Mechanisms and Open Issues of Non-Invasive Brain Stimulation

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Non-invasive brain stimulation (NIBS) techniques induce a mild magnetic or electric field in the brain to modulate behavior and cortical activation. NIBS comprises of different techniques based on magnetic or electrical stimulation of the scalp: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation techniques (tES), such as transcranial direct currect stimulation (tDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). While TMS directly induces action potentials, tDCS induces modifications in the resting membrane potentials altering the spontaneous firing rate . tACS allows the entrainment of intrinsic brain oscillations through the administration of sinusoidal currents at specific frequencies , while tRNS is based on the application of several frequencies within a normally distributed frequency spectrum .
Despite the great body of literature demonstrating promising results, unexpected or even paradoxical outcomes are sometimes observed. This might be due either to technical and methodological issues (e.g., stimulation parameters, stimulated brain area), or to participants' expectations and beliefs before and during the stimulation sessions.

non-invasive brain stimulation | transcranial magnetic stimulation | transcranial direct current stimulation | placebo effect | nocebo effect | expectation

1. Mechanisms of Action

NIBS have been extensively applied in clinical and cognitive neuroscience, making a significant contribution to a better understanding of the neurophysiological correlates of several cognitive functions. NIBS comprises of different techniques based on magnetic or electrical stimulation of the scalp. TMS consists of a transient magnetic field applied on the scalp through a coil, inducing in turn a transitory electric current in the brain. The magnetic pulse induces a rapid depolarization of the cell membranes under the coil[1][2], followed by depolarization or hyperpolarization of other neural populations, i.e., TMS directly elicits action potentials in the stimulated neurons. TMS is used as a therapeutic aid to treat patients with neurological or psychiatric disorders [3][4][5][6], as well as for experimental purposes [5]. TMS can be applied as one stimulus at a time (single pulse), as trains of stimuli delivered at a fixed frequency, usually of 1–20 Hz (repetitive TMS), or in trains combining different frequencies (i.e., 50 Hz pulse trains repeated at a rate of 5 Hz), described as theta burst stimulation (TBS)[7].

In contrast, tES, such as tDCS, tRNS and tACS, are neuromodulation tools, in which a weak electrical current is applied on the scalp through two or more electrodes[8][9][10][11]. tDCS induces a subthreshold polarization of cortical neurons and acts by changing neuronal excitability, by inducing modifications in the resting membrane potentials. tDCS can alter the spontaneous firing rate, leading to changes in synaptic activity [12][13][14][15]. When the anode is positioned over the cortical site of interest and the cathode is positioned over a reference point (either cephalic or extra-cephalic), a depolarization of the resting membrane potential is induced in the stimulated brain area, together with an increase in neuronal excitability and firing rate. Conversely, when the cathode is positioned over the cortical site of interest and the anode over a reference point, a hyperpolarization and a decrease in neuronal excitability is induced in the stimulated brain area[8][9] [8,9]. The former approach is known as "anodal stimulation" and the latter as "cathodal stimulation". The reported polarity-dependent effects are, however, not consistent, being mainly described in the motor domain and to a lesser extent in cognitive investigations[16] .

2. Issues Regarding NIBS

The effects of both TMS and tDCS on the brain and on motor and cognitive functions may depend on a variety of characteristics, such as position of the coil or electrodes, direction and intensity of the current (and also frequency and duration in the case of tDCS)[9][17][18], properties of the stimulated brain tissue[19], demographic variables of the stimulated individual (e.g., gender and age) [20][21][22], and the cognitive state of the stimulated brain area [23][24]. All these conditions have been proposed as explanations for the inconsistencies in results found across studies. In 2013, Miniussi and colleagues proposed a unified model which posited that the effects of NIBS are linked to noise induction, which in turn interacts with several parameters, such as the characteristics of the stimulation and the task performed during the stimulation[25]. More specifically, the authors reasoned that the final response to a target stimulus does not depend solely on the strength of the signal induced by the target itself but depends also on the ratio between the signal and other irrelevant activity, namely, the noise [25]. Thus, successful performance in behavioral tasks depends on the relation between the signal (i.e., neurons coding for the target in a particular task) and the noise (i.e., neurons whose activity is non-specific for the task at hand). This hypothesis is strongly linked to so-called state dependency that refers to the state of the system at the time at which the stimulation is applied (TMS or tDCS). It has been shown that the effects of TMS are proportional to the level of neuronal activation during the application of the pulses [26]. In the case of tDCS, the stimulation does not directly induce action potentials, but modulates the neuronal response threshold, facilitating the neural activation of all neurons, even those not involved in the task. This could result in an increase not only of the signal, but also of the noise. Consequently, the effect of the stimulation will be highly influenced by the pre-existing state of the system because its effect depends on the activity of the stimulated area.

3. The Need of Blinding in Sham Protocols

Expectations can be defined as the belief in the likelihood of something happening. The outcome following placebo administration is not ascribable to the intrinsic therapeutic properties of the (inert) treatment but to verbal suggestions, rituals, and symbols surrounding the therapy [27]. If "coated with" positive meaning, these elements have been found to induce positive expectations of symptom improvement, which can lead to an actual clinical amelioration, at both subjective and objective levels (placebo effect). For example, positive verbal suggestions alone may be sufficient to reduce pain perception and pain sensation [28], and modulate motor [29] and cognitive performance [30]. Furthermore, verbal suggestions may affect anxiety, which has been shown to worsen symptoms [31]. Indeed, the opposite counterpart of the placebo effect, i.e., the nocebo effect, refers to a worsening in symptoms following the administration of an inert treatment along with negative verbal suggestions or cues of symptom worsening [32].

Classically, participants' thoughts, beliefs, and expectations about NIBS have been conceptualized as confounding factors to be controlled for in order to unravel the effect of active stimulation. Hence, the development of NIBS techniques has required the implementation of effective control procedures, to rule out any non-specific effects due to acoustic or tactile sensations experienced by the participants during the stimulation, and to avoid unblinding. To achieve these aims, sham stimulation protocols have been developed to mimic the sensations experienced by participants during active stimulation, without substantially stimulating the brain. It should be noted that whereas these procedures could control for participants' specific beliefs on the type of stimulation received, they do not necessarily control for more general prior beliefs or expectations about the effects of the stimulation on the brain and on performance.

Sham procedures are crucial for demonstrating the effects of real stimulation in experimental and clinical domains. However, recent work has suggested that the specific effects of rTMS may be blurred by placebo effects, whereby active and sham rTMS induce the same effects on symptom relief [33][34]. Inconsistencies in the literature are present regarding tDCS [35], reporting paradoxical effects or lack of modulation, which could be due to issues related to sham blinding rather than to failure in active tDCS protocols. Concerning other tES, tACS induces less side effects, such as muscle twitching, discomfort, and nausea [36], thus minimizing subjective sensations that could undermine blinding. Similarly, tRNS induces less noticeable skin sensations than tDCS, thus allowing for good blinding control[37] .

4. Toward a Systematic Assessment of Participants' Expectations in NIBS Studies

Literature suggests that the outcomes of NIBS can be affected by participants' beliefs about the type of stimulation received and by the expectations and prior beliefs about the effects of the stimulation, for TMS [33][34][38][39][40][41] and tDCS[42][43][44][45][46][47][48][49][50][51]. These observations emphasize the importance of systematically assessing subjective expectation and beliefs in NIBS trials. For instance, between-groups designs present the important problem of whether the groups are balanced for expectation. If positive expectations about the effects of stimulation on performance are present in the sham group, but not in the active stimulation group, it is possible to find no advantage of the active stimulation over the sham, which could somehow "mask" the real effect of the stimulation. On the other hand, the presence of positive expectations in the active stimulation group, but not in the sham group, might result in a significant difference between groups due only to the different expectation levels and not to the intervention itself. In this framework, ensuring similar expectations in the two groups could allow the drawing of more definitive conclusions about the effectiveness of the treatment. An even more complex issue arises if consider the interaction between positive and negative expectations and activating versus inhibiting stimulation protocols. This is particularly true if we assume a polarity-dependent effect of tDCS, whereby anodal tDCS is understood to enhance brain activity and cathodal tDCS is taken to reduce it[8]. Within this reference frame, when the protocol administered is thought to enhance the neural activation (e.g., through anodal tDCS), but the subjective expectations are low, it is possible to observe no modulation or even improved performance after sham. Conversely, when the protocol administered is thought to inhibit the activation (e.g., though cathodal tDCS), but the subjective expectations are high, might observe improved performance, despite the type of stimulation administered. Finally, when expectations are consistent with the type of stimulation to be administered (e.g., anodal tDCS and high expectations, cathodal tDCS and low expectations), better or worse performance might be due to the combination of expectations and stimulation, and not only to the stimulation itself.

In within-subjects designs the critical issue is the possibility that participants could “guess” the stimulation applied by comparing the sensations felt on the skin during the stimulation sessions. However, it is possible, even in this case, that different expectations are present in the same subject during different stimulation sessions, depending on the participant’s emotions and mood at that moment, or in interaction with the researchers.

The implications related to the assessment of participants’ expectations are twofold. First, the possibility that participants “guess” the stimulation type is critical for the blinding procedure and might have crucial consequences in the interpretation of the collected data. In particular, the presence of positive expectations about the effects of stimulation during sham, but not active stimulation, might induce a failure in detecting a significant difference between the protocols, blurring the effect of real stimulation. Conversely, positive expectations about active stimulation, but not sham stimulation, might influence the results in the opposite way, with a possible greater enhancement after active stimulation due only to expectations, and not to the real stimulation per se. In these cases, expectations might act as an uncontrolled, confounding factor. This possibility is corroborated by experimental evidence: it was demonstrated that blinding issues are present both in sham TMS and in sham tDCS, with participants “guessing” the type of stimulation administered based on the different perceptual sensations experienced during the stimulation[52]. This is particularly problematic in within-subjects designs or when participants have already taken part in NIBS experiments. Moreover, it was demonstrated that participants’ expectations might be influenced by the mere act of positioning the coil or the electrodes on the scalp [44], thus making sham stimulation suitable for studying placebo effects in different domains. Another issue raised in recent investigations is the possible neurophysiological effects of weak intensity current in those sham protocols which apply mild but continuous stimulation[53]. This problem is present in both tDCS and TMS research, because some sham modalities, such as those consisting of active stimulation applied on cortical areas considered not involved in the modulation to be achieved, can still induce uncontrolled neurophysiological effects.

Second, the literature provides convincing evidence that it is possible to directly induce expectations in participants through active manipulation. Interestingly, some researchers have found an interaction between tDCS and the expectations that are experimentally induced [42], although investigations in this direction are still lacking. Shedding new light on these mechanisms might be crucial also in clinical applications and in experiments seeking to enhance the effects of brain stimulation. It remains to be investigated whether NIBS coupled with the induction of positive expectations about the interventions might result in a greater enhancement of cognitive functions or clinical outcomes, potentially making this manipulation an optimal strategy to achieve better results.

References

1. Barker, A.T.; Jalinous, R.; Freeston, I.L. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985, 325, 1106–1107. [Google Scholar] [CrossRef]
2. Barker, A.T.; Freeston, I.L.; Jalinous, R.; Jarratt, J.A. Magnetic stimulation of the human brain and peripheral nervous system: An introduction and the results of an initial clinical evaluation. Neurosurgery 1987, 20, 100–109. [Google Scholar] [CrossRef]
3. Hallett, M. Transcranial magnetic stimulation and the human brain. Nature 2000, 406, 147–150. [Google Scholar] [CrossRef]
4. Pascual-Leone, A.; Walsh, V.; Rothwell, J. Transcranial magnetic stimulation in cognitive neuroscience–virtual lesion, chronometry, and functional connectivity. Curr. Opin. Neurobiol. 2000, 10, 232–237. [Google Scholar] [CrossRef]
5. Walsh, V.; Cowey, A. Transcranial magnetic stimulation and cognitive neuroscience. Nat. Rev. Neurosci. 2000, 1, 73–80. [Google Scholar] [CrossRef]
6. Sack, A.T. Transcranial magnetic stimulation, causal structure–function mapping and networks of functional relevance. Curr. Opin. Neurobiol. 2006, 16, 593–599. [Google Scholar] [CrossRef]
7. Huang, Y.Z.; Edwards, M.J.; Rounis, E.; Bhatia, K.P.; Rothwell, J.C. Theta burst stimulation of the human motor cortex. Neuron 2005, 45, 201–206. [Google Scholar] [CrossRef]
8. Nitsche, M.A.; Paulus, W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 2000, 527, 633. [Google Scholar] [CrossRef]
9. Nitsche, M.A.; Paulus, W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001, 57, 1899–1901. [Google Scholar] [CrossRef]
10. Priori, A.; Berardelli, A.; Rona, S.; Accornero, N.; Manfredi, M. Polarization of the human motor cortex through the scalp. Neuroreport 1998, 9, 2257–2260. [Google Scholar] [CrossRef]
11. Ruffini, G.; Wendling, F.; Sanchez-Todo, R.; Santarnecchi, E. Targeting brain networks with multichannel transcranial current stimulation (tCS). Curr. Opin. Biomed. Eng. 2018, 8, 70–77. [Google Scholar] [CrossRef]
12. Bindman, L.J.; Lippold, O.C.J.; Redfearn, J.W.T. Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. Nature 1962, 196, 584–585. [Google Scholar] [CrossRef]

13. Bindman, L.J.; Lippold, O.C.J.; Redfearn, J.W.T. Relation between the size and form of potentials evoked by sensory stimulation and the background electrical activity in the cerebral cortex of the rat. J. Physiol. 1964, 171, 1. [Google Scholar] [CrossRef]
14. Bindman, L.J.; Lippold, O.C.; Milne, A.R. Prolonged changes in excitability of pyramidal tract neurones in the cat: A post-synaptic mechanism. J. Physiol. 1979, 286, 457–477. [Google Scholar] [CrossRef]
15. Creutzfeldt, O.D.; Fromm, G.H.; Kapp, H. Influence of transcortical dc currents on cortical neuronal activity. Exp. Neurol. 1962, 5, 436–452. [Google Scholar] [CrossRef]
16. Jacobson, L.; Koslowsky, M.; Lavidor, M. tDCS polarity effects in motor and cognitive domains: A meta-analytical review. Exp. Brain Res. 2012, 216, 1–10. [Google Scholar] [CrossRef]
17. Nitsche, M.A.; Paulus, W. Transcranial direct current stimulation–update 2011. Restor. Neurol. Neurosci. 2011, 29, 463–492. [Google Scholar] [CrossRef]
18. Sandrini, M.; Umiltà, C.; Rusconi, E. The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. Neurosci. Biobehav. Rev. 2011, 35, 516–536. [Google Scholar] [CrossRef]
19. Radman, T.; Su, Y.; An, J.H.; Parra, L.C.; Bikson, M. Spike timing amplifies the effect of electric fields on neurons: Implications for endogenous field effects. J. Neurosci. 2007, 27, 3030–3036. [Google Scholar] [CrossRef]
20. Landi, D.; Rossini, P.M. Cerebral restorative plasticity from normal ageing to brain diseases: A “never ending story”. Restor. Neurol. Neurosci. 2010, 28, 349–366. [Google Scholar] [CrossRef]
21. Lang, N.; Nitsche, M.A.; Dileone, M.; Mazzone, P.; Ares, J.D.A.; Diaz-Jara, L.; Paulus, W.; Di Lazzaro, V.; Oliviero, A. Transcranial direct current stimulation effects on I-wave activity in humans. J. Neurophysiol. 2011, 105, 2802–2810. [Google Scholar] [CrossRef]
22. Ridding, M.C.; Ziemann, U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J. Physiol. 2010, 588, 2291–2304. [Google Scholar] [CrossRef]
23. Miniussi, C.; Ruzzoli, M.; Walsh, V. The mechanism of transcranial magnetic stimulation in cognition. Cortex 2010, 46, 128. [Google Scholar] [CrossRef]
24. Silvanto, J.; Muggleton, N.; Walsh, V. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn. Sci. 2008, 12, 447–454. [Google Scholar] [CrossRef]
25. Miniussi, C.; Harris, J.A.; Ruzzoli, M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci. Biobehav. Rev. 2013, 37, 1702–1712. [Google Scholar] [CrossRef]
26. Epstein, C.M.; Rothwell, J.C. Therapeutic uses of rTMS. In Plasticity in the Human Nervous System; Investigation with Transcranial Magnetic Stimulation; Boniface, S., Ziemann, U., Eds.;

Cambridge University Press: Cambridge, UK, 2003; pp. 246–263. [Google Scholar]

27. Carlino, E.; Piedimonte, A.; Benedetti, F. Nature of the placebo and nocebo effect in relation to functional neurologic disorders. Handb. Clin. Neurol. 2016, 139, 597–606. [Google Scholar] [CrossRef]
28. Benedetti, F.; Pollo, A.; Lopiano, L.; Lanotte, M.; Vighetti, S.; Rainero, I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J. Neurosci. 2003, 23, 4315–4323. [Google Scholar] [CrossRef]
29. Fiorio, M.; Emadi Andani, M.; Marotta, A.; Classen, J.; Tinazzi, M. Placebo-induced changes in excitatory and inhibitory corticospinal circuits during motor performance. J. Neurosci. 2014, 34, 3993–4005. [Google Scholar] [CrossRef]
30. Weger, U.W.; Loughnan, S. Mobilizing unused resources: Using the placebo concept to enhance cognitive performance. Q. J. Exp. Psychol. 2013, 66, 23–28. [Google Scholar] [CrossRef]
31. Benedetti, F.; Lanotte, M.; Lopiano, L.; Colloca, L. When words are painful: Unraveling the mechanisms of the nocebo effect. Neuroscience 2007, 147, 260–271. [Google Scholar] [CrossRef]
32. Colloca, L.; Miller, F.G. The nocebo effect and its relevance for clinical practice. Psychosom. Med. 2011, 73, 598. [Google Scholar] [CrossRef] [PubMed]
33. Malhi, G.S.; Bell, E. Is the response to rTMS largely the result of non-specific effects? Aust. N. Z. J. Psychiatry 2021, 55, 445–450. [Google Scholar] [CrossRef]
34. Davis, N.J.; Gold, E.; Pascual-Leone, A.; Bracewell, R.M. Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. Eur. J. Neurosci. 2013, 38, 2973–2977. [Google Scholar] [CrossRef]
35. Lefaucheur, J.-P.; Antal, A.; Ayache, S.S.; Benninger, D.; Brunelin, J.; Cogiamanian, F.; Cotelli, M.; De Ridder, D.; Ferrucci, R.; Langguth, B.; et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). J. Clin. Neurophysiol. 2017, 128, 56–92. [Google Scholar] [CrossRef] [PubMed]
36. Rossi, S.; Hallett, M.; Rossini, P.M.; Pascual-Leone, A.; The Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. 2009, 120, 2008–2039. [Google Scholar] [CrossRef] [PubMed]
37. Ambrus, G.G.; Paulus, W.; Antal, A. Cutaneous perception thresholds of electrical stimulation methods: Comparison of tDCS and tRNS. Clin. Neurophysiol. 2010, 121, 1908–1914. [Google Scholar] [CrossRef]

38. Razza, L.B.; Moffa, A.H.; Moreno, M.L.; Carvalho, A.F.; Padberg, F.; Fregni, F.; Brunoni, A.R. A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2018, 81, 105–113. [Google Scholar] [CrossRef]
39. Brunoni, A.R.; Lopes, M.; Kaptchuk, T.J.; Fregni, F. Placebo response of non-pharmacological and pharmacological trials in major depression: A systematic review and meta-analysis. PLoS ONE 2009, 4, e4824. [Google Scholar] [CrossRef]
40. Meister, R.; Jansen, A.; Härter, M.; Nestoriuc, Y.; Kriston, L. Placebo and nocebo reactions in randomized trials of pharmacological treatments for persistent depressive disorder. A meta-regression analysis. J. Affect. Disord. 2017, 215, 288–298. [Google Scholar] [CrossRef]
41. Rief, W.; Nestoriuc, Y.; Weiss, S.; Welzel, E.; Barsky, A.J.; Hofmann, S.G. Meta-analysis of the placebo response in antidepressant trials. J. Affect. Disord. 2009, 118, 1–8. [Google Scholar] [CrossRef]
42. Rabipour, S.; Wu, A.D.; Davidson, P.S.; Iacoboni, M. Expectations may influence the effects of transcranial direct current stimulation. Neuropsychologia 2018, 119, 524–534. [Google Scholar] [CrossRef]
43. Rabipour, S.; Vidjen, P.S.; Remaud, A.; Davidson, P.S.; Tremblay, F. Examining the interactions between expectations and tDCS effects on motor and cognitive performance. Front. Neurosci. 2019, 12, 999. [Google Scholar] [CrossRef]
44. Bin Dawood, A.B.; Dickinson, A.; Aytemur, A.; Howarth, C.; Milne, E.; Jones, M. Investigating the effects of tDCS on visual orientation discrimination task performance: “The possible influence of placebo”. J. Cogn. Enhanc. 2019, 4, 235–249. [Google Scholar] [CrossRef]
45. Kober, S.E.; Witte, M.; Grinschgl, S.; Neuper, C.; Wood, G. Placebo hampers ability to self-regulate brain activity: A double-blind sham-controlled neurofeedback study. Neuroimage 2018, 181, 797–806. [Google Scholar] [CrossRef] [PubMed]
46. Knotkova, H.; Nitsche, M.A.; Cruciani, R.A. Putative physiological mechanisms underlying tDCS analgesic effects. Front. Hum. Neurosci. 2013, 7, 628. [Google Scholar] [CrossRef] [PubMed]
47. Aslaksen, P.M.; Vasylenko, O.; Fagerlund, A.J. The effect of transcranial direct current stimulation on experimentally induced heat pain. Exp. Brain Res. 2014, 232, 1865–1873. [Google Scholar] [CrossRef]
48. Samartin-Veiga, N.; Pidal-Miranda, M.; González-Villar, A.J.; Bradley, C.; Garcia-Larrea, L.; O’Brien, A.T.; Carrillo-De-La-Peña, M.T. Transcranial direct current stimulation of three cortical targets is no more effective than placebo as treatment for fibromyalgia: A double-blind sham-controlled clinical trial. Pain 2021. [Google Scholar] [CrossRef] [PubMed]

49. Wang, P.; Hooyman, A.; Schambra, H.M.; Lohse, K.R.; Schaefer, S.Y. Expectations from the general public about the efficacy of transcranial direct current stimulation for improving motor performance. Brain Stimul. 2021, 14, 500–502. [Google Scholar] [CrossRef] [PubMed]
50. Ray, M.K.; Sylvester, M.D.; Helton, A.; Pittman, B.R.; Wagstaff, L.E.; McRae, T.R.; Turan, B.; Fontaine, K.R.; Amthor, F.R.; Boggiano, M.M. The effect of expectation on transcranial direct current stimulation (tDCS) to suppress food craving and eating in individuals with overweight and obesity. Appetite 2019, 136, 1–7. [Google Scholar] [CrossRef] [PubMed]
51. Van Elk, M.; Groenendijk, E.; Hoogeveen, S. Placebo Brain Stimulation Affects Subjective but Not Neurocognitive Measures of Error Processing. J. Cogn. Enhanc. 2020, 4, 389–400. [Google Scholar] [CrossRef]
52. O'Connell, N.E.; Cossar, J.; Marston, L.; Wand, B.M.; Bunce, D.; Moseley, L.; De Souza, L.H. Rethinking clinical trials of transcranial direct current stimulation: Participant and assessor blinding is inadequate at intensities of 2 mA. PLoS ONE 2012, 7, e47514. [Google Scholar] [CrossRef]
53. Fonteneau, C.; Mondino, M.; Arns, M.; Baeken, C.; Bikson, M.; Brunoni, A.R.; Burke, M.J.; Neuvonen, T.; Padberg, F.; Pascual-Leone, A.; et al. Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul. 2019, 12, 668–673. [Google Scholar] [CrossRef]