

Epigenetics, resilience and brain stimulation

Citation for published version (APA):

Nagy Adel, Y. (2020). *Epigenetics, resilience and brain stimulation: advances in the mechanistic and therapeutic utility in patients with affective (PTSD and mood) disorders*. [Doctoral Thesis, Maastricht University]. <https://doi.org/10.26481/dis.20200123ny>

Document status and date:

Published: 01/01/2020

DOI:

[10.26481/dis.20200123ny](https://doi.org/10.26481/dis.20200123ny)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Summary

Psychological adaptation or resilience reflects functional, cognitive and/or behavioral adjustment to contextual (environmental) changes that comprises a key factor in psychological well-being. Lack of (or dysfunctional) adaptation/resilience might contribute to stress-related disorders such as mood disorders and Posttraumatic Stress Disorder (PTSD). Stress-related disorders are also good models to study the interaction between nature and nurture (as both have significant genetic-environmental (GxE) interaction). They can also help study undesirable changes in neuronal function, adaptability, and neuroplasticity to understand how to reverse them to produce remission of symptoms. At the molecular biological level, epigenetic mechanisms may have an important role in the response to rapid environmental change and adaptation.

This thesis focuses and converges on two promising and rapidly evolving areas of neuroscience and psychiatry. These areas are epigenetics and brain stimulation. These 2 evolving fields can help to modify neuronal function, adaptability, and neuroplasticity and to investigate underlying (biological) processes. Stimulation of the brain also reflects exogenously induced interventions and can be seen as an environmental exposure. Thus, the research compiled in this thesis can be divided in two main sections: 'Epigenetics and Resilience' and 'Brain Stimulation' with ECT as the prototype for the purpose of this thesis.

The first section of this thesis focuses on epigenetics as one possible molecular mechanism underlying risk and resilience to stress-related disorders. It starts by providing an overview of recent advances in epigenetics as biomarkers in depression and an overview on epigenetics and PTSD, especially the evolving transgenerational transmission of the effects of PTSD via epigenetic methylation. It then presents our studies showing that higher resilience (that also have an epigenetic/biological component) predicts lower suicidality at 3-year follow-up, as well as lower depression as shown in another study we conducted. It also examines racial differences on the effect of trauma on development of depression. In a third study, non-biological factors such as moral injury and spirituality were also examined in how it impacts and correlates with PTSD symptoms. Finally, it presents our group efforts of establishing epigenetic consortium in PTSD and pooling data to increase the sample size for well-powered more definitive studies.

The second section of this thesis focuses on electroconvulsive therapy (ECT). It starts by reviewing the best way to prevent relapse after induction of remission (using a clinically-indicated acute course of ECT) for depressive episode of mood disorders. It also reviews other indications for ECT, including the emerging evidence that ECT might be of help in treatment-resistant PTSD, and the future direction for ECT research. As a related inquiry to the common indication of ECT in treatment-resistant depression, it also presents our randomized multicenter clinical trial on the effects of continuation of ECT plus medications versus continuation of medication alone on how the combination has significantly better improvement on quality of life. Then, it discusses cutting-edge research in the field, including research into biomarkers and neuroplasticity related to ECT response.

Moreover, in order to find ways to avoid (or minimize) the cognitive side effects of ECT, we examine a novel and focal form of stimulation: Low Pulse Amplitude Seizure Therapy (LAP-ST) for treatment of depressive episodes. In this clinical trial, we specifically examine the feasibility and preliminary evidence that it has less cognitive adverse effects compared to standard ECT. Our proof of concept clinical trial showed that this technique is feasible, and initial data showed LAP-ST to be safe, and with minimal cognitive side effects compared to the standard ECT while retaining efficacy.

Much work needs to be done, but we hope that the work in this thesis gets us a few steps closer to advancing the fields of epigenetics and ECT. We also hope there will be more examination of the interaction of these fields as presented in the discussion in the last chapter of this thesis, where we present a plan for future steps of research in this direction. We then present an addendum chapter on valorization of this knowledge so as to benefit the society, stakeholders, policy makers, as well as, researchers and clinicians and the efforts made to disseminate this information.

Acknowledgements

I highly appreciate the support and contributions of Professor Rutten, thesis promotor as well as those of Professor Sienaert, thesis co-promotor. I also thank the assessment and defense committees for their time and help. I thank the staff and colleagues at Maastricht University for their help and kindness. I am also very appreciative for my family and friends who endured with me during the PhD process as well as their feedback and encouragement.

This PhD journey and the thesis would have not been possible without all the generosity of all the above individuals, as well as that of my patients and my research participants who volunteered for the advancement of science, finding transformative treatments (and a future cures) and to whom I am greatly in dept; and from whom I learned a lot thought-out my medical career.

About the Author

Nagy Youssef's medical training included medical school at Cairo University, Egypt; psychiatry residency at University of South Alabama (Mobile, AL, USA) and postgraduate Consultation-Liaison training at Yale University (New Haven, CT, USA). He also completed a 3-year research fellowship at both Durham VA and Duke University (Durham, NC, USA) and electroconvulsive therapy (ECT) & Transcranial Magnetic Stimulation (TMS) fellowship at Duke University. As a faculty at Duke University, he established and directed a Treatment-Resistant Mood Disorders Outpatient Clinic, supervised residents and medical students in the clinic, in the Duke ECT service, and during weekly ECT rounding. He was one of the ECT and TMS faculty and investigators in the Division of Brain Stimulation & Neurophysiology at Duke. He also taught physicians in the Duke ECT fellowship program and TMS fellowship.

After moving to Augusta, GA, USA, and as a faculty at Medical College of Georgia (MCG), he served as the medical director of acute psychiatric services (psychiatry inpatient and the psychiatric emergency department) at the affiliated Veterans Affairs Medical Center, then developed and currently directs a Mood and Trauma Clinic at MCG, where he also supervises residents and students in the clinic and is an ECT and brain stimulation faculty as well as directs a student clerkship in Mood Disorders.

His primary research interests include mechanistic and therapeutic innovation for treatment-resistant mood disorders, PTSD, and suicide prevention. His methodology and interventions within these areas include: 1) multiple brain stimulation mechanistic probes and therapeutics, including ECT, Transcranial Magnetic Stimulation (TMS), Magnetic Seizure Therapy (MST), and Transcranial Direct Current Stimulation (tDCS), and 2) genomics research. His studies involve primary clinical research, but he has occasionally studied non-human primates and translated the findings to humans.

He has presented his research in over 150 scientific papers and published abstracts. Dr. Youssef has lectured nationally and internationally on many research findings. The research studies he was involved in has been supported by the Department of Veterans Affairs, National Institute of Health, several research foundations, academic institutions, and pharmaceutical and device industries.

His service to the scientific community locally and internationally includes being a member of the Research Ethics Committee for 5 years at the Medical College of Georgia and as a member on the editorial board of several scientific journals.