Transcorneal Electrical Stimulation for Depression

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Contributor: Lee Wei Lim , Wing Shan Yu

The potential neuroprotective properties of Transcorneal Electrical Stimulation (TES) are possibly achieved through regulating neuroplasticity, neurotrophic expression, inflammatory responses, apoptosis, glutamate metabolism, and retinal blood flow. The putative neuroprotective effects of TES on mood control are supported by its shared mechanisms of action with current antidepressant treatments, including its neuroprotective effects against apoptosis and inflammation, as well as its ability to promote neurotrophic expression. This entry aims to discuss the neuromodulation potential of TES as a treatment for depressive disorders and the neuroprotective mechanisms of action that might contribute to the antidepressant-like responses.

TES transcorneal electrical stimulation neuromodulation depression antidepressant neuroprotection

1. Introduction

Major depressive disorder, commonly known as depression, is the leading cause of disability worldwide [1]. It is considered a major global disease burden, with more than 4.4% of the world's population estimated to suffer from depression, and 800,000 depression-related suicide cases annually [2]. The economic cost of depression in US adults exceeded USD 300 billion in 2018 [3]. According to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V), depression is primarily characterized by anhedonia and sadness persisting for at least 2 weeks, which is accompanied by secondary symptoms such as fatigue, sense of worthlessness, psychomotor agitation, changes in appetite or weight, sleep difficulties, loss of concentration, and/or recurrent thoughts of suicide [4]. The burden of depression is further compounded by the high comorbidity of physical disorders [5], as evidenced by its close association with pain [6][7], dementia [8], type 2 diabetes [9][10], cardiovascular diseases [11][12][13][14], and cancers [15]. Depression not only leads to additional medical and financial costs, but also aggravates the prognosis or even mortality in diseased populations.

Depression is commonly treated with psychotherapy and medications that generally target the reuptake of neurotransmitters [16]. Nevertheless, up to 60% of patients inadequately respond to drug treatments, in which approximately 10–30% of patients develop treatment-resistant depression (TRD) with failure to respond to two or more types of antidepressant treatments [17][18][19][20]. Electroconvulsive therapy (ECT) is considered a common treatment for TRD and the remission rate is reported at approximately 50%, with nearly half of the patients relapsing within the first year following ECT [21][22][23][24][25]. Given the increasing prevalence of depression and

unsatisfactory outcomes of currently available treatments, there is an urgent need to develop alternative therapeutic options for the treatment of depression.

Neuromodulation is a technology which utilizes electrical stimulation to modulate the nervous system functioning [26]. It is emerging as a promising therapeutic approach against various psychiatric and neurological disorders [20]. Among the different types of neuromodulation-based techniques, transcorneal electrical stimulation (TES) is a non-invasive treatment that is reported to improve visual functions in various ophthalmological conditions [27]. Although current studies on TES mostly focus on its use in ophthalmology, TES is also demonstrated to induce neurobehavioural changes including antidepressant-like behaviour in corneally kindled models [28]. Surprisingly, apart from activating the retina and associated downstream visual structures, enhanced activities are additionally reported in the prefrontal cortex (PFC) and parahippocampal gyrus (PHG) following TES application [29][30][31]. Although the modulation effects of TES in these non-visual brain regions have yet to be confirmed, both PFC and PHG are involved in mood alterations [32], suggesting that TES may have a role in regulating emotion. The potential neuroprotective properties of TES are possibly achieved through regulating neuroplasticity [30][33], neurotrophic expression [34][35][36][37][38][39][40] , inflammatory responses [39][41][42][43][44], apoptosis [36][45][46][47], glutamate metabolism [48], and retinal blood flow [49][50]. The putative neuroprotective effects of TES on mood control are further supported by its shared mechanisms of action with current antidepressant treatments, including its neuroprotective effects against apoptosis and inflammation, as well as its ability to promote neurotrophic expression.

2. Potential Antidepressant-like Activities of TES

The application of TES as a treatment for vision restoration was widely investigated. Interestingly, TES was shown to stimulate not only brain regions related to visual processing, but also other unrelated brain regions. A human study utilizing 18F-fluorodeoxyglucose positron emission tomography examined brain regions stimulated during TES [29], which showed activation in the occipital cortex, including Brodmann's Area (BA) 17 in the primary visual cortex, and BA 18 and BA 19 in the secondary visual cortex. There was also activation in the inferior temporal gyrus, which is part of the ventral visual stream involved in visual processing. Aside from the visual cortex activation, enhanced brain activity was also recorded in the bilateral PFC and PHG. Rodent electrophysiological studies found that prolonged TES led to a sustained excitation of the PFC, suggesting that the stimulating effects of TES could diffuse beyond the visual pathway [30][31]. Although the functional implications of increased activity in PFC and PHG by TES remain obscure, they suggest that TES may exert effects on emotional regulation by activating brain regions highly associated with depression. Indeed, antidepressant treatments or psychotherapy were shown to normalize the PFC glucose hypometabolism observed in depressed patients [51][52], suggesting a positive association between PFC activity and the remission of depressive symptoms. A functional magnetic resonance imaging study demonstrated the involvement of the PFC in emotional control, as indicated by an increase in PFC activity during voluntary suppression of negative emotions [53][54]. Similarly, the PHG was shown to have a pathophysiological role in depression, as indicated by the high discriminative power of its functional connectivity in identifying depressed patients from healthy controls [55].

The effects of TES on behavioural alterations were previously demonstrated in corneally kindled rodent models [28][56][57]. Corneal kindling is an epileptic model generated through repeated TES at sub-convulsive doses until a generalized seizure is achieved. Wlaź et al. reported that TES induced a significant reduction in despair-like behaviour in fully kindled rats, as demonstrated by a decrease in force swim immobility [28]. Interestingly, such an antidepressant-like response was accompanied by an increase in anxiety-like behaviour in the elevated plus maze test. On the contrary, 6 Hz corneal kindling did not produce an anxiety-like response, instead it resulted in anhedonic-like behaviour in both saccharin preference and novelty suppressed feeding tests [56]. Furthermore, results reported by Wlaź et al. contradicted the findings of another study by Koshal et al., which showed corneally kindled mice had depressive-like behaviour in the tail suspension test [57]. Although TES was shown to induce behavioural changes in kindled models, its prodepressant or antidepressant effects remains unclear due to inconsistent results among studies. More importantly, these investigations were conducted in a fully kindled model, which is not a proper animal model of depression, and could display abnormal behavioural phenotypes that would confound the effects of TES on regulating mood-related behaviour. Moreover, the high stimulation intensities of TES (up to 19 mA amplitude) used to trigger epileptic seizures were inappropriate for examining the antidepressant potential of TES, as such extreme stimulation parameters could lead to tissue damage. Although TES was demonstrated to alter behaviour, its potential therapeutic use in depression needs to be investigated further in a proper animal model of depression using appropriate stimulation parameters.

3. Comparison of FDA-Approved Treatments for Major Depression

Interestingly, TES shares several mechanisms of action with some of the existing antidepressant treatments, which can provide a basis for identifying its putative antidepressant properties and the underlying molecular pathways. We compared selective serotonin reuptake inhibitors (SSRIs), repetitive transcranial magnetic stimulation (rTMS), and ECT. These depression treatments are approved by the United States Food and Drug Administration (FDA) and are representative therapeutic options for major depression and TRD. Among the different SSRIs options, fluoxetine and escitalopram act to increase serotonin activity by maintaining its extracellular concentration. They are the most commonly prescribed first-line antidepressants with proven safety and efficacy for use in paediatric and adult patients [58][59]. As a non-surgical, non-convulsive brain stimulation therapy, rTMS utilizes a time-varying magnetic field to modulate cortical plasticity and excitability [60][61]. Another non-invasive neuromodulation technique is ECT, which is conducted under general anaesthesia. It intentionally triggers a brief generalized cerebral seizure via the delivery of a small electrical charge to the patient's scalp [62]. It is speculated that the neurotrophic, anti-apoptotic, and anti-inflammatory activities of TES greatly resemble the biomarker changes observed in the aforementioned antidepressant pharmacological and neuromodulation interventions.

A growing body of evidence suggests the regulation of neurotrophic signalling has tremendous potential for treating depression. Impaired neuroplasticity is thought to arise from the dysregulated expression of neurotrophins, which have dual roles in regulating neuronal survival and activity-dependent synaptic plasticity [63][64]. Specifically, it has long been speculated that BDNF, a major neurotrophic factor that supports the growth, maturation, and

maintenance of nerve cells, plays a direct role in the pathophysiology of depression [65]. A decreased plasma BDNF level was found to be significantly associated with suicidal behaviour in major depression [66]. Similar to TES, the administration of rTMS, ECT, and SSRIs in depressed subjects also led to a neurotrophic enhancement, particularly the enhanced expression of BDNF. Indeed, a 12-week escitalopram treatment in depressed patients reversed the downregulated BDNF mRNA levels in peripheral leukocytes, which normalised serum BDNF levels and alleviated depressive symptoms [67]. Similarly, a small cohort of depressed older patients was treated with escitalopram for 2 months, which resulted in a significant increase in BDNF serum level associated with improvements in the geriatric depression score [68]. Likewise, prolonged rTMS administration in a chronic unpredictable mild stress (CUMS) model of depression upregulated hippocampal BDNF expression for up to 2 weeks after treatment discontinuation and reversed the stress-induced depressive-like behavioural changes [69][70]. Concordantly, several lines of evidence demonstrated that TRD patients who received rTMS showed remarkable increases in peripheral BDNF levels [71][72][73]. Similarly, ECT was shown to upregulate BDNF expression in depressed subjects in both preclinical and clinical studies [74][75][76]. A recent meta-analysis showed that ECT increased peripheral BDNF levels in depressed patients consistent with pharmacological antidepressant interventions, and further highlighted the association between BDNF and the risk of depression [75]. Although the effects of TES on enhancing BDNF levels in the retina are consistently reported [36][38][39][46], its effects on regulating neurotrophin expression in various brain regions involved in emotional regulation, and its associated therapeutic potential, require further investigation.

In major depression, chronic stress can induce excessive apoptotic cell death leading to neurodegeneration in the central nervous system [77]. A balance between pro-apoptotic factors (e.g., Bax and Bak) and anti-apoptotic factors (e.g., Bcl-2 and Bcl-xl) plays a crucial role in controlling the activation of apoptotic pathways [78]. Studies showed that TES could upregulate anti-apoptotic Bcl-2 expression and downregulate pro-apoptotic Bax expression [36][45][46]. Similarly, SSRIs were shown to protect neurons from apoptosis by modulating the expression of the Bcl-2 gene family members that regulate caspase activation and cell death [79]. Fluoxetine treatment in a CUMS model enhanced Bcl-2 expression in the central nucleus of the amygdala, frontal, and cingulate cortices, and reduced Bax expression in the hippocampus, which are all critical brain regions implicated in depression [80][81]. Concordantly, changes in apoptotic markers such as the downregulation of Bcl-2 and upregulation of caspase-3 were remarkably attenuated in CUMS rats after 3 weeks of fluoxetine treatment, further supporting an anti-apoptotic mechanism of SSRIs [82]. Similarly, ECT was found to positively affect Bcl-2 mRNA expression in various sub-regions of the limbic system, while also selectively increasing Bcl-xl mRNA expression in the hippocampus [80]. On the other hand, rTMS was able to repress Bax and augment Bcl-2 expression levels in the hippocampus of CUMS rats, which were accompanied by the amelioration of depression-like behaviour [70][83]. Although TES was also shown to possess anti-apoptotic properties, whether these resulted in antidepressant activity remains an interesting topic for future investigation.

The inflammatory hypothesis of depression is supported by the heightened inflammatory responses found in a significant proportion of the depressed population [84], including increased levels of neuroinflammatory cytokines, which are believed to cause serotonin and melatonin depletion via the neurotoxic kynurenine pathway [85]. Interestingly, changes in the pro- and anti-inflammatory profile of TES greatly paralleled that of rTMS, ECT, and

SSRIs. A meta-analysis reported SSRIs to have suppressive effects on inflammatory factors in depressed patients who exhibited increased serum levels of major inflammatory cytokines such as IL-6, IL-1β, and TNF-α [86]. The anti-inflammatory role of SSRIs was further supported by a clinical study on 98 depressed patients which found that treatment with either fluoxetine or escitalopram for 2 months significantly reduced inflammatory markers [87]. Notably, TRD patients treated with rTMS had gradually attenuated serum levels of pro-inflammatory IL-1β and TNF-α accompanied by positive changes in Hamilton Depression Rating Scale-24 scores [73]. Moreover, rTMS exerted antidepressant-like effects in a CUMS model via a nuclear factor-E2-related factor 2 (Nrf2)-dependent anti-inflammatory mechanism, which suppressed the production of pro-inflammatory TNF-α, iNOS, IL-1β, and IL-6 in hippocampal regions [88]. A substantial body of evidence consistently showed that ECT could alleviate pro-inflammatory cytokine secretion in depressed patients, as indicated by a notable reduction in peripheral TNFα, IL-6, eotaxin-3, and IL-5 levels [89][90][91][92]. Moreover, ECT was also reported to increase the level of blood IL-10 [93], which is a well-established anti-inflammatory cytokine that prevents neuronal and glial cell death [94]. Given that TES was demonstrated to reduce inflammatory responses via regulating cytokine expression and suppressing microglial activation [39][42][43][44], its putative anti-depressant effects on inflammation warrant investigation in the future.

4. Benefits and Risks of TES As a Depression Treatment

A major advantage of TES is that it is a non-invasive, reversible, and highly adjustable stimulation method. Numerous pre-clinical and clinical studies demonstrated an excellent safety profile of TES and no serious adverse side effects were reported. On the contrary, invasive neuromodulation approaches such as deep brain stimulation carry a risk of infection and haemorrhage during invasive neurosurgery [95][96][97]. Moreover, there is a risk of seizure during stimulation in rTMZ [98], while ECT has potential cognitive side effects including retrograde and anterograde amnesia [99][100]. Compared with conventional antidepressant drugs that affect the entire body, TES can deliver its effects in specifically targeted brain regions [101]. Furthermore, TES avoids the common side effects of antidepressants such as weight change, hepatotoxicity, and gastrointestinal problems [102][103]. The adjustable nature of TES allows the stimulation parameters to be fine-tuned depending on the individual patient's condition and disease progression. The stimulator can be quickly turned off if an adverse event occurs and the stimulating electrodes can be easily removed. Additionally, the simple administration of TES could allow for self-administration by patients, which greatly enhances its flexibility throughout the treatment period [104].

Although TES is well tolerated in humans with only mild and transient side effects, even after prolonged use, there are some commonly observed side effects, including foreign body sensation, dry eye symptoms, and corneal punctate keratopathy, which can be mostly resolved without further treatment [105][104][106][107]. Other infrequent adverse events include unilateral cataracts, the sensation of flashing lights, muscle twitching, vomiting, and a tingling sensation on the side of the head [104]. Moreover, there were two reported cases of retinal perforation in rats, possibly as a result of mechanical pressure or high charge density stimulation [36]. Considering the potential ocular damage caused by high amplitude stimulation, the optimal stimulation parameters need to be well validated. Furthermore, both antidepressant-like and depressive-like behaviour was reported in the corneal kindling model,

and it raised the possibility that TES could resolve or exacerbate depressive-like symptoms. It is therefore important to examine the therapeutic effects of TES using an animal model of depression with proper control, and further investigate of the putative TES-induced activation in brain structures associated with depression in order to delineate the underlying mechanisms of action.

References

1. WHO. WHO Depression Fact Sheet; World Health Organization (WHO): Geneva, Switzerland, 2020.
2. WHO. Depression and Other Common Mental Disorders: Global Health Estimates; World Health Organization (WHO): Geneva, Switzerland, 2017.
3. Greenberg, P.E.; Fournier, A.A.; Sisitsky, T.; Simes, M.; Berman, R.; Koenigsberg, S.H.; Kessler, R.C. The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018). Pharmacoeconomics 2021, 39, 653–665.
4. Association, A.P. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®); American Psychiatric Pub: Arlington, VA, USA, 2013.
5. Kang, H.-J.; Kim, S.-Y.; Bae, K.-Y.; Kim, S.-W.; Shin, I.-S.; Yoon, J.-S.; Kim, J.-M. Comorbidity of depression with physical disorders: Research and clinical implications. Chonnam. Med. J. 2015, 51, 8–18.
6. Kroenke, K.; Wu, J.; Bair, M.J.; Krebs, E.E.; Damush, T.M.; Tu, W. Reciprocal relationship between pain and depression: A 12-month longitudinal analysis in primary care. J. Pain 2011, 12, 964–973.
7. Stubbs, B.; Vancampfort, D.; Veronese, N.; Thompson, T.; Fornaro, M.; Schofield, P.; Solmi, M.; Mugisha, J.; Carvalho, A.F.; Koyanagi, A. Depression and pain: Primary data and meta-analysis among 237,952 people across 47 low-and middle-income countries. Psychol. Med. 2017, 47, 2906–2917.
8. Byers, A.L.; Yaffe, K. Depression and risk of developing dementia. Nat. Rev. Neurol. 2011, 7, 323–331.
9. Knol, M.; Twisk, J.W.; Beekman, A.T.; Heine, R.; Snoek, F.J.; Pouwer, F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006, 49, 837.
10. Bădescu, S.V.; Tătaru, C.; Kobylinska, L.; Georgescu, E.L.; Zahiu, D.M.; Zăgrean, A.M.; Zăgrean, L. The association between Diabetes mellitus and Depression. J. Med. Life 2016, 9, 120–125.
11. Van der Kooy, K.; van Hout, H.; Marwijk, H.; Marten, H.; Stehouwer, C.; Beekman, A. Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. Int J. Geriatr.

Psychiatry 2007, 22, 613–626.

12. Khawaja, I.S.; Westermeyer, J.J.; Gajwani, P.; Feinstein, R.E. Depression and coronary artery disease: The association, mechanisms, and therapeutic implications. Psychiatry 2009, 6, 38–51.
13. Gump, B.B.; Matthews, K.A.; Eberly, L.E.; Chang, Y.F.; Group, M.R. Depressive symptoms and mortality in men: Results from the Multiple Risk Factor Intervention Trial. Stroke 2005, 36, 98–102.
14. Pan, A.; Sun, Q.; Okereke, O.I.; Rexrode, K.M.; Hu, F.B. Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. JAMA 2011, 306, 1241–1249.
15. Spiegel, D.; Giese-Davis, J. Depression and cancer: Mechanisms and disease progression. Biol. Psychiatry 2003, 54, 269–282.
16. Hillhouse, T.M.; Porter, J.H. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Exp. Clin. Psychopharmacol. 2015, 23, 1–21.
17. Al-Harbi, K.S. Treatment-resistant depression: Therapeutic trends, challenges, and future directions. Patient Prefer. Adherence 2012, 6, 369.
18. Mrazek, D.A.; Hornberger, J.C.; Altar, C.A.; Degtiar, I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. Psychiatr. Serv. 2014, 65, 977–987.
19. Morishita, T.; Fayad, S.M.; Higuchi, M.-A.; Nestor, K.A.; Foote, K.D. Deep brain stimulation for treatment-resistant depression: Systematic review of clinical outcomes. Neurotherapeutics 2014, 11, 475–484.
20. Temel, Y.; Hescham, S.A.; Jahanshahi, A.; Janssen, M.L.; Tan, S.K.; van Overbeeke, J.J.; Ackermans, L.; Oosterloo, M.; Duits, A.; Leentjens, A.F.; et al. Neuromodulation in psychiatric disorders. Int. Rev. Neurobiol. 2012, 107, 283–314.
21. Kolshus, E.; Jelovac, A.; McLoughlin, D. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: A systematic review and meta-analysis of randomized controlled trials. Psychol. Med. 2017, 47, 518–530.
22. Brus, O.; Cao, Y.; Gustafsson, E.; Hultén, M.; Landen, M.; Lundberg, J.; Nordanskog, P.; Nordenskjöld, A. Self-assessed remission rates after electroconvulsive therapy of depressive disorders. Eur. Psychiatry 2017, 45, 154–160.
23. Bahji, A.; Hawken, E.; Sepehry, A.; Cabrera, C.; Vazquez, G. ECT beyond unipolar major depression: Systematic review and meta—Analysis of electroconvulsive therapy in bipolar depression. Acta Psychiatr. Scand. 2019, 139, 214–226.
24. Tokutsu, Y.; Umene-Nakano, W.; Shinkai, T.; Yoshimura, R.; Okamoto, T.; Katsuki, A.; Hori, H.; Ikenouchi-Sugita, A.; Hayashi, K.; Atake, K. Follow-up study on electroconvulsive therapy in

treatment-resistant depressed patients after remission: A chart review. Clin. Psychopharmacol. Neurosci. 2013, 11, 34.

25. Jelovac, A.; Kolshus, E.; McLoughlin, D.M. Relapse following successful electroconvulsive therapy for major depression: A meta-analysis. Neuropsychopharmacology 2013, 38, 2467–2474.
26. Krames, E.S.; Peckham, P.H.; Rezai, A.; Aboelsaad, F. What is neuromodulation? In Neuromodulation; Elsevier: Amsterdam, The Netherlands, 2009; pp. 3–8.
27. Tao, Y.; Chen, T.; Liu, B.; Wang, L.-Q.; Peng, G.-H.; Qin, L.-M.; Yan, Z.-J.; Huang, Y.-F. The transcorneal electrical stimulation as a novel therapeutic strategy against retinal and optic neuropathy: A review of experimental and clinical trials. Int. J. Ophthalmol. 2016, 9, 914.
28. Wlaź, P.; Poleszak, E.; Serefko, A.; Wlaź, A.; Rundfeldt, C. Anxiogenic-and antidepressant-like behavior in corneally kindled rats. Pharmacol. Rep. 2015, 67, 349–352.
29. Xie, J.; Wang, G.-J.; Yow, L.; Cela, C.J.; Humayun, M.S.; Weiland, J.D.; Lazzi, G.; Jadvar, H. Modeling and percept of transcorneal electrical stimulation in humans. IEEE Trans. Biomed. Eng. 2011, 58, 1932–1939.
30. Agadagba, S.K.; Li, X.; Chan, L.L. Electroencephalogram power alterations in retinal degeneration mice after prolonged transcorneal electrical stimulation. In Proceedings of the 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER), Manhattan, NY, USA, 2019; pp. 219–222.
31. Agadagba, S.K.; Li, X.; Chan, L.L.H. Excitation of the Pre-frontal and Primary Visual Cortex in Response to Transcorneal Electrical Stimulation in Retinal Degeneration Mice. Front. Neurosci. 2020, 14, 572299:1–572299:13.
32. Habel, U.; Klein, M.; Kellermann, T.; Shah, N.J.; Schneider, F. Same or different? Neural correlates of happy and sad mood in healthy males. Neuroimage 2005, 26, 206–214.
33. Sergeeva, E.G.; Fedorov, A.B.; Henrich-Noack, P.; Sabel, B.A. Transcorneal alternating current stimulation induces EEG “aftereffects” only in rats with an intact visual system but not after severe optic nerve damage. J. Neurophysiol. 2012, 108, 2494–2500.
34. Morimoto, T.; Miyoshi, T.; Matsuda, S.; Tano, Y.; Fujikado, T.; Fukuda, Y. Transcorneal electrical stimulation rescues axotomized retinal ganglion cells by activating endogenous retinal IGF-1 system. Investig. Ophthalmol. Vis. Sci. 2005, 46, 2147–2155.
35. Tagami, Y.; Kurimoto, T.; Miyoshi, T.; Morimoto, T.; Sawai, H.; Mimura, O. Axonal regeneration induced by repetitive electrical stimulation of crushed optic nerve in adult rats. Jpn. J. Ophthalmol. 2009, 53, 257–266.
36. Ni, Y.-Q.; Gan, D.-K.; Xu, H.-D.; Xu, G.-Z. Neuroprotective effect of transcorneal electrical stimulation on light-induced photoreceptor degeneration. Exp. Neurol. 2009, 219, 439–452.

37. Sato, T.; Fujikado, T.; Morimoto, T.; Matsushita, K.; Harada, T.; Tano, Y. Effect of electrical stimulation on IGF-1 transcription by L-type calcium channels in cultured retinal Müller cells. Jpn. J. Ophthalmol. 2008, 52, 217–223.

38. Sato, T.; Fujikado, T.; Lee, T.-S.; Tano, Y. Direct effect of electrical stimulation on induction of brain-derived neurotrophic factor from cultured retinal Muller cells. Investig. Ophthalmol. Vis. Sci. 2008, 49, 4641–4646.

39. Zhou, W.-T.; Ni, Y.-Q.; Jin, Z.-B.; Zhang, M.; Wu, J.-H.; Zhu, Y.; Xu, G.-Z.; Gan, D.-K. Electrical stimulation ameliorates light-induced photoreceptor degeneration in vitro via suppressing the proinflammatory effect of microglia and enhancing the neurotrophic potential of Müller cells. Exp. Neurol. 2012, 238, 192–208.

40. Enayati, S.; Chang, K.; Achour, H.; Cho, K.-S.; Xu, F.; Guo, S.; Enayati, K.Z.; Xie, J.; Zhao, E.; Turunen, T. Electrical stimulation induces retinal müller cell proliferation and their progenitor cell potential. Cells 2020, 9, 781.

41. Langmann, T. Microglia activation in retinal degeneration. J. Leukoc. Biol. 2007, 81, 1345–1351.

42. Fu, L.; Fung, F.K.; Lo, A.C.-Y.; Chan, Y.-K.; So, K.-F.; Wong, I.Y.-H.; Shih, K.C.; Lai, J.S.-M. Transcorneal electrical stimulation inhibits retinal microglial activation and enhances retinal ganglion cell survival after acute ocular hypertensive injury. Transl. Vis. Sci. Technol. 2018, 7, 7.

43. Yin, H.; Yin, H.; Zhang, W.; Miao, Q.; Qin, Z.; Guo, S.; Fu, Q.; Ma, J.; Wu, F.; Yin, J. Transcorneal electrical stimulation promotes survival of retinal ganglion cells after optic nerve transection in rats accompanied by reduced microglial activation and TNF-α expression. Brain Res. 2016, 1650, 10–20.

44. Jassim, A.H.; Cavanaugh, M.; Shah, J.S.; Willits, R.; Inman, D.M. Transcorneal Electrical Stimulation Reduces Neurodegenerative Process in a Mouse Model of Glaucoma. Ann. Biomed. Eng. 2021, 49, 858–870.

45. Willmann, G.; Schäferhoff, K.; Fischer, M.D.; Arango-Gonzalez, B.; Bolz, S.; Naycheva, L.; Röck, T.; Bonin, M.; Bartz-Schmidt, K.U.; Zrenner, E. Gene expression profiling of the retina after transcorneal electrical stimulation in wild-type Brown Norway rats. Investig. Ophthalmol. Vis. Sci. 2011, 52, 7529–7537.

46. Tao, Y.; Chen, T.; Liu, Z.-Y.; Wang, L.-Q.; Xu, W.-W.; Qin, L.-M.; Peng, G.-H.; Yi-Fei, H. Topographic Quantification of the Transcorneal Electrical Stimulation (TES)–Induced Protective Effects on N-Methyl-N-Nitrosourea–Treated Retinas. Investig. Ophthalmol. Vis. Sci. 2016, 57, 4614–4624.

47. Momeni, H.R. Role of calpain in apoptosis. Cell J. 2011, 13, 65.

48. Wang, X.; Mo, X.; Li, D.; Wang, Y.; Fang, Y.; Rong, X.; Miao, H.; Shou, T. Neuroprotective effect of transcorneal electrical stimulation on ischemic damage in the rat retina. Exp. Eye Res. 2011, 93,

753–760.

49. Kurimoto, T.; Oono, S.; Oku, H.; Tagami, Y.; Kashimoto, R.; Takata, M.; Okamoto, N.; Ikeda, T.; Mimura, O. Transcorneal electrical stimulation increases chorioretinal blood flow in normal human subjects. Clin. Ophthalmol. 2010, 4, 1441.
50. Bittner, A.K.; Seger, K.; Salveson, R.; Kayser, S.; Morrison, N.; Vargas, P.; Mendelsohn, D.; Han, J.; Bi, H.; Dagnelie, G. Randomized controlled trial of electro—Stimulation therapies to modulate retinal blood flow and visual function in retinitis pigmentosa. Acta Ophthalmol. 2018, 96, e366–e376.
51. Mayberg, H.S.; Brannan, S.K.; Tekell, J.L.; Silva, J.A.; Mahurin, R.K.; McGinnis, S.; Jerabek, P.A. Regional metabolic effects of fluoxetine in major depression: Serial changes and relationship to clinical response. Biol. Psychiatry 2000, 48, 830–843.
52. Brody, A.L.; Saxena, S.; Mandelkern, M.A.; Fairbanks, L.A.; Ho, M.L.; Baxter, L.R. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biol. Psychiatry 2001, 50, 171–178.
53. Lévesque, J.; Eugène, F.; Joanette, Y.; Paquette, V.; Mensour, B.; Beaudoin, G.; Leroux, J.-M.; Bourgouin, P.; Beauregard, M. Neural circuitry underlying voluntary suppression of sadness. Biol. Psychiatry 2003, 53, 502–510.
54. Phan, K.L.; Fitzgerald, D.A.; Nathan, P.J.; Moore, G.J.; Uhde, T.W.; Tancer, M.E. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. Biol. Psychiatry 2005, 57, 210–219.
55. Zeng, L.-L.; Shen, H.; Liu, L.; Wang, L.; Li, B.; Fang, P.; Zhou, Z.; Li, Y.; Hu, D. Identifying major depression using whole-brain functional connectivity: A multivariate pattern analysis. Brain 2012, 135, 1498–1507.
56. Albertini, G.; Walrave, L.; Demuyser, T.; Massie, A.; De Bundel, D.; Smolders, I. 6 Hz corneal kindling in mice triggers neurobehavioral comorbidities accompanied by relevant changes in c—Fos immunoreactivity throughout the brain. Epilepsia 2018, 59, 67–78.
57. Koshal, P.; Kumar, P. Effect of liraglutide on corneal kindling epilepsy induced depression and cognitive impairment in mice. Neurochem. Res. 2016, 41, 1741–1750.
58. Dwyer, J.B.; Bloch, M.H. Antidepressants for pediatric patients. Curr. Psychiatr. 2019, 18, 26.
59. Segi-Nishida, E. The effect of serotonin-targeting antidepressants on neurogenesis and neuronal maturation of the hippocampus mediated via 5-HT1A and 5-HT4 receptors. Front. Cell. Neurosci. 2017, 11, 142.
60. Hardy, S.; Bastick, L.; O'Neill-Kerr, A.; Sabesan, P.; Lankappa, S.; Palaniyappan, L. Transcranial magnetic stimulation in clinical practice. BJPsych Adv. 2016, 22, 373–379.

61. Turi, Z.; Normann, C.; Domschke, K.; Vlachos, A. Transcranial magnetic stimulation in psychiatry: Is there a need for electric field standardization? Front. Hum. Neurosci. 2021, 15, 639640:1–639640:7.

62. Salik, I.; Marwaha, R. Electroconvulsive Therapy. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2021.

63. Yang, T.; Nie, Z.; Shu, H.; Kuang, Y.; Chen, X.; Cheng, J.; Yu, S.; Liu, H. The role of BDNF on neural plasticity in depression. Front. Cell. Neurosci. 2020, 14, 82.

64. Hennigan, A.; O'callaghan, R.; Kelly, A. Neurotrophins and their receptors: Roles in plasticity, neurodegeneration and neuroprotection. Biochem. Soc. Trans. 2007, 35, 424–427.

65. Bathina, S.; Das, U.N. Brain-derived neurotrophic factor and its clinical implications. Arch. Med Sci. 2015, 11, 1164.

66. Kim, Y.-K.; Lee, H.-P.; Won, S.-D.; Park, E.-Y.; Lee, H.-Y.; Lee, B.-H.; Lee, S.-W.; Yoon, D.; Han, C.; Kim, D.-J. Low plasma BDNF is associated with suicidal behavior in major depression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2007, 31, 78–85.

67. Cattaneo, A.; Bocchio-Chiavetto, L.; Zanardini, R.; Milanesi, E.; Placentino, A.; Gennarelli, M. Reduced peripheral brain-derived neurotrophic factor mRNA levels are normalized by antidepressant treatment. Int. J. Neuropsychopharmacol. 2010, 13, 103–108.

68. Martocchia, A.; Curto, M.; Scaccianoce, S.; Comite, F.; Xenos, D.; Nasca, C.; Falaschi, G.M.; Ferracuti, S.; Girardi, P.; Nicoletti, F. Effects of escitalopram on serum BDNF levels in elderly patients with depression: A preliminary report. Aging Clin. Exp. Res. 2014, 26, 461–464.

69. Feng, S.-F.; Shi, T.-Y.; Wang, W.-N.; Chen, Y.-C.; Tan, Q.-R. Long-lasting effects of chronic rTMS to treat chronic rodent model of depression. Behav. Brain Res. 2012, 232, 245–251.

70. Wang, H.-N.; Wang, L.; Zhang, R.-G.; Chen, Y.-C.; Liu, L.; Gao, F.; Nie, H.; Hou, W.-G.; Peng, Z.-W.; Tan, Q. Anti-depressive mechanism of repetitive transcranial magnetic stimulation in rat: The role of the endocannabinoid system. J. Psychiatr. Res. 2014, 51, 79–87.

71. Zanardini, R.; Gazzoli, A.; Ventriglia, M.; Perez, J.; Bignotti, S.; Rossini, P.M.; Gennarelli, M.; Bocchio-Chiavetto, L. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. J. Affect. Disord. 2006, 91, 83–86.

72. Yukimasa, T.; Yoshimura, R.; Tamagawa, A.; Uozumi, T.; Shinkai, K.; Ueda, N.; Tsuji, S.; Nakamura, J. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. Pharmacopsychiatry 2006, 39, 52–59.

73. Zhao, X.; Li, Y.; Tian, Q.; Zhu, B.; Zhao, Z. Repetitive transcranial magnetic stimulation increases serum brain-derived neurotrophic factor and decreases interleukin-1β and tumor necrosis factor-α

in elderly patients with refractory depression. J. Int. Med Res. 2019, 47, 1848–1855.

74. Taliaz, D.; Nagaraj, V.; Haramati, S.; Chen, A.; Zangen, A. Altered brain-derived neurotrophic factor expression in the ventral tegmental area, but not in the hippocampus, is essential for antidepressant-like effects of electroconvulsive therapy. Biol. Psychiatry 2013, 74, 305–312.
75. Brunoni, A.R.; Baeken, C.; Machado-Vieira, R.; Gattaz, W.F.; Vanderhasselt, M.-A. BDNF blood levels after electroconvulsive therapy in patients with mood disorders: A systematic review and meta-analysis. World J. Biol. Psychiatry 2014, 15, 411–418.
76. Vanicek, T.; Kranz, G.S.; Vyssoki, B.; Fugger, G.; Komorowski, A.; Höflich, A.; Saumer, G.; Milovic, S.; Lanzenberger, R.; Eckert, A. Acute and subsequent continuation electroconvulsive therapy elevates serum BDNF levels in patients with major depression. Brain Stimul. 2019, 12, 1041–1050.
77. McKernan, D.P.; Dinan, T.G.; Cryan, J.F. “Killing the Blues”: A role for cellular suicide (apoptosis) in depression and the antidepressant response? Prog. Neurobiol. 2009, 88, 246–263.
78. Duman, R.S. Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: Stress and depression. Dialogues Clin. Neurosci. 2009, 11, 239.
79. Kale, J.; Osterlund, E.J.; Andrews, D.W. BCL-2 family proteins: Changing partners in the dance towards death. Cell Death Differ. 2018, 25, 65–80.
80. Kosten, T.A.; Galloway, M.P.; Duman, R.S.; Russell, D.S.; D’sa, C. Repeated unpredictable stress and antidepressants differentially regulate expression of the bcl-2 family of apoptotic genes in rat cortical, hippocampal, and limbic brain structures. Neuropsychopharmacology 2008, 33, 1545–1558.
81. Pandya, M.; Altinay, M.; Malone, D.A.; Anand, A. Where in the brain is depression? Curr. psychiatry Rep. 2012, 14, 634–642.
82. Yang, Y.; Hu, Z.; Du, X.; Davies, H.; Huo, X.; Fang, M. miR-16 and fluoxetine both reverse autophagic and apoptotic change in chronic unpredictable mild stress model rats. Front. Neurosci. 2017, 11, 428.
83. Zhao, L.; Ren, H.; Gu, S.; Li, X.; Jiang, C.; Li, J.; Zhang, M.; Mu, J.; Li, W.; Wang, W. rTMS ameliorated depressive-like behaviors by restoring HPA axis balance and prohibiting hippocampal neuron apoptosis in a rat model of depression. Psychiatry Res. 2018, 269, 126–133.
84. Patel, A. The role of inflammation in depression. Psychiatr. Danub. 2013, 25, S216–S223.
85. Gałecki, P.; Talarowska, M. Inflammatory theory of depression. Psychiatr. Pol. 2018, 52, 437–447.
86. Hannestad, J.; DellaGioia, N.; Bloch, M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: A meta-analysis. Neuropsychopharmacology 2011, 36, 2452–2459.

87. Chavda, N.; Kantharia, N.; Charan, J. Effects of fluoxetine and escitalopram on C-reactive protein in patients of depression. J. Pharmacol. Pharmacother. 2011, 2, 11–16.
88. Tian, L.; Sun, S.-S.; Cui, L.-B.; Wang, S.-Q.; Peng, Z.-W.; Tan, Q.-R.; Hou, W.-G.; Cai, M. Repetitive transcranial magnetic stimulation elicits antidepressant-and anxiolytic-like effect via nuclear factor-E2-related factor 2-mediated anti-inflammation mechanism in rats. Neuroscience 2020, 429, 119–133.
89. Hestad, K.A.; Tønseth, S.; Støen, C.D.; Ueland, T.; Aukrust, P. Raised plasma levels of tumor necrosis factor α in patients with depression: Normalization during electroconvulsive therapy. J. ECT 2003, 19, 183–188.
90. Rotter, A.; Biermann, T.; Stark, C.; Decker, A.; Demling, J.; Zimmermann, R.; Sperling, W.; Kornhuber, J.; Henkel, A. Changes of cytokine profiles during electroconvulsive therapy in patients with major depression. J. ECT 2013, 29, 162–169.
91. Sorri, A.; Järventausta, K.; Kampman, O.; Lehtimäki, K.; Björkqvist, M.; Tuohimaa, K.; Hämäläinen, M.; Moilanen, E.; Leinonen, E. Low tumor necrosis factor-α levels predict symptom reduction during electroconvulsive therapy in major depressive disorder. Brain Behav. 2018, 8, e00933.
92. Belge, J.-B.; Van Diermen, L.; Sabbe, B.; Parizel, P.; Morrens, M.; Coppens, V.; Constant, E.; de Timary, P.; Sienaert, P.; Schrijvers, D. Inflammation, Hippocampal Volume, and Therapeutic Outcome following Electroconvulsive Therapy in Depressive Patients: A Pilot Study. Neuropsychobiology 2020, 79, 222–232.
93. Zincir, S.; Öztürk, P.; Bilgen, A.E.; Izci, F.; Yükselir, C. Levels of serum immunomodulators and alterations with electroconvulsive therapy in treatment-resistant major depression. Neuropsychiatr. Dis. Treat. 2016, 12, 1389.
94. Roque, S.; Correia-Neves, M.; Mesquita, A.R.; Palha, J.A.; Sousa, N. Interleukin-10: A key cytokine in depression? Cardiovasc. Psychiatry Neurol. 2009, 2009, 187894:1–187894:5.
95. Lozano, A.M.; Lipsman, N.; Bergman, H.; Brown, P.; Chabardes, S.; Chang, J.W.; Matthews, K.; McIntyre, C.C.; Schlaepfer, T.E.; Schulder, M.; et al. Deep brain stimulation: Current challenges and future directions. Nat. Rev. Neurol. 2019, 15, 148–160.
96. Fenoy, A.J.; Simpson, R.K., Jr. Risks of common complications in deep brain stimulation surgery: Management and avoidance. J. Neurosurg. 2014, 120, 132–139.
97. Hamurcu, M.S.; Aydogmuş, S.A.; Saricaoğlu, M.S. Evaluation of the efficacy of transcorneal electric stimulation therapy in retinitis pigmentosa patients with electrophysiological and structural tests. Int. J. Clin. Exp. Ophthalmol. 2020, 4, 31–37.
98. Bae, E.H.; Schrader, L.M.; Machii, K.; Alonso-Alonso, M.; Riviello, J.J., Jr.; Pascual-Leone, A.; Rotenberg, A. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with

epilepsy: A review of the literature. Epilepsy Behav. 2007, 10, 521–528.

99. Brakemeier, E.-L.; Berman, R.; Prudic, J.; Zwillenberg, K.; Sackeim, H.A. Self-evaluation of the cognitive effects of electroconvulsive therapy. J. ECT 2011, 27, 59–66.
100. Porter, R.J.; Baune, B.T.; Morris, G.; Hamilton, A.; Bassett, D.; Boyce, P.; Hopwood, M.J.; Mulder, R.; Parker, G.; Singh, A.B. Cognitive side-effects of electroconvulsive therapy: What are they, how to monitor them and what to tell patients. BJPsych Open 2020, 6, e40:1–e40:7.
101. Holtzheimer, P.E.; Mayberg, H.S. Neuromodulation for treatment-resistant depression. F1000 Med. Rep. 2012, 4.
102. Uher, R.; Farmer, A.; Henigsberg, N.; Rietschel, M.; Mors, O.; Maier, W.; Kozel, D.; Hauser, J.; Souery, D.; Placentino, A. Adverse reactions to antidepressants. Br. J. Psychiatry 2009, 195, 202–210.
103. Carvalho, A.F.; Sharma, M.S.; Brunoni, A.R.; Vieta, E.; Fava, G.A. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother. Psychosom. 2016, 85, 270–288.
104. Jolly, J.K.; Wagner, S.K.; Martus, P.; MacLaren, R.E.; Wilhelm, B.; Webster, A.R.; Downes, S.M.; Charbel Issa, P.; Kellner, U.; Jägle, H.; et al. Transcorneal Electrical Stimulation for the Treatment of Retinitis Pigmentosa: A Multicenter Safety Study of the OkuStim® System (TESOLA-Study). Ophthalmic Res. 2020, 63, 234–243.
105. Fujikado, T.; Morimoto, T.; Matsushita, K.; Shimojo, H.; Okawa, Y.; Tano, Y. Effect of transcorneal electrical stimulation in patients with nonarteritic ischemic optic neuropathy or traumatic optic neuropathy. Jpn. J. Ophthalmol. 2006, 50, 266–273.
106. Morimoto, T.; Fukui, T.; Matsushita, K.; Okawa, Y.; Shimojyo, H.; Kusaka, S.; Tano, Y.; Fujikado, T. Evaluation of residual retinal function by pupillary constrictions and phosphenes using transcorneal electrical stimulation in patients with retinal degeneration. Graefe’s Arch. Clin. Exp. Ophthalmol. 2006, 244, 1283.
107. Wagner, S.K.; Jolly, J.K.; Pefkianaki, M.; Gekeler, F.; Webster, A.R.; Downes, S.M.; Maclaren, R.E. Transcorneal electrical stimulation for the treatment of retinitis pigmentosa: Results from the TESOLAUK trial. BMJ open Ophthalmol. 2017, 2, e000096.