, tACS | stroke | Intracerebral haemorrhage | | + effects |
| 35 | Wang et al., 2021 |  |  |  |  |  |  |  | 36, m | 7, 20 min, 0.2 mA, 10 Hz | tPCS | stroke | Locomotive function | |  |
| 36 | Ma et al., 2019 |  | | | | | | | 35, 8-12 weeks | 2 sec & 5min, 0.1- 0.35 mA, 2 Hz | a-tPCS | Calcium response, astrocytes | | |  |

a-tPCS: anodal-transcranial pulsed current stimulation, a-tDCS: anodal-transcranial direct current stimulation, HRV: heart rate variability, HbO2: hyperbaric oxygen, rs-FC: resting state functional connectivity, fMRI: functional magnetic resonance imaging, MEPs: motor evoked potentials, tRNS: transcranial random noise stimulation, GOT: grating orientation task, c-tPCS: cathodal pulsed current stimulation, EEG: electroencephalography, tACS: transcranial alternating current stimulation, SEP-PPD: somatosensory evoked potential- paired pulsed depression, ERP: evoked related potential, PPT: pressure pain threshold, MHF- tPCS: Multi high definition function- tPCS, bi-tPCS: biphasic-tPCS; Bi- tPCS: bihemispheric- tPCS, PLAT: Paired associative learning task, AST: attention switching task, BART: balloon analogue risk task, SIPI: short inter-pulse interval, LIPI: long inter-pulse interval, CES: Cranial electrotherapy stimulation, U-tPCS: unihemispheric- tPCS, cSCI: cervical spinal cord injury, TENS: transcutaneous electrical nerve stimulation, SCP: Spastic cerebral palsy, CVP: chronic visceral pain.

**3.1.5. TPCS protocols**

The number of tPCS sessions varied from 1 to 8, with random frequencies from 0.5 Hz to 100 Hz and 0.5 to 2 mA intensity. However, a study indicated the significant long-term tolerability of high-frequency based on multi-high-definition function tPCS (MHF-tPCS) using adjustable 7–11 kHz frequencies and 5–7 mA intensity for 18–30 sessions (Paneri et al., 2016). Another study employed combined tPCS and transcutaneous electrical nerve stimulation (TENS) at 400 Hz for 60 sessions as an effective treatment protocol for spastic cerebral palsy (SCP) children (Liu et al., 2021). Additionally, because of direct cellular stimulation, the amplitude of animal studies ranged from 0.1 to 0.35 mA (Heidarzadegan et al., 2022, Wang et al., 2021, Ma et al., 2019). Since human studies used the 10–20 EEG system for electrode setups, most papers reported active electrodes on the primary motor cortex (M1) on c3 (Dissanayaka et al., Dissanayaka et al., 2022, Dissanayaka et al., 2020a, Dissanayaka et al., 2020b, Iddings et al., 2019, Saito et al., 2019, Thibaut et al., 2017a, Jaberzadeh et al., 2015, Jaberzadeh et al., 2014, Sours et al., 2014, Alon et al., 2012); six studies positioned electrodes on the frontal lobe (F3, F4, F8, and Fp2) (Wu et al., 2022a, Wu et al., 2022b, Shen et al., 2022, Barra et al., 2022, Mansouri et al., 2019, Paneri et al., 2016), two studies located electrodes on the occipital lobe (P3, P4) (Saito et al., 2022, Singh et al., 2019), and a study reported on Cz (Liu et al., 2021). Some studies to find the optimal protocol focused on different montages (Vasquez et al., 2017) or uni- and bi-hemispheric tPCS (Iddings et al., 2021, Iddings et al., 2019), as well as a computer-based head model (Luu et al., 2016, Datta et al., 2013) with a high-definition setup (Paneri et al., 2016).

**3.1.6. Types of tPCS in included studies**

The included studies examined different types of tPCS based on the applied waveforms and polarity. Eight studies indicated that biphasic tPCS significantly improved cognitive-physical behaviours (Castro et al., 2021, Morales-Quezada et al., 2015b) and cortical coherence (Thibaut et al., 2017a, Morales-Quezada et al., 2015a); however, a study indicated no effect on learning or attention (Morales-Quezada et al., 2016). Some studies delivered by the a-tPCS reported significant modulation of CSE (Dissanayaka et al., Dissanayaka et al., 2022, Dissanayaka et al., 2020a, Jaberzadeh et al., 2015, Jaberzadeh et al., 2014). Other studies applying a-tPCS also reported considerable effects on balance movement (Alon et al., 2012) and calcium activities on astrocyte neurons (Ma et al., 2019) However, this type of stimulation does not affect resting-state functional connectivity (Dissanayaka et al.) or tactile discrimination (Saito et al., 2022), and compared with a-tDCS and tACS, a-tPCS has less effect on the tactile cortex (Saito et al., 2019). On the other hand, a study showed that c-tPCS at delta and gamma frequencies could modulate intracortical facilitation (Dissanayaka et al., 2020a). Although c-tPCS has a similar LTP mechanism to a-tPCS (Luu et al., 2016), a study employing c-tPCS demonstrated that it has no effect on delta power and reduces high gamma power (Dissanayaka et al., 2020b). Finally, other studies also did not report the type of waveform or polarity of the stimulation.

**3.2. The underlying mechanisms behind the physiological and therapeutic effects of tPCS (aim 2)**

Given that tPCS exhibits similar static and dynamic effects to those of tDCS and tACS, respectively, it is reasonable to hypothesize that the underlying mechanisms of these techniques could also apply to tPCS. For instance, tDCS based on polarity modulates the resting membrane potential of neurons, influencing synaptic plasticity (Nitsche and Paulus, 2000), which can lead to cortical excitability by changing the firing rate of neurons. On the other hand, tACS can entrain endogenous brain oscillations based on frequency, amplifying neural connections through resonance and STDP. Furthermore, recent research suggests that stochastic resonance could be a potential mechanism of tACS (Elyamany et al., 2021). To enhance comprehension of these mechanisms, some tPCS studies that examined cortical excitability and neural connectivity have been categorized into subtypes based on either fixed frequency or random frequency stimulation.

**3.2.1. TPCS at fixed frequencies**

Since tPCS generates frequency effects that rely on the pulsatile nature of the current, some studies have emphasized the significance of specific frequencies on neural modulation.

**3.2.1.1. Mechanisms based on the static effects**

Findings from a-tPCS studies, like tDCS, have demonstrated a considerable increase in CSE measured by single-pulsed TMS-induced motor-evoked potentials (MEPs) (Jaberzadeh et al., 2015, Jaberzadeh et al., 2014). However, cathodal and anodal high-definition tPCS at low frequency (0.5 Hz) could induce LTD to decrease CSE (Luu et al., 2016). Recent findings demonstrated that anodal and cathodal tPCS at 4 Hz and 75 Hz significantly modulate CSE. Additionally, paired-pulsed TMS showed that a-tPCS at both later frequencies increases ICF related to glutamate activity on the LTP mechanism and decreases short-interval intra-cortical inhibition (SICI) related to receptor-mediated inhibitory effects on LTD (Dissanayaka et al., 2022). However, in the c-tPCS, the ICF and the SICI revealed a significant increase (Dissanayaka et al., 2020a). The cellular and neurobiological mechanisms are associated with the tPCS effects on voltage-gated carrier proteins in the neural membrane (Wang et al., 2021) and excessive calcium activity in astrocyte neurons (Ma et al., 2019).

**3.2.1.2. Mechanisms based on the dynamic effect**

Research has demonstrated that tPCS can also enhance the power and connectivity of brain oscillations generated endogenously through entrainment mechanisms that promote synchronization of cortical activity within the applied frequencies. In this regard, resting-state functional connectivity (rs-FC) is a method of neuroimaging that uses functional magnetic resonance imaging (fMRI) to measure the level of co-activation between the functions of time series in different brain regions. The relevant fMRI studies found altered rs-FC between M1 and surrounding neural networks during a-tPCS at 15 Hz. This inter-regional correlation of signal intensities has suggested the capability of the stimulation to modulate brain regions that are functionally connected (Sours et al., 2014, Alon et al., 2011). However, a report of a-tPCs at 75 Hz on M1 has shown that they are less related to functional connectivity behind the stimulatory effects. A similar study based on EEG investigated the modulation of oscillatory brain activity by a-tPCS at 4 Hz to increase theta power and 75 Hz to increase high gamma power. Nevertheless, in c-tPCS, 75 Hz decreases high gamma power, and 4 Hz has no effect (Dissanayaka et al., 2020b).

**3.2.2. TPCS at random frequencies**

Further research based on EEG outcomes has demonstrated that tPCS at random range frequencies, including 6–10 Hz (Vasquez et al., 2017, Thibaut et al., 2017b, Vasquez et al., 2016, Morales-Quezada et al., 2015a) and 1–5 Hz (Morales-Quezada et al., 2015a, Morales-Quezada et al., 2014, Saavedra et al., 2014), can entrain brain oscillations. Nonetheless, 4–8 Hz has no entrainment changes (Mansouri et al., 2019). On the other hand, some studies have proposed that the underlying mechanism of tPCS may be stochastic resonance. This phenomenon involves the addition of noise, which allows for the detection of weak signals and affects various neural brain functions through random signal disturbances (Vasquez et al., 2016). Furthermore, the tPCS effect observed in the 11–15 Hz frequency range, which causes a reduction in alpha power, may be attributed to the disruptive noise acting as supra-threshold modulation (Morales-Quezada et al., 2015a).The presence of alpha-like random frequencies can help maintain the affected networks in a homeostatic state by keeping the modulation of the networks stable in the presence of noise.

**3.3. Types of research in published tPCS studies (aim 3)**

To implement a novel approach in clinical practice, it is essential to have conducted studies from theoretical knowledge to clinical protocols. In our study, we utilized the Australian Standard Research Classification (ASRC, 1998) framework, which consists of four categories, to showcase the developmental journey of tPCS knowledge from its inception to the achievement of clinical objectives.

**3.3.1. Basic research**

In this category, studies focus on advancing the understanding of a new technique rather than investigating its long-term benefits. Within this classification, we identified nine studies that delved into the underlying mechanisms of tPCS. These studies encompassed various methodologies such as cellular analysis (Ma et al., 2019), entrainment oscillation based on EEG resting state (Dissanayaka et al., 2020b, Thibaut et al., 2017b), fMRI (Dissanayaka et al., Sours et al., 2014, Alon et al., 2011), and ERP (Mansouri et al., 2019). Additionally, the size of the changes in cortical excitability assessed by single and paired-pulse TMS could elucidate further potential underlying mechanisms of tPCS based on LTP and LTD effects on glutamatergic and GABAergic synapses (Dissanayaka et al., 2022, Dissanayaka et al., 2020b) (Table 3).

**3.3.2. Strategic research**

This research approach is crucial for acquiring the necessary knowledge to devise effective solutions using a novel approach. Studies that aimed to determine the optimal parameters for tPCS were categorized as this type of research. Within this category, two studies investigated the effects of random frequencies on cortical excitability (Morales-Quezada et al., 2015a, Saavedra et al., 2014), while two other studies assessed different frequencies with varying intensities (Paneri et al., 2016, Morales-Quezada et al., 2014). Additionally, three papers utilized different montages based on computer design and high-definition electrode setups (Vasquez et al., 2017, Luu et al., 2016, Datta et al., 2013). Only two studies reported on the effects of different pulse durations (PDs) (Jaberzadeh et al., 2015) and inter-pulse intervals (IPIs) (Jaberzadeh et al., 2014) on CSE changes and the underlying mechanisms behind these changes. These studies collectively contribute to the understanding of optimal tPCS parameters for achieving desired outcomes (Table 3).

**3.3.3. Applied research**

This category of studies involves utilizing tPCS protocols to investigate pre-clinical issues. We identified research that focused on symptoms of diseases that affect fatigue (Shen et al., 2022, Wu et al., 2022a, Wu et al., 2022b), tactile discrimination (Saito et al., 2022, Saito et al., 2019), cognitive behaviours (Morales-Quezada et al., 2016, Morales-Quezada et al., 2015b), as well as the effects of tPCS on intracerebral haemorrhage (Heidarzadegan et al., 2022) and locomotive functions (Wang et al., 2021) in stroke patients. These studies collectively contribute to our understanding of the potential therapeutic applications of tPCS in addressing various clinical manifestations associated with different diseases (Table 3).

**3.3.4. Experimental research**

These types of studies help provide evidence for the clinical applications of tPCS as a new tES technique. TPCS clinical studies have shown that it is effective in several pathological conditions, including brain injury (Barra et al., 2022), cervical spinal cord injury (cSCI) (Iddings et al., 2021, Iddings et al., 2019), SCP (Liu et al., 2021), fibromyalgia (Castro et al., 2021), schizophrenia (Singh et al., 2019), chronic visceral pain (CVP) (Thibaut et al., 2017a), and Parkinson (Alon et al., 2012) (Table 3).

**Table 3: classification of types of research for the published tPCS studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number** | **Publications** | **Basic research** | **Strategic research** | **Applied research** | **Experimental research** |
| **Human studies conducted on healthy participants** | | | | | |
| 1 | Wu et al., 2022a |  |  |  |  |
| 2 | Wu et al., 2022b |  |  |  |  |
| 3 | Shen et al., 2022 |  |  |  |  |
| 4 | Dissanayaka et al., 2022a |  |  |  |  |
| 5 | Dissanayaka et al., 2022b |  |  |  |  |
| 6 | Saito et al., 2022 |  |  |  |  |
| 7 | Dissanayaka et al., 2020b |  |  |  |  |
| 8 | Dissanayaka et al., 2020a |  |  |  |  |
| 9 | Saito et al., 2019 |  |  |  |  |
| 10 | Mansouri et al., 2019 |  |  |  |  |
| 11 | Vasquez et al., 2017 |  |  |  |  |
| 12 | Thibaut et al., 2017a |  |  |  |  |
| 13 | Luu et al., 2016 |  |  |  |  |
| 14 | Vasquez et al., 2016 |  |  |  |  |
| 15 | Paneri et al., 2016 |  |  |  |  |
| 16 | MoralesQuezada et al., 2016 |  |  |  |  |
| 17 | MoralesQuezada et al., 2015b |  |  |  |  |
| 18 | MoralesQuezada et al., 2015a |  |  |  |  |
| 19 | Jaberzadeh et al., 2015 |  |  |  |  |
| 20 | Jaberzadeh et al., 2014 |  |  |  |  |
| 21 | MoralesQuezada et al., 2014 |  |  |  |  |
| 22 | Saavedra et al., 2014 |  |  |  |  |
| 23 | Sours et al., 2014 |  |  |  |  |
| 24 | Datta et al., 2013 |  |  |  |  |
| 25 | Alon et al., 2011 | |  | | --- | |  | |  |  |  |
| **Human studies conducted on patients with pathological conditions** | | | | | |
| 26 | Barra et al., 2022 |  |  |  |  |
| 27 | Iddings et al., 2021 |  |  |  |  |
| 28 | Liu et al., 2021 |  |  |  |  |
| 29 | Castro et al., 2021 |  |  |  |  |
| 30 | Singh et al., 2019 |  |  |  |  |
| 31 | Iddings et al., 2019 |  |  |  |  |
| 32 | Thibaut et al., 2017b |  |  |  |  |
| 33 | Alon et al., 2012 |  |  |  |  |
| **Animal studies (rats)** | | | | | |
| 34 | Heidarzadegan et al., 2022 |  |  |  |  |
| 35 | Wang et al., 2021 |  |  |  |  |
| 36 | Ma et al., 2019 |  |  |  |  |

**3.4. Research gaps in current literature (aim 4)**

Despite a limited number of studies investigating the effects of tPCS on neuroplasticity, the underlying mechanisms of these changes remain largely unexplored. Further research is needed to advance our theoretical understanding of the mechanisms behind the effects of tPCS. While existing literature on tPCS primarily focuses on applied and experimental categories of research in clinical conditions, there is a need for more investigation in the strategic research category.

Various parameters of tPCS, such as polarity, frequency, IPI and PD, stimulation duration, electrode size, montages, intensity, and waveform type (monophasic or biphasic), have not been thoroughly investigated in the strategic research category. The effects of a-tPCS on the motor cortex have been studied to some extent, but c-tPCS remains largely unexplored. The cellular and synaptic inhibitory or excitatory processes involved in different polarities of tPCS are still unclear.

Investigating the effects of different frequency bands of tPCS, ranging from low delta to high gamma, and understanding their impact on cortical excitability and the underlying mechanisms is necessary, as different frequencies may have varying therapeutic potentials.

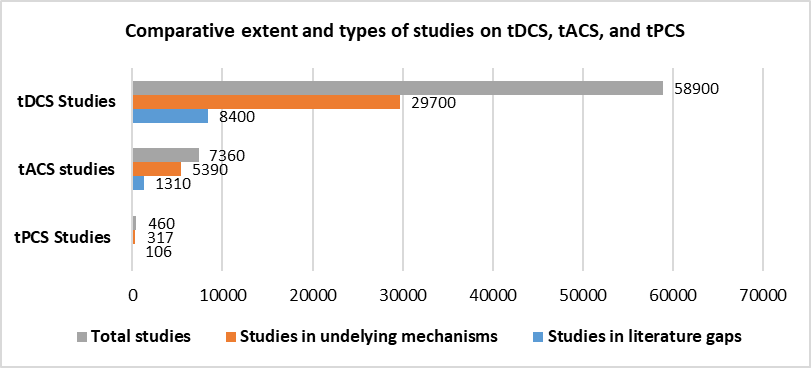
Considering the nonlinear effect of tPCS, exploring different stimulation times to determine the optimal duration for inducing modulation is a crucial area of research. Controlling the potential side effects of tPCS in clinical applications is vital, so investigating different montages with variable electrode sizes and intensities to determine the dosage of stimulation and possible adverse effects of tPCS is necessary.

Assessing the long-term effects of tPCS in single-session or multi-session applications is also significant for treatment protocols in the future. Finally, as a novel neuromodulatory technique with diverse parameters, effects, and mechanisms, tPCS offers a wide range of research prospects that are worth exploring in future studies.

**3.5. Discussion**

This scoping review is a pioneering investigation into the breadth and characteristics of publications, underlying mechanisms, and existing gaps in the literature on tPCS research. With tPCS utilizing diverse parameters and underlying mechanisms, it holds promise to develop personalized protocols for clinical applications in neurological disorders. However, the findings of this review reveal limited research on the mechanisms of action and the impact of tPCS on various pathological conditions.

The primary objective of this review was to assess the extent and nature of the existing literature on tPCS as a neuromodulatory technique. Totally, 36 identified papers were categorized into three groups: studies involving healthy human participants, patients with pathological conditions, and animal studies. In comparison to other neuromodulatory techniques, tDCS emerged as the most extensively studied, with over 56,900 publications found on Google Scholar as of May 1, 2023. Among these, 29,700 studies focused on the underlying mechanisms, and 8,400 identified gaps in the literature. A similar search in the same database revealed 7,360 publications on tACS, with 5,390 studies on underlying mechanisms and 1,310 papers on research gaps. However, tPCS had the lowest number of studies recorded on Google Scholar, with only 460 publications, of which 317 focused on underlying mechanisms and 106 discussed literature gaps in this field. In conclusion, our findings highlight that tPCS is a relatively new neuromodulatory technique with less extensive studies (Figure 4).



**Figure 4:** Comparing the scope and varieties of research on main neuromodulation techniques.

The second objective of this study was to investigate the underlying mechanisms responsible for the effects of tPCS on cortical outcome measures, which remain poorly understood. As indicated in literature, A-tPCS monophasichas both static and dynamic effects (Ref). Static effect is due to the presence of NDCC which produces an effect similar to the effects of tDCS (as shown in Figure 1C). NDCC in a-tPCS monophasicis dependent on the duration of the pulses and the inter-pulse interval. When the pulse duration is shorter and the inter-pulse interval is longer, NDCC decreases, while longer pulse durations and shorter inter-pulse intervals increase NDCC. Thus, like tDCS, a-tPCS monophasiccan modulate cortical excitability through a polarity-based spike timing dependent mechanism, and also modulation of discharge rate at fixed frequencies (Figure 5).

**tDCS**

**tPCS**

**Polarity based static effects (tDCS)**

- Polarity-based spike-timing- dependent plasticity

- Modulation of discharge rates

**Frequency based dynamic effects (tACS)**

- Modulation of spike-timing-dependent plasticity

- Entrainment of brain oscillations

**tACS**

**Static and dynamic effects in tPCS**

- Entrainment of brain oscillations

- Stochastic resonance

**Figure 5:** The underlying mechanisms of main neuromodulation techniques.

The dynamic effects of A-tPCS monophasic are attributed to the pulsatile nature of the current, which turns on and off and produces an effect similar to that of transcranial alternating current stimulation (tACS), as depicted in Figure 1C. This pulsatile effect is directly proportional to the frequency of the applied current. Consequently, higher frequencies result in increased dynamic effects, while lower frequencies lead to decreased dynamic effects. Similar to tACS, A-tPCS monophasic can modulate cortical excitability through a spike timing dependent mechanism and entrainment of brain oscillations. These effects are achieved at fixed frequencies. As shown in Figure 5, A-tPCS monophasic can entrain brain oscillations by synchronizing neural firing patterns to the frequency of the applied current. Future mechanistic studies are required to probe how these mechanisms take part in induction of the effects.

In order for tPCS to advance as a promising clinical application, it is imperative to establish a systematic classification system that can identify the underlying mechanisms and optimal therapeutic protocols. To this end, we have categorized tPCS studies into four types: basic research investigating the underlying mechanisms, strategic research focusing on parameters, applied research evaluating pre-clinical outcomes, and experimental research examining clinical outcomes. However, it is worth noting that there is a scarcity of studies in the basic and strategic categories of investigations, with most research focusing on applied and experimental studies. This classification highlights significant gaps in our understanding of the fundamental mechanisms and optimal parameters of tPCS for designing effective clinical protocols. Therefore, a comprehensive classification system not only serves as a framework for identifying opportunities for further research, but also aids in expanding our knowledge in this rapidly evolving field.

**3.6. Limitations of the study**

The results of this review need to be considered with caution due to several limitations. The primary concern is the scarcity of tPCS studies in the existing literature, which restricts the generalizability of the findings. Additionally, since this review only included peer-reviewed articles written in English, it may not fully represent all relevant research conducted in other languages. Furthermore, the variability in outcome measures across different studies precluded the possibility of conducting a meta-analysis, which means that the conclusions regarding the effects of tPCS are not based on meta-analytic evidence.

**3.7. Suggestions for future research**

As tPCS is relatively a new and understudied technique, several research gaps could inform numerous future studies. Therefore, it is necessary to conduct comprehensive investigations into the mechanisms behind the effects of tPCS:

1) Since the results of tPCS studies suggest that different frequencies may have different effects on CSE, further investigations using different frequencies are necessary to determine how tPCS may affect CSE and also mechanisms behind the changes in CSE.

2) As previously noted, different frequencies of tPCS can have varying effects on EEG-band power and neural connectivity. Future studies using EEG are suggested to examine the impact of different tPCS frequencies on EEG-band power and neural connectivity. These studies could provide information on the degree of entrainment and synchronization between different neural networks.

3) Further tPCS studies are necessary to establish the most effective protocols for different pathological conditions.

**4. Conclusions**

As outlined in this review, tPCS has considerable potential as an effective neuromodulation technique. However, there are limited publications in this field, which we have categorized into human studies with healthy participants, patients with pathological conditions, and animal studies. Few studies have focused on the underlying mechanisms of this technique, including modulation of brain oscillations, neuronal entrainment, and stochastic resonance. Based on our analysis of the existing tPCS literature based on ASRC classification, we conclude that further research is needed to investigate the underlying mechanisms and optimize protocols for clinical applications.

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