Epigenetics, resilience and brain stimulation

Valorization of Knowledge

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Affective disorders, including major depressive disorder (MDD), are a leading cause of disability worldwide with a high burden of morbidity and mortality (World Health Organization, 2017). Affective disorders are also a major risk factor for mortality, including both death due to suicide and other medical conditions.

Affective disorders and depressive episodes have long been recognized to result from an interplay between environmental and biological factors (Wankerl et al., 2014). Epigenetics involves functional modifications of genes that are affected by environmental factors. Thus, epigenetics is likely an important mechanism that contributes to the development of and/or relapse from affective disorders. Several studies showed that certain epigenetic changes (mainly hypermethylation) to be associated with suicide and depression.

Treatment-resistant depression (TRD) is defined as MDD that is not responsive to treatment despite two different antidepressant regimens of adequate duration and dosage; 1 out of 3 patients suffering from MDD has TRD (European Medicines Agency, 2013; Kular & Kular, 2018; U.S. Department of Health and Human Services, 2018). Many patients who do not respond to medications and psychotherapy may have a robust response and remission to Electroconvulsive Therapy (ECT).

Another stress related disorder is Posttraumatic Stress Disorder (PTSD), which also causes substantial burden and suffering (American Psychiatric Association, 2013; Department of Veterans Affairs and Department of Defense, 2017). PTSD has a high prevalence in many countries, and is more prevalent in combat veterans representing up to 17% (American Psychiatric Association, 2013; Department of Veterans Affairs and Department of Defense, 2017; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Miao, Chen, Wei, Tao, & Lu, 2018). PTSD has a strong genetic component, evidenced by numerous research studies. For instance, twin studies found estimated heritability ranging from 30% to as high as 72% (Sartor et al., 2011; Stein, Jang, Taylor, Vernon, & Livesley, 2002). Transgenerational studies done with children of holocaust survivors show that PTSD is more likely to occur in certain families, for review see e.g. Youssef et al. (Youssef, Lockwood, Su, Hao, & Rutten, 2018). However, PTSD etiologically involves multifactorial processes and a dynamic and complex interplay of different biological systems and psychological trauma (Ratanatharathorn et al., 2017). Even though it is known that PTSD is heritable, the complex underlying genetic architecture of this disorder is unknown (Ratanatharathorn et al., 2017).

Within the nature-nurture discussions, scholars have proposed to study the complex interaction between genetics and the environment in stress-related mental disorders (depression and PTSD) using epigenetics. Similar research has proven fruitful in the field of cancer genomics. This approach may in fact be uniquely suited to be applied to PTSD research, since the effect of trauma on mental health is suspected to be mediated through epigenetic changes. Consequently, there is growing appreciation of the role of epigenetics in the etiology of PTSD.

Potential applications of the knowledge gained for future research of stress related disorders.

A. Progress in the scientific areas of research of epigenetics and resilience can advance our understanding of the mechanism underlying these stress-related mental disorders and on the other hand may innovate treatment modalities to manage these disorders. The research progress may thereby assist in several manners in the following 2 ways:
   1) Sub-classifying PTSD and depressive episodes of mood disorders with the help of epigenetic biological markers. This can improve possibilities in personalizing diagnosis and treatment interventions (Feng & Youssef, 2019).
   2) Epigenetics plays an important role in improving our understanding of the interplay between environment and underlying genetics, and identifying mediating biological processes, which may be targeted for modulation by interventions, such as medication, lifestyle and dietary components.
B. Also, based on the findings of this thesis, the identification of factors and mechanisms involved in co-determining and/or mediating differential susceptibility and resilience to the effects of trauma and other exposures may enable novel preventative and treatment modalities for stress-related disorders. Moreover, brain stimulation interventions also can play important roles in the treatment of stress disorders especially the most powerful of these interventions, namely ECT (Lisanby, 2007; Rush et al., 2006).

Potential applications of the knowledge gained for improving patient care and translational research to prevent and/or treat stress-related disorders:[*]

Some studies have already identified epigenetics markers that can be tested clinically and can be used in clinical care not too far in the future. This can, for instance, help in attempts for predicting inter-individual differences in response to treatment modalities, i.e. personalized medicine.

Precision medicine can benefit both the patient and clinician in terms of saving suffering, money, time, and frustration (Feng & Youssef, 2019). Epigenetic biomarkers have been suggested (at least in some initial studies) to predict response to pharmacological treatment in depression (Goud Alladi, Etain, Bellivier, & Marie-Claire, 2018). Promising studies found that hypomethylation of genes related to the serotonin transporter (Domschke et al., 2014) and receptor (Wang et al., 2018) predicted impaired response to escitalopram. Also, another study found hypermethylation at a different gene, the IL-11 gene promoter, predicted favorable response to escitalopram and decreased response to nortriptyline (Powell et al., 2013). However, in order to reduce false-positive findings, the field warrants adequately powered studies with an agnostic, genome-wide approach and using a discovery as well as a replication approach.

Regarding epigenetics and ECT, data have both suggested epigenetic modifications by ECT in animals, and on a different front, initial human data examined epigenetics as biomarkers of treatment response (Feng & Youssef, 2019). Initial data of epigenetic modifications produced by electroconvulsive seizures (ECS) has been presented by a review paper (de Jong et al., 2014). This paper reviewed all rodent studies. All studies in the review have multiple epigenetic effects that are suggested to modulate the therapeutic effects of ECT. This included increased histone acetylation in c-Fos, BDNF, and CREB genes, demethylation of the BDNF promoter, and changes in levels of various micro-RNAs.

Initial human studies also examined epigenetics as predictors of treatment response for ECT (Kleimann et al., 2015), and was further supported by a follow-up study (Neyazi et al., 2018). The initial human study found that both ECT remitters and responders had significantly lower baseline methylation percentage in the BDNF promoter when compared to non-responders (Kleimann et al., 2015). They proposed the potential application of BDNF promoter methylation as a predictive biomarker for ECT. The follow-up study examined the methylation of the promoter for p11, (a molecule involved in serotonin signaling and upregulation of BDNF) (Neyazi et al., 2018). The researcher studied p11 promoter methylation in a mouse model of depression, and then did a translational proof-of-concept study in humans.

In mice, ECS responders showed hypermethylation of p11 promoter and increased p11 mRNA expression in the PFC. Patients undergoing ECT showed similar findings in serum samples at all-time points, and patients with higher baseline p11 promoter methylation had significantly less depression after ECT treatment. The results suggest that p11 methylation can predict ECT response, which was tested (Feng & Youssef, 2019).

In a separate patient sample, p11 promoter methylation above 72.15% predicted response to ECT with a positive predictive value (PPV) of 90%. The test identified responders with a sensitivity of 70% and specificity of 73%.

This line of inquiry seems promising, and if pursued, can lead to fruitful epigenetic biomarkers of treatment response and precision psychiatry (Yao et al., 2019).

Further studies should also replicate the information in this thesis regarding that hypermethylation of brain-derived neurotrophic factor (BDNF) and tropomycin receptor kinase B (TrkB) hypermethylation are potential biomarkers for suicide. This could, if replicated, be used as a biomarker to help in focused efforts of suicide prevention.

Similarly, further replication studies should examine the accumulating evidence suggesting enduring effects of trauma exposure being passed down to offspring transgenerationally via DNA methylation alterations. This can inform and direct further public health efforts in preventing traumatic child abuse and partner violence and boosting resilience among other programs and initiatives.

Policy, stakeholders, and society:

As mentioned above, epigenetic research can provide both mechanistic understanding and biomarkers of treatment response. Policy makers should improve and allocate funding for the development of epigenetic research and support epigenetic consortia to increase sample size and for the statistical power needed for such research, which involves many multiple comparisons and thousands to millions of variables. We have demonstrated such an example in our collective efforts in developing Epigenome-Wide Consortium in PTSD. We demonstrated that epigenetic meta-analysis (as part of combined effort by the consortium) can be well-powered to identify epigenetic associations.

Also, further programs to boost resilience in both civilians and military veterans can be of help as adjunct treatment of depression and PTSD, or in boosting resilience for prior known traumatic events, for example, prior to deployment in order to prevent PTSD in veterans going to combat zones.

Traumatic experiences violating a certain moral code or specific religious beliefs can be associated with moral injury, and possibly block recovery from PTSD and/or depression. Further

allocation of resources to improve future research in areas related to resilience, the relationship between moral injury and PTSD, as well as the impact of religious involvement and other violations of moral values are warranted, as these help in fostering resilience and providing meaning to life.

Another important movement related to policy makers and society at large is improvement of education about the potential benefit of approved brain stimulation modalities such as Transcranial Magnetic Stimulation (TMS) and ECT. Although ECT is the most effective treatment in psychiatry (especially for treatment resistant mood disorder), it has bad publicity due to lack of education of the public, and erroneous media depictions of ECT as a method of torture rather than treatment. This can have deleterious effects on our patients and provide a serious barrier for care. In many cases, this results in avoiding a much-needed lifesaving treatment. Education campaigns about the role of ECT and these misconceptions, in addition to providing resources for studies to improve the cognitive side effects of ECT, would prove very helpful. Another application for this thesis is the use of both medications and ECT, rather than either alone, for maintenance of treatment-resistant patients with depression. We have shown in both a review of the literature, as well as in the analysis of the Prolonged Remission in Depressed Elderly (PRIDE) study, that the combination of ECT with medications helps patients to stay well in remission and also to improve quality of life and overall net health benefits compared with medications alone in treatment-resistant depression.

In order to mitigate the cognitive side effects of ECT that can discourage many patients indicated for ECT from receiving it, we presented a novel and promising technique of ECT named Low Pulse Amplitude Seizure Therapy (LAP-ST). We have presented a proof of concept clinical trial showing it to be feasible, safe, and with minimal or no cognitive side effects compared to the standard ECT techniques. We followed also with another pilot randomized clinical trial (not included in this thesis) using low amplitude-titrated seizure therapy, which was similarly promising (Youssef et al., 2019). A replication with a larger clinical trial may confirm these results can have substantial benefits on patients in terms of minimizing or avoiding memory and cognitive side effects during such treatments.

Much work needs to be done, but we hope that this work does not only get us a bit closer to advancing these fields, but also sheds some light on the important questions in these fields with widespread implication in helping patients and the society at large.

Dissemination towards implementation:

All the studies presented in this thesis have been submitted and are now published in peer-reviewed journals to help dissemination and implementation by clinicians, educators and policy makers. In addition, many of these studies have been presented as abstracts, posters and/or oral presentations in targeted scientific meetings for researchers, and others for clinicians. Some were presented as oral presentations to patient advocacy groups. Some studies also motivated media requests for interviews, and the information was disseminated by the interviews with journalists and presented in newspaper articles about the research and its findings, as well as radio and TV interviews locally, nationally, and internationally in an effort to speed the knowledge dissemination and subsequent implementation (including directions on how it can be implemented). These efforts would benefit the largest number of patients possible, help direct policy, and help decrease stigma of mental illness and of certain treatment modalities.

*****Parts adopted from Feng T, Youssef NA. Can epigenetic biomarkers lead us to precision medicine in predicting treatment response and remission for patients being considered for ECT? Psychiatry Res. 2019 Oct 28:112659. doi: 10.1016/j.psychres.2019.112659. [Epub ahead of print] PubMed PMID: 31703983.