REVIEW

Potential Mechanisms Underlying the Therapeutic Effects of Electroconvulsive Therapy

Jiangling Jiang¹ · Jijun Wang^{1,2,3} · Chunbo Li^{1,2,3}

Received: 5 August 2016 / Accepted: 23 November 2016 / Published online: 28 December 2016

© Shanghai Institutes for Biological Sciences, CAS and Springer Science+Business Media Singapore 2016

Abstract In spite of the extensive application of electroconvulsive therapy (ECT), how it works remains unclear. So far, researchers have made great efforts in figuring out the mechanisms underlying the effect of ECT treatment *via* determining the levels of neurotransmitters and cytokines and using genetic and epigenetic tools, as well as structural and functional neuroimaging. To help address this question and provide implications for future research, relevant clinical trials and animal experiments are reviewed.

Keywords Electroconvulsive therapy · Neurotransmitters · Neurotrophins · Inflammatory factors · Epigenetics · Neuroimaging

Introduction

Electroconvulsive therapy (ECT) was first used to treat mental disorders in 1938 as a substitute for the chemical induction of seizures [1]. It involves deliberately inducing seizures for therapeutic purposes by administering an electrical stimulus to a patient's brain *via* electrodes

applied to the scalp. Although modified ECT (using anesthesia and muscle relaxants) significantly alleviates the discomfort during the procedure and prevents severe adverse side-effects such as fractures, unmodified ECT is still preferred in Asia, Africa, and Latin America [1]. Today, brief-pulse wave ECT rather than sine-wave ECT with a constant voltage and energy is recommended [2]. Bilateral placement is the most common electrode placement [1]. Almost 80 years have passed since its first use, and ECT is still widely administered worldwide [1]. It is largely considered to be a treatment for affective disorders in most western countries, while in many eastern countries such as India, Thailand, and Japan, as well as in parts of Africa, ECT is mainly applied as a first-line treatment for schizophrenia [1]. For depression, ECT is probably more effective than pharmacotherapy [3]. For schizophrenia, ECT combined with antipsychotics is a treatment option when the patient does not respond to pharmacotherapy alone or rapid improvement is desired [4]. ECT is also used for other severe conditions such as refractory status epilepticus [5] and malignant catatonia [6]. Despite the extensive use of ECT, the mechanisms of how its broad and notable therapeutic effectiveness is generated remain poorly understood.

Discredited Theories of ECT

Although ECT has proven to be an effective and safe intervention [3, 4], its image in the media and in the public domain remains negative [7, 8]. McCall *et al.* have listed some misconceptions concerning the mechanism underlying the treatment effects of ECT, such as brain damage and the placebo effect [9]. Anderson *et al.* performed a post-mortem brain examination on an 84-year-old man after 422 ECT sessions and found no identifiable structural changes

✉ Chunbo Li
chunbo_li@163.com

¹ Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, China

² Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Ministry of Education, Shanghai Jiao Tong University, Shanghai 200030, China

³ Brain Science and Technology Research Center, Shanghai Jiao Tong University, Shanghai 200030, China

in his brain [10], which further confirmed the results of previous research [11, 12]. It is notable that in Anderson's study, the time interval between the last ECT treatment and the postmortem examination was less than a month, which is much shorter than in the previous reports (one year and 12 years). This provided evidence that ECT has no impact on the structure of the brain even immediately after the end of substantive ECT treatments. Besides pathological changes, researchers have also explored the relationship between ECT and brain damage by analyzing relevant biomarkers. In previous trials, no elevations were found for neuron-specific enolase or protein S-100 (S100b), which are highly-specific and widely-used biomarkers of nervous tissue damage [13–16]. There were also studies identifying small and transient increases in S100b after ECT, which showed no association with cognitive impairment [17, 18]; rather, such alterations of S100b may indicate neural growth and synaptogenesis [19]. To date, both *in vivo* and *ex vivo* evidence indicates that the therapeutic effects of ECT are not generated by damaging the central nervous system, although there is great concern about this issue [20, 21].

Although ECT is known to be significantly more effective than a sham procedure [3], discussion about whether the placebo effect plays an important role in ECT continues. Reviewers have criticized such trials in that there are particular methodological and ethical limitations with regard to the adequacy of placebo controls as a consequence of insufficient allocation concealment [22]. Since sham ECT is ineffective and it would be ethically wrong to mimic the common side-effects of real ECT, participants may be able to guess their allocation. As a consequence, we are not able to rule out the possibility that the placebo effect does contribute to its therapeutic effects. In fact, emerging evidence favors ECT over active controls like antidepressants and repetitive transcranial magnetic stimulation [23, 24], further demonstrating that ECT may be the most effective treatment for major depression. Placebo effects cannot be the mainstay of such a powerful weapon against various severe mental disorders. However, discussion concerning the role of the placebo effect in ECT is likely to continue until the mechanism is fully understood.

ECT and Neurotransmitters

ECT is mainly used to treat depression and schizophrenia [1]. The main treatments of both disorders are pharmacotherapies involving the modulation of serotonin (5-HT) in the case of antidepressants and an antagonistic effect on dopamine D2 receptors in the case of antipsychotics [25, 26]. Thus, many researchers have investigated the mechanism underlying the effects of ECT by identifying its impact on the 5-HT and the dopamine systems in the brain.

Most studies have shown no significant changes in 5-hydroxyindoleacetic acid, a major metabolite of 5-HT, in cerebrospinal fluid (CSF) with ECT [27–31]. Using a positron emission tomography (PET), Lakshmi *et al.* found a widespread reduction in 5-HT_{2A} receptor binding in all of the cortical regions of patients with major depressive disorder (MDD) [32]. These results are consistent with the findings from studies on antidepressant agents [33–35] and in non-human primates [36]. Moreover, the reductions in the right medial prefrontal cortex, right lingual gyrus, and parahippocampal gyrus showed a trend to be correlated with improvement in depressive symptoms. In addition, variation in the 5-HT_{2A} receptor gene is a potential predictor of the response to ECT [37] and antidepressants [38, 39]. Lanzenberger *et al.* found a widespread reduction in 5-HT_{1A} receptor binding in cortical areas and the hippocampus-amygdala region [40], while Saijo *et al.* reported no significant changes in the brains of MDD patients [41]. On the basis of the limited data from these three trials, one might hypothesize that ECT and antidepressant agents share a common mechanism, the down-regulation of 5-HT receptors, in the treatment of depressive disorders. However, these findings in human participants are inconsistent with most of the preclinical experiments, which indicate that electroconvulsive shocks (ECS) up-regulate 5-HT receptors in the central nervous system [42].

Similarly, ECT did not produce any significant changes in CSF homovanillic acid, a major metabolite of dopamine, in most studies [27–31]. Using PET with [¹¹C]FLB 457, Saijo *et al.* found that dopamine D2 receptor binding decreases in the anterior cingulate among patients with depression following ECT [43]. Nevertheless, Tiger *et al.* reported a 98% increase in dopamine D2 receptor binding with [¹¹C]raclopride in half of the patients, while there was virtually no change in the other half [44]. This sharp discrepancy might partially be attributed to the impact of dopamine receptor polymorphism on the ECT response [45–47]. The results of preclinical studies are relatively consistent, and most indicate that ECT activates the dopamine system at various levels, including hormone release, neurotransmission, and receptor binding [42].

ECT and Neurotrophins

Brain-derived neurotrophic factor (BDNF) plays an important role in mediating the differentiation and survival of neurons, as well as in synaptic plasticity [48]. It is the most extensively-studied neurotrophin in psychiatry, and numerous meta-analytic reviews have suggested that BDNF decreases in various mental disorders and increases after pharmacological treatments [49–56].

Polyakova *et al.* have performed a comprehensive meta-analysis concerning the impact of ECS/ECT on BDNF

levels in experimental animals and in patients with MDD or bipolar disorder [57]. They reported an increase in the BDNF protein and its mRNA in the brains of rodents, with the greatest change in the dentate gyrus, as well as an increase in blood BDNF levels in patients irrespective of their response to ECT. The increase in BDNF after ECT/ECS is correlated with the number of intervention sessions. It seems that ECT does raise the BDNF levels in the brain but the increase has nothing to do with its therapeutic effects. However, subgroup analysis revealed more information. Although there were no significant differences between responders and non-responders, the BDNF increase (pre- *versus* post-treatment) was significant only in responders (pre- and post-treatment). And an increase in blood BDNF levels was found in the plasma of participants, but there was no change in the serum of either rats or humans. More recent evidence has confirmed the potential of BDNF as a predictor of the response to ECT [58–61]. Nevertheless, it is notable that most of the results are markedly heterogeneous, and this cannot be settled by subgroup analysis, thus, the findings of this study are not conclusive. In addition to the direct assessment of BDNF, researchers have also explored the role of BDNF in the effects of ECT by investigating the influence of BDNF gene polymorphisms on its efficacy [47, 62–64]. Yet only the polymorphism rs11030101 has been associated with the therapeutic effects of ECT [63].

Although not as thoroughly evaluated as BDNF, an association between vascular endothelial growth factor (VEGF) and the efficacy of ECT has also been evaluated. VEGF, a key growth factor for blood vessels, has various effects on neurons [65] and is increased in the blood of MDD patients [66]. Minelli *et al.* conducted a series of trials, and consistently found that a serum VEGF increase is associated with a reduction of depressive symptoms [67–69]. These results further confirm the conclusions drawn from preclinical research that VEGF plays an important role in the mechanism of ECT [70–73].

ECT and the Immune System

Meta-analytic reviews have revealed significant changes in inflammatory cytokines in various mental diseases [74–80] as well as their potential as predictors of disease development and treatment response in depression and psychosis [81–84]. Increases in C-reactive protein, interleukin-6, and tumor necrosis factor alpha (TNF- α) in the blood of patients with depression or psychosis are consistently reported by these studies.

Despite the great efforts to identify cytokine changes following ECT since the beginning of the twenty-first century [85–92], only a few studies have shown that ECT works by normalizing the inflammatory factor levels in the

same way as pharmacotherapy [93, 94]. In fact, many studies have suggested that ECT raises the concentration of these cytokines which were already elevated before treatment. But some relatively promising results have been reported, such as a reduction in TNF- α , a consistently raised inflammatory cytokine in depressed patients [86]. In addition, significantly low serum interleukin-5 (IL-5) and tumor necrosis factor beta (TNF- β) have been reported, both correlated with the severity of depressive symptoms [89]. These results are consistent with previous findings of up-regulated IL-5 and TNF- β in MDD patients [95–98]. In addition, an increase in indoleamine 2,3 dioxygenase (IDO) has been found in MDD and its level drops following ECT [91], providing evidence for the IDO activation theory of mood disorders [99]. In another study, lower serum levels of TGF- β in schizophrenic patients have been reported, and they increase following ECT, showing a negative correlation with a reduction of psychotic symptoms [92]. Nevertheless, these results contradict previous evidence that TGF- β increases in schizophrenic patients and is normalized after antipsychotic treatments [81].

ECT and Epigenetics

Epigenetics commonly refers to a stably heritable phenotype as a consequence of chromosome modification without changing DNA sequences [100]. It may be involved in the development of various mental diseases and thus indicate new directions for treatment [101–104]. It is a novel approach to investigating the mechanism of ECT, but most research remains preclinical and methodologically limited. The main findings from these very preliminary studies include an increase in histone H4 acetylation, alterations of DNA methylation patterns, and changes in miRNA levels [105]. We found two reports concerning the epigenetic effects of ECT on human subjects. In MDD patients, Kleimann *et al.* found a lower methylation rate in the BDNF promoter in ECT responders than in non-responders, and a negative correlation between the methylation rate and serum BDNF levels [106]. In addition, changes in the blood concentrations of several miRNAs following ECT in MDD patients have been reported by Kolshus *et al.* [107]. In short, a limited number of studies preliminarily reveal the potential of investigating the mechanism of ECT *via* epigenetic means.

ECT and Structural Neuroplasticity

In addition to the molecular-level changes noted above, ECT may also be able to reverse the structural abnormalities found in patients with mental diseases. Examples of these abnormalities are the multiple structural and microstructural changes in both the cortical and subcortical areas among MDD patients [108–113], and hippocampal

Table 1 Summary of relatively consistent findings

Levels	Relatively consistent findings	Symptomatic correlations	Genetic correlations
Neurotransmitters	Cortical 5-HT _{2A} receptor binding↓ [32, 36]	± [32]	+ [37]
Neurotrophins	Blood BDNF↑ [57–61]	+ [58–61]	+ [63, 106]
	Blood VEGF↑ [67–72]	+ [67, 69]	–
Inflammatory factors	Blood TNF- α ↓ [86]	–	–
	Blood TNF- β ↓ [89]	+ [89]	–
	Blood IL-5↓ [89]	+ [89]	–
Structural changes in brain	Hippocampus↑ [115–121]	+ [115, 120]	–
	Amygdala↑ [115, 117, 119, 120]	+ [115, 120]	–
Functional changes in brain	Frontal glucose uptake↓ [141–145]	+ [142]	–
	Resting state network↑ [118, 146–150]	+ [118, 146–150]	–

↑ Increase; ↓ decrease; + statistically significant; ± showing a trend; – neither significant nor showing a trend.

size is a potential predictor of response to medication [114].

Recently, Joshi *et al.* found that ECT normalizes the decreased volumes of the hippocampus and the amygdala, and the changes are correlated with clinical improvement [115]. Several other studies showed that ECT enlarges the hippocampus and the amygdala [116–119], with correlations between volume increases and symptomatological improvement [120]. One study suggested that such increases reverse within six months and are not likely to be induced by edema [121]. These results are consistent with previous findings that the hippocampus and the amygdala are involved in the dysfunction of emotion regulation among depressive patients [122]. Although evidence of an association between hippocampal volume changes and autobiographical memory function has been found [123], a reasonable explanation of the discrepancy in hippocampal volume increases and autobiographical memory dysfunction following ECT has yet to be provided [124].

As for microstructural changes, fractional anisotropy (FA), which is a measure of white matter coherence, is the most used image biomarker in research on depression. Decreased FA is a stable finding in depression despite the fact that the reported regions are relatively inconsistent with different analytical methods [109, 111, 113]. In addition, there is evidence associating non-remitters with lower FA [125]. However, the results of recent studies concerning the impact of ECT on brain FA values vary substantially. Two studies have revealed increased FA [126, 127], one revealed no changes [128], and one revealed a decreased FA [119].

ECT and Neural Functional Changes

Using various techniques such as single positron emission computer tomography, near-infrared spectroscopy, and

PET, investigators have examined the impact of ECT on regional cerebral blood flow, but found mixed results [129–140]. Interestingly, one study showed significant normalization of frontal hypoperfusion in MDD patients with an excellent response to ECT but not in those with a minimal or moderate response [133]. In addition, a higher degree of perfusion was found in ECT treatments producing generalized seizures than in those which did not induce such seizures [139]. Changes in glucose metabolism are stably reported following ECT. Most relevant studies report decreased uptake in some frontal regions after ECT [141–145], and a correlation between such decreases and the reduction of depressive symptoms has also been reported [142]. In contrast, most resting-state network analysis has revealed increased connectivity correlated with clinical improvement, but the reported regions are inconsistent [118, 146–150]. Notably, van Waarde *et al.* claimed promising accuracy of two networks in predicting the ECT response, one centered in the dorsomedial prefrontal cortex with a sensitivity of 84% and specificity of 85%, and the other centered in the anterior cingulate cortex with a sensitivity of 80% and a specificity of 75% [150]. In addition, normalization of default mode network coherence was found in ECT responders but not in non-responders [151].

Summary

Despite decades of tremendous effort, a comprehensive understanding of how ECT works is still a distant goal. With regard to molecular changes, consistent positive results towards normalization correlated with symptom improvement are rare. For neuroimaging changes, inconsistencies in altered regions are the main limitation. The small number of samples, the diversity of methods used in

both data collection and data analysis, and the heterogeneity within a certain mental disorders may all contribute to the inconsistency of current findings. Large trials and meta-analytic reviews are necessary to tackle these shortcomings.

Fortunately, there are still some promising findings despite the fact that they cannot fully explain the mechanism of ECT. Relatively consistent findings are listed in Table 1. Among the molecular biomarkers, neurotrophins seem more likely to be able to solve the mystery of the therapeutic effects of ECT and have become a hotspot in this field. Increases in blood BDNF and VEGF are consistently found after ECT, and many studies have revealed a positive correlation between the improvement of symptoms and these two neurotrophins. For similar reasons, we also recognize the volume increases of the hippocampus and amygdala to be the most promising structural imaging biomarkers, and increased connectivity of the resting state network to be the most promising functional imaging biomarker.

Besides exploring new biomarkers, what we already have must be fully utilized. For example, whether volume and functional changes of brain structures are mediated by neurotrophins must be further investigated. In addition, models using these biomarkers either separately or in an integrated manner should be built to see whether they can accurately predict clinical responses. The work discussed above may not only provide a better understanding of the mechanism of action of ECT, but also eventually facilitate clinical decision-making.

Acknowledgements This review was supported by the grants of Shanghai Hospital Development Center, China (SHDC12014111), the Science and Technology Commission of Shanghai Municipality, China (14411961400 and 13dz2260500), and the Shanghai Health System Leadership in Health Research Program, China (XBR2011005).

References

- Leiknes KA, Schweder LJ-v, Høie B. Contemporary use and practice of electroconvulsive therapy worldwide. *Brain Behav* 2012, 2: 283–344.
- American Psychiatric Association. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (A task force report of the American Psychiatric Association). American Psychiatric Pub, 2008.
- The UKECTRG. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 2003, 361: 799–808.
- Tharyan P, Adams Clive E. Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev* 2005, 2: CD000076. doi: [10.1002/14651858.CD000076.pub2](https://doi.org/10.1002/14651858.CD000076.pub2).
- Lambrecq V, Villéga F, Marchal C, Michel V, Guehl D, Rotge JY, *et al.* Refractory status epilepticus: Electroconvulsive therapy as a possible therapeutic strategy. *Seizure* 2012, 21: 661–664.
- Bartolommei N, Lattanzi L, Callari A, Cosentino L, Luchini F, Mauri M. Catatonia: A critical review and therapeutic recommendations. *J Psychopathol* 2012, 18: 234–246.
- McDonald A, Walter G. The portrayal of ECT in American movies. *J ECT* 2001, 17: 264–274.
- Lauber C, Nordt C, Falcato L, Rössler W. Can a seizure help? The public's attitude toward electroconvulsive therapy. *Psychiatry Res* 2005, 134: 205–209.
- McCall WV, Andrade C, Sienaert P. Searching for the Mechanism(s) of ECT's Therapeutic Effect. *J ECT* 2014, 30: 87–89.
- Anderson D, Wollmann R, Dinwiddie SH. Neuropathological evaluation of an 84-year-old man after 422 ECT treatments. *J ECT* 2014, 30: 248–250.
- Lippman S, Manshadi M, Wehry M, Byrd R, Past W, Keller W, *et al.* 1,250 electroconvulsive treatments without evidence of brain injury. *Br J Psychiatry* 1985, 147: 203–204.
- Scalia J, Lisanby SH, Dwork AJ, Johnson JE, Bernhardt ER, Arango V, *et al.* Neuropathologic examination after 91 ECT treatments in a 92-year-old woman with late-onset depression. *J ECT* 2007, 23: 96–98.
- Berrouschot J, Rolle K, Kühn HJ, Schneider D. Serum neuron-specific enolase levels do not increase after electroconvulsive therapy. *J Neurol Sci* 1997, 150: 173–176.
- Agelink MW, Andrich J, Postert T, Würzinger U, Zeit T, Klotz P, *et al.* Relation between electroconvulsive therapy, cognitive side effects, neuron specific enolase, and protein S-100. *J Neurol Neurosurg Psychiatry* 2001, 71: 394–396.
- Kranaster L, Janke C, Mindt S, Neumaier M, Sartorius A. Protein S-100 and neuron-specific enolase serum levels remain unaffected by electroconvulsive therapy in patients with depression. *J Neural Transm (Vienna)* 2014, 121: 1411–1415.
- Dorofeykov V, Petrova N, Dorofeykova M, Ivanov M, Zubov D. Measurement of neuron-specific enolase and S100B protein for determining neuronal damage during/after electroconvulsive therapy combined with pharmacotherapy in treatment-resistant schizophrenia. *Clin Chem Lab Med* 2015, 53: S1347.
- Arts B, Peters M, Ponds R, Honig A, Menheere P, Van Os J. S100 and impact of ECT on depression and cognition. *J ECT* 2006, 22: 206–212.
- Palmio J, Huuhka M, Laine S, Huhtala H, Peltola J, Leinonen E, *et al.* Electroconvulsive therapy and biomarkers of neuronal injury and plasticity: Serum levels of neuron-specific enolase and S-100b protein. *Psychiatry Res* 2010, 177: 97–100.
- Busnello JV, Leke R, Osés JP, Feier G, Bruch R, Quevedo J, *et al.* Acute and chronic electroconvulsive shock in rats: Effects on peripheral markers of neuronal injury and glial activity. *Life Sci* 2006, 78: 3013–3017.
- Breggin PR. The FDA should test the safety of ECT machines. *Ethical Hum Psychol Psychiatry* 2010, 12: 139–143.
- Goodman WK. Electroconvulsive therapy in the spotlight. *New Engl J Med* 2011, 364: 1785–1787.
- Blease CR. Electroconvulsive therapy, the placebo effect and informed consent. *J Med Ethics* 2013, 39: 166–170.
- Ren J, Li H, Palaniyappan L, Liu H, Wang J, Li C, *et al.* Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2014, 51: 181–189.
- Song GM, Tian X, Shuai T, Yi LJ, Zeng Z, Liu S, *et al.* Treatment of adults with treatment-resistant depression: Electroconvulsive therapy plus antidepressant or electroconvulsive therapy alone? Evidence from an indirect comparison meta-analysis. *Medicine (Baltimore)* 2015, 94. doi: [10.1097/MD.0000000000001052](https://doi.org/10.1097/MD.0000000000001052).
- National Collaborating Centre for Mental Health (UK). Depression: The Treatment and Management of Depression in

- Adults (Updated Edition) . Leicester (UK): British Psychological Society; 2010. In: National Institute for Health and Clinical Excellence: Guidance. London: National Institute for Health and Care Excellence (UK), 2003.
26. National Collaborating Centre for Mental Health (UK). Psychosis and Schizophrenia in Adults: Treatment and Management: Updated Edition 2014. In: National Institute for Health and Clinical Excellence: Guidance. London: National Institute for Health and Care Excellence (UK), 2003.
 27. Nordin G, Ottosson JO, Roos BE. Influence of convulsive therapy on 5-hydroxyindoleacetic acid and homovanillic acid in cerebrospinal fluid in endogenous depression. *Psychopharmacologia* 1971, 20: 315–320.
 28. Abrams R, Essman W, Taylor M, Fink M. Concentration of 5-hydroxyindoleacetic acid, homovanillic acid, and tryptophan in the cerebrospinal fluid of depressed patients before and after ECT. *Biol Psychiatry* 1976, 11: 85–90.
 29. Härnryd C, Bjerkenstedt L, Grimm V, Sedvall G. Reduction of MOPEG levels in cerebrospinal fluid of psychotic women after electroconvulsive treatment. *Psychopharmacology* 1979, 64: 131–134.
 30. Åberg-Wistedt A, Mårtensson B, Bertilsson L, Malmgren R. Electroconvulsive therapy effects on cerebrospinal fluid monoamine metabolites and platelet serotonin uptake in melancholia. *J ECT* 1986, 2: 97–98.
 31. Cooper S, Leahey W, Green D, King D. The effect of electroconvulsive therapy on CSF amine metabolites in schizophrenic patients. *Br J Psychiatry* 1988, 152: 59–63.
 32. Yatham LN, Liddle PF, Lam RW, Zis AP, Stoessl AJ, Sossi V, *et al.* Effect of electroconvulsive therapy on brain 5-HT₂ receptors in major depression. *Br J Psychiatry* 2010, 196: 474–479.
 33. Yatham LN, Liddle PF, Dennie J, Shiah IS, Adam MJ, Lane CJ, *et al.* Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: a positron emission tomography study with fluorine-18-labeled setoperone. *Arch Gen Psychiatry* 1999, 56: 705–711.
 34. Meyer JH, Kapur S, Eisfeld B, Brown GM, Houle S, DaSilva J, *et al.* The effect of paroxetine on 5-HT(2A) receptors in depression: an [(18)F]setoperone PET imaging study. *Am J Psychiatry* 2001, 158: 78–85.
 35. Mischoulon D, Dougherty DD, Bottonari KA, Gresham RL, Sonawalla SB, Fischman AJ, *et al.* An open pilot study of nefazodone in depression with anger attacks: relationship between clinical response and receptor binding. *Psychiatry Res* 2002, 116: 151–161.
 36. Strome EM, Clark CM, Zis AP, Doudet DJ. Electroconvulsive shock decreases binding to 5-HT₂ receptors in nonhuman primates: an in vivo positron emission tomography study with [(18)F]setoperone. *Biol Psychiatry* 2005, 57: 1004–1010.
 37. Van De Bilt MT, Do Prado CM, Nicola BV, Rigonatti LF, Talib LL, Rigonatti SP, *et al.* ABCB1 and HTR2A polymorphism may be related to treatment response in a sample of mood disorders patients undergoing electroconvulsive therapy. *Biol Psychiatry* 2015, 77: 221S–222S.
 38. Glessier F, Porcelli S, Calati R, Serretti A. Pharmacogenetics of clozapine response and induced weight gain: A comprehensive review and meta-analysis. *Eur Neuropsychopharmacol* 2016, 26: 163–185.
 39. Lin JY, Jiang MY, Kan ZM, Chu Y. Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants in the treatment of major depressive disorder: A meta-analysis. *J Affect Disord* 2014, 168: 430–438.
 40. Lanzenberger R, Baldinger P, Hahn A, Ungersboeck J, Mitterhauser M, Winkler D, *et al.* Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression measured by PET. *Mol Psychiatry* 2013, 18: 93–100.
 41. Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, *et al.* Effect of electroconvulsive therapy on 5-HT_{1A} receptor binding in patients with depression: A PET study with [(11)C]WAY 100635. *Int J Neuropsychopharmacol* 2010, 13: 785–791.
 42. Baldinger P, Lotan A, Frey R, Kasper S, Lerer B, Lanzenberger R. Neurotransmitters and electroconvulsive therapy. *J ECT* 2014, 30: 116–121.
 43. Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, *et al.* Electroconvulsive therapy decreases dopamine D₂ receptor binding in the anterior cingulate in patients with depression: A controlled study using positron emission tomography with radioligand [(11)C]FLB 457. *J Clin Psychiatry* 2010, 71: 793–799.
 44. Tiger M, Halldin C, Farde L, Lundberg J. Effects of ECT against depression on [(11)C] raclopride binding. *Eur J Nucl Med Mol Imaging* 2013, 40: S208–S208.
 45. Huuhka K, Anttila S, Huuhka M, Hietala J, Huhtala H, Mononen N, *et al.* Dopamine 2 receptor C957T and catechol-o-methyltransferase Val158Met polymorphisms are associated with treatment response in electroconvulsive therapy. *Neurosci Lett* 2008, 448: 79–83.
 46. Dannlowski U, Domschke K, Biersova E, Lawford B, Young R, Voisey J, *et al.* Dopamine D₃ receptor gene variation: impact on electroconvulsive therapy response and ventral striatum responsiveness in depression. *Int J Neuropsychopharmacol* 2013, 16: 1443–1459.
 47. Bousman CA, Katalinic N, Martin DM, Smith DJ, Ingram A, Dowling N, *et al.* Effects of COMT, DRD₂, BDNF, and APOE genotypic variation on treatment efficacy and cognitive side effects of electroconvulsive therapy. *J ECT* 2015, 31: 129–135.
 48. Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci* 2001, 2: 24–32.
 49. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry* 2008, 64: 527–532.
 50. Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor (BDNF) levels in schizophrenia: A systematic review with meta-analysis. *Aust N Z J Psychiatry* 2010, 44: A30.
 51. Brandys MK, Kas MJH, Van Elburg AA, Campbell IC, Adan RAH. A meta-analysis of circulating BDNF concentrations in anorexia nervosa. *World J Biol Psychiatry* 2011, 12: 444–454.
 52. Lin PY. Increase in brain-derived neurotrophic factor in patients with schizophrenia treated with olanzapine: A systemic review and meta-analysis. *J Exp Clin Med* 2012, 4: 119–124.
 53. Fernandes BS, Berk M, Gonçalves C. Decreased peripheral brain-derived neurotrophic factor levels are not specific for bipolar disorder, major depressive disorder or schizophrenia: A meta-analysis. *Bipolar Disord* 2013, 15: 40.
 54. Molendijk ML, Spinhoven P, Polak M, Bus BAA, Penninx BWJH, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: Evidence from a systematic review and meta-analyses on 179 associations (N=9484). *Mol Psychiatry* 2014, 19: 791–800.
 55. Fernandes BS, Molendijk ML, Köhler CA, Soares JC, Leite CMGS, Machado-Vieira R, *et al.* Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: A meta-analysis of 52 studies. *BMC Med* 2015.
 56. Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenkecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis. *J Affect Disord* 2015, 174: 432–440.

57. Polyakova M, Schroeter ML, Elzinga BM, Holiga S, Schoenkecht P, De Kloet ER, *et al.* Brain-derived neurotrophic factor and antidepressive effect of electroconvulsive therapy: Systematic review and meta-analyses of the preclinical and clinical literature. *PLoS One* 2015, 10.
58. Freire TFV, de Almeida Fleck MP, da Rocha NS. Remission of depression following electroconvulsive therapy (ECT) is associated with higher levels of brain-derived neurotrophic factor (BDNF). *Brain Res Bull* 2016, 121: 263–269.
59. Li J, Ye F, Xiao W, Tang X, Sha W, Zhang X, *et al.* Increased serum brain-derived neurotrophic factor levels following electroconvulsive therapy or antipsychotic treatment in patients with schizophrenia. *Eur Psychiatry* 2016, 36: 23–28.
60. Psomiades M, Haesebaert F, Mondino M, Didier A, Galvao F, Brunelin J, *et al.* Early serum BDNF level changes predict remission in patients with treatment-resistant depression receiving electroconvulsive therapy. Preliminary evidence. *Biol Psychiatry* 2016, 79: 401S.
61. Rutten BPF, Arts B, Guloksuz S, Walter S, Drukker M, Peerbooms O, *et al.* Longitudinal alterations in mRNA expression of the BDNF-neurotrophin signaling cascade in lymphocytes correlate with the antidepressant response to electroconvulsive therapy. *Biol Psychiatry* 2016, 79: 400S.
62. Kaija H, Sami A, Martti H, Esa L, Riikka R, Kari M, *et al.* Brain-derived neurotrophic factor (BDNF) polymorphisms G196A and C270T are not associated with response to electroconvulsive therapy in major depressive disorder. *Eur Arch Psychiatry Clin Neurosci* 2007, 257: 31–35.
63. Viikki ML, Järventausta K, Leinonen E, Huuhka M, Mononen N, Lehtimäki T, *et al.* BDNF polymorphism rs11030101 is associated with the efficacy of electroconvulsive therapy in treatment-resistant depression. *Psychiatric Genet* 2013, 23: 134–136.
64. Stephani C, Wolff-Menzler C. Polymorphism of the brain derived neurotrophic factor and electroconvulsive therapy. *Clin Neurophysiol* 2015, 126: e143.
65. Storkebaum E, Lambrechts D, Carmeliet P. VEGF: once regarded as a specific angiogenic factor, now implicated in neuroprotection. *BioEssays* 2004, 26: 943–954.
66. Tseng PT, Cheng YS, Chen YW, Wu CK, Lin PY. Increased levels of vascular endothelial growth factor in patients with major depressive disorder: A meta-analysis. *Eur Neuropsychopharmacol* 2015, 25: 1622–1630.
67. Minelli A, Zanardini R, Abate M, Bortolomasi M, Gennarelli M, Bocchio-Chiavetto L. Vascular Endothelial Growth Factor (VEGF) serum concentration during electroconvulsive therapy (ECT) in treatment resistant depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2011, 35: 1322–1325.
68. Minelli A, Maffioletti E, Zanardini R, Abate M, Bortolomasi M, Gennarelli M, *et al.* Vascular endothelial growth factor (VEGF) serum: Putative predictive biomarkers for the electroconvulsive therapy (ECT) in depressed patients. *Int J Neuropsychopharmacol* 2012, 15: 190–191.
69. Minelli A, Maffioletti E, Bortolomasi M, Conca A, Zanardini R, Rilloso L, *et al.* Association between baseline serum vascular endothelial growth factor levels and response to electroconvulsive therapy. *Acta Psychiatr Scand* 2014, 129: 461–466.
70. Segi-Nishida E, Warner-Schmidt JL, Duman RS. Electroconvulsive seizure and VEGF increase the proliferation of neural stem-like cells in rat hippocampus. *Proc Natl Acad Sci U S A* 2008, 105: 11352–11357.
71. Warner-Schmidt JL, Madsen TM, Duman RS. Electroconvulsive seizure restores neurogenesis and hippocampus-dependent fear memory after disruption by irradiation. *Eur J Neurosci* 2008, 27: 1485–1493.
72. Fujiki M, Abe E, Nagai Y, Shiqi K, Kubo T, Ishii K, *et al.* Electroconvulsive seizure-induced VEGF is correlated with neuroprotective effects against cerebral infarction: Involvement of the phosphatidylinositol-3 kinase/Akt pathway. *Exp Neurol* 2010, 225: 377–383.
73. Elfving B, Wegener G. Electroconvulsive seizures stimulate the vegf pathway via mTORC1. *Synapse* 2012, 66: 340–345.
74. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: A meta-analysis of 30 studies. *Biol Psychiatry* 2013, 74: 15–25.
75. Liu Y, Ho RCM, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF- α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. *J Affect Disord* 2012, 139: 230–239.
76. Hiles SA, Baker AL, de Malmanche T, Attia J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: Exploring the causes of heterogeneity. *Brain Behav Immun* 2012, 26: 1180–1188.
77. Bai YM. Comparison of inflammatory cytokine levels among type I/type II and hypomanic/euthymic/ depressive states of bipolar disorder. *Eur Neuropsychopharmacol* 2014, 24: S430.
78. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, *et al.* A meta-analysis and meta-regression of immune activation in posttraumatic stress disorder. *Biol Psychiatry* 2015, 77: 61S–62S.
79. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimäki M. Cumulative meta-analysis of interleukins 6 and 1 β , tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun* 2015, 49: 206–215.
80. Guo J, Liu C, Wang Y, Feng B, Zhang X. Role of T helper lymphokines in the immune-inflammatory pathophysiology of schizophrenia: Systematic review and meta-Analysis. *Nord J Psychiatry* 2015, 69: 364–372.
81. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biol Psychiatry* 2011, 70: 663–671.
82. Yoshimura R, Nakamura J. Plasma levels of IL-6, 5-HTT gene polymorphism, and SSRIs responses in patients with major depressive disorder. *Eur Neuropsychopharmacol* 2013, 23: S398.
83. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *J Affect Disord* 2013, 150: 736–744.
84. Khandaker G, Pearson R, Zammit S, Lewis G, Jones P. Serum interleukin-6 and c-reactive protein in childhood as predictors of depression and psychosis in young adult life: A population-based longitudinal study. *Schizophr Bull* 2015, 41: S144–S145.
85. Du B, Lu L, Zhao H, Li H, Zhang S. The influence of modified electroconvulsive therapy on serum interleukin-6 in schizophrenic patients. *Chin J Clin Rehabil* 2003, 7: 520.
86. Hestad KA, Tønseth S, Støen CD, 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.
87. Lehtimäki K, Keränen T, Huuhka M, Palmio J, Hurme M, Leinonen E, *et al.* Increase in plasma proinflammatory cytokines after electroconvulsive therapy in patients with depressive disorder. *J ECT* 2008, 24: 88–91.
88. Fluitman SBAHA, Heijnen CJ, Denys DAJP, Nolen WA, Balk FJ, Westenberg HGM. Electroconvulsive therapy has acute immunological and neuroendocrine effects in patients with major depressive disorder. *J Affect Disord* 2011, 131: 388–392.
89. Rotter A, Biermann T, Stark C, Decker A, Demling J, Zimmermann R, *et al.* Changes of cytokine profiles during

- electroconvulsive therapy in patients with major depression. *J ECT* 2013, 29: 162–169.
90. Stelzhammer V, Guest PC, Rothermundt M, Sondermann C, Michael N, Schwarz E, *et al.* Electroconvulsive therapy exerts mainly acute molecular changes in serum of major depressive disorder patients. *Eur Neuropsychopharmacol* 2013, 23: 1199–1207.
 91. Boufidou F, Zoga M, Oulis P, Pliatsika P, Fotelin S, Papadimitriou GN, *et al.* Immune changes related to tryptophan metabolism after electroconvulsive therapy (ECT) in major depressive disorder (MDD) patients. *Neurol Psychiatry Brain Res* 2014, 20: 7–8.
 92. Kartalci S, Karabulut AB, Erbay LG, Acar C. Effects of Electroconvulsive Therapy on Some Inflammatory Factors in Patients With Treatment-Resistant Schizophrenia. *J ECT* 2016.
 93. 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.
 94. Tourjman V, Kouassi T, Koué MT, Rocchetti M, Fortin-Fournier S, Fusar-Poli P, *et al.* Antipsychotics' effects on blood levels of cytokines in schizophrenia: A meta-analysis. *Schizophr Res* 2013, 151: 43–47.
 95. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA, *et al.* Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Mol Psychiatry* 2011, 16: 751–762.
 96. Elomaa AP, Niskanen L, Herzig KH, Viinamäki H, Hintikka J, Koivumaa-Honkanen H, *et al.* Elevated levels of serum il-5 are associated with an increased likelihood of major depressive disorder. *BMC Psychiatry* 2012, 12.
 97. Dahl J, Ormstad H, Aass HCD, Malt UF, Bendz LT, Sandvik L, *et al.* The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. *Psychoneuroendocrinology* 2014, 45: 77–86.
 98. Dahl J, Andreassen OA, Verkerk R, Malt UF, Sandvik L, Brundin L, *et al.* Ongoing episode of major depressive disorder is not associated with elevated plasma levels of kynurenine pathway markers. *Psychoneuroendocrinology* 2015, 56: 12–22.
 99. Maes M, Berk M, Goehler L, Song C, Anderson G, Galecki P, *et al.* Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med* 2012, 10.
 100. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. *Genes Dev* 2009, 23: 781–783.
 101. Sun H, Kennedy PJ, Nestler EJ. Epigenetics of the depressed brain: Role of histone acetylation and methylation. *Neuropsychopharmacology* 2013, 38: 124–137.
 102. Cha DS, Kudlow PA, Baskaran A, Mansur RB, McIntyre RS. Implications of epigenetic modulation for novel treatment approaches in patients with schizophrenia. *Neuropharmacology* 2014, 77: 481–486.
 103. Andersen AM, Dogan MV, Beach SRH, Philibert RA. Current and future prospects for epigenetic biomarkers of substance use disorders. *Genes* 2015, 6: 991–1022.
 104. Lockwood LE, Su S, Youssef NA. The role of epigenetics in depression and suicide: A platform for gene-environment interactions. *Psychiatry Res* 2015, 228: 235–242.
 105. de Jong JOZ, Arts B, Boks MP, Sienaert P, van den Hove DLA, Kenis G, *et al.* Epigenetic effects of electroconvulsive seizures. *J ECT* 2014, 30: 152–159.
 106. Kleimann A, Kotsiari A, Sperling W, Gröschl M, Heberlein A, Kahl KG, *et al.* BDNF serum levels and promoter methylation of BDNF exon I, IV and VI in depressed patients receiving electroconvulsive therapy. *J Neural Transmiss* 2015, 122: 925–928.
 107. Kolshus E, Blackshields G, McLoughlin D, Ryan K. A deep sequencing study of circulating microRNA levels in peripheral whole blood following ECT for severe depression. *Int J Neuropsychopharmacol* 2014, 17: 120–121.
 108. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in Major Depressive Disorder: A meta-analysis of voxel based morphometry studies. *J Affect Disord* 2012, 138: 9–18.
 109. Murphy ML, Frodl T. Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. *Biol Mood Anxiety Disord* 2011, 1: 3.
 110. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. *Eur Neuropsychopharmacol* 2012, 22: 1–16.
 111. Liao Y, Huang X, Wu Q, Yang C, Kuang W, Du M, *et al.* Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *J Psychiatry Neurosci* 2013, 38: 49–56.
 112. Wen MC, Steffens DC, Chen MK, Zainal NH. Diffusion tensor imaging studies in late-life depression: Systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2014, 29: 1173–1184.
 113. Wise T, Radua J, Nortje G, Cleare AJ, Young AH, Arnone D. Voxel-Based Meta-Analytical Evidence of Structural Disconnectivity in Major Depression and Bipolar Disorder. *Biol Psychiatry* 2016, 79: 293–302.
 114. Chi KF, Korgaonkar M, Grieve SM. Imaging predictors of remission to anti-depressant medications in major depressive disorder. *J Affect Disord* 2015, 186: 134–144.
 115. Joshi SH, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, *et al.* Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. *Biol Psychiatry* 2016, 79: 282–292.
 116. Nordanskog P, Dahlstrand U, Larsson MR, Larsson EM, Knutsson L, Johanson A. Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *J ECT* 2010, 26: 62–67.
 117. Tendolkar I, van Beek M, van Oostrom I, Mulder M, Janzing J, Voshaar RO, *et al.* Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: a longitudinal pilot study. *Psychiatry Res* 2013, 214: 197–203.
 118. Abbott CC, Jones T, Lemke NT, Gallegos P, McClintock SM, Mayer AR, *et al.* Hippocampal structural and functional changes associated with electroconvulsive therapy response. *Transl Psychiatry* 2014, 4: e483.
 119. Jorgensen A, Magnusson P, Hanson LG, Kirkegaard T, Benveniste H, Lee H, *et al.* Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression. *Acta Psychiatr Scand* 2016, 133: 154–164.
 120. Dukart J, Regen F, Kherif F, Colla M, Bajbouj M, Heuser I, *et al.* Electroconvulsive therapy-induced brain plasticity determines therapeutic outcome in mood disorders. *Proc Natl Acad Sci U S A* 2014, 111: 1156–1161.
 121. Nordanskog P, Larsson MR, Larsson EM, Johanson A. Hippocampal volume in relation to clinical and cognitive outcome after electroconvulsive therapy in depression. *Acta Psychiatr Scand* 2014, 129: 303–311.
 122. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. *Neurosci Biobehav Rev* 2013, 37: 152–163.
 123. Talarowska M, Berk M, Maes M, Galecki P. Autobiographical memory dysfunctions in depressive disorders. *Psychiatry Clin Neurosci* 2016, 70: 100–108.

124. Fraser LM, O'Carroll RE, Ebmeier KP. The effect of electroconvulsive therapy on autobiographical memory: A systematic review. *J ECT* 2008, 24: 10–17.
125. Hoogenboom WS, Perlis RH, Smoller JW, Zeng-Treitler Q, Gainer VS, Murphy SN, *et al.* Limbic system white matter microstructure and long-term treatment outcome in major depressive disorder: a diffusion tensor imaging study using legacy data. *World J Biol Psychiatry* 2014, 15: 122–134.
126. Nobuhara K, Okugawa G, Minami T, Takase K, Yoshida T, Yagyu T, *et al.* Effects of electroconvulsive therapy on frontal white matter in late-life depression: a diffusion tensor imaging study. *Neuropsychobiology* 2004, 50: 48–53.
127. Lyden H, Espinoza RT, Pirnia T, Clark K, Joshi SH, Leaver AM, *et al.* Electroconvulsive therapy mediates neuroplasticity of white matter microstructure in major depression. *Transl Psychiatry* 2014, 4: e380.
128. Nickl-Jockschat T, Gallagher NP, Kumar V, Hoffstaedter F, Brüggemann E, Habel U, *et al.* Are morphological changes necessary to mediate the therapeutic effects of electroconvulsive therapy? *Eur Arch Psychiatry Clin Neurosci* 2015: 1–7.
129. Saito S, Yoshikawa D, Nishihara F, Morita T, Kitani Y, Amaya T, *et al.* The cerebral hemodynamic response to electrically induced seizures in man. *Brain Res* 1995, 673: 93–100.
130. Uesugi H, Toyoda J, Iio M. Positron emission tomography and plasma biochemistry findings in schizophrenic patients before and after electroconvulsive therapy. *Psychiatry Clin Neurosci* 1995, 49: 131–135.
131. Escobar R, Rios A, Montoya ID, Lopera F, Ramos D, Carvajal C, *et al.* Clinical and cerebral blood flow changes in catatonic patients treated with ECT. *J Psychosom Res* 2000, 49: 423–429.
132. Mervaala E, Könönen M, Föhr J, Husso-Saastamoinen M, Valkonen-Korhonen M, Kuikka JT, *et al.* SPECT and neuropsychological performance in severe depression treated with ECT. *J Affect Disord* 2001, 66: 47–58.
133. Milo TJ, Kaufman GE, Barnes WE, Konopka LM, Crayton JW, Ringelstein JG, *et al.* Changes in regional cerebral blood flow after electroconvulsive therapy for depression. *J ECT* 2001, 17: 15–21.
134. Fabbri F, Henry ME, Renshaw PF, Nadgir S, Ehrenberg BL, Franceschini MA, *et al.* Bilateral near-infrared monitoring of the cerebral concentration and oxygen-saturation of hemoglobin during right unilateral electro-convulsive therapy. *Brain Res* 2003, 992: 193–204.
135. Johanson A, Gustafson L, Risberg J, Rosén I, Sjöbeck M, Silfverskiöld P. Long-term follow-up in depressed patients treated with electroconvulsive therapy. *J ECT* 2005, 21: 214–220.
136. Takano H, Kato M, Inagaki A, Watanabe K, Kashima H. Time course of cerebral blood flow changes following electroconvulsive therapy in depressive patients - Measured at 3 time points using single photon emission computed tomography. *Keio J Med* 2006, 55: 153–160.
137. Kohn Y, Freedman N, Lester H, Krausz Y, Chisin R, Lerer B, *et al.* 99mTc-HMPAO SPECT study of cerebral perfusion after treatment with medication and electroconvulsive therapy in major depression. *J Nucl Med* 2007, 48: 1273–1278.
138. Fujita Y, Takebayashi M, Hisaoka K, Tsuchioka M, Morinobu S, Yamawaki S. Asymmetric alternation of the hemodynamic response at the prefrontal cortex in patients with schizophrenia during electroconvulsive therapy: A near-infrared spectroscopy study. *Brain Res* 2011, 1410: 132–140.
139. Takano H, Motohashi N, Uema T, Ogawa K, Ohnishi T, Nishikawa M, *et al.* Differences in cerebral blood flow between missed and generalized seizures with electroconvulsive therapy: A positron emission tomographic study. *Epilepsy Res* 2011, 97: 225–228.
140. Berggren Å, Gustafson L, Höglund P, Johanson A. A long-term follow-up of clinical response and regional cerebral blood flow changes in depressed patients treated with ECT. *J Affect Disord* 2014, 167: 235–243.
141. Volkow ND, Bellar S, Mullani N, Jould L, Dewey S. Effects of electroconvulsive therapy on brain glucose metabolism: A preliminary study. *Convuls Ther* 1988, 4: 199–205.
142. Henry ME, Schmidt ME, Matochik JA, Stoddard EP, Potter WZ. The effects of ECT on brain glucose: A pilot FDG PET study. *J ECT* 2001, 17: 33–40.
143. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell C, Sackeim HA, *et al.* Decreased regional brain metabolism after ECT. *Am J Psychiatry* 2001, 158: 305–308.
144. Yuuki N, Ida I, Oshima A, Kumano H, Takahashi K, Fukuda M, *et al.* HPA axis normalization, estimated by DEX/CRH test, but less alteration on cerebral glucose metabolism in depressed patients receiving ECT after medication treatment failures. *Acta Psychiatr Scand* 2005, 112: 257–265.
145. Suwa T, Namiki C, Takaya S, Oshita A, Ishizu K, Fukuyama H, *et al.* Corticolimbic balance shift of regional glucose metabolism in depressed patients treated with ECT. *J Affect Disord* 2012, 136: 1039–1046.
146. Beall EB, Malone DA, Dale RM, Muzina DJ, Koenig KA, Bhattacharya PK, *et al.* Effects of electroconvulsive therapy on brain functional activation and connectivity in depression. *J ECT* 2012, 28: 234–241.
147. Abbott CC, Lemke NT, Gopal S, Thoma RJ, Bustillo J, Calhoun VD, *et al.* Electroconvulsive therapy response in major depressive disorder: a pilot functional network connectivity resting state fmri investigation. *Front Psychiatry* 2013, 4: 10.
148. Wei Q, Tian Y, Yu Y, Zhang F, Hu X, Dong Y, *et al.* Modulation of interhemispheric functional coordination in electroconvulsive therapy for depression. *Transl Psychiatry* 2014, 4: e453.
149. Liu Y, Du L, Li Y, Liu H, Zhao W, Liu D, *et al.* Antidepressant Effects of Electroconvulsive Therapy Correlate With Subgenual Anterior Cingulate Activity and Connectivity in Depression. *Medicine* 2015, 94: e2033.
150. Van Waarde JA, Scholte HS, van Oudheusden LJB, Verwey B, Denys D, van Wingen GA. A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. *Mol Psychiatry* 2015, 20: 609–614.
151. Mulders PCR, van Eijndhoven PFP, Pluijmen J, Schene AH, Tendolkar I, Beckmann CF. Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy. *J Affect Disord* 2016, 205: 130–137.