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EPIGENETICS, RESILIENCE, COMORBIDITY AND TREATMENT OUTCOME

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SUMMARY

Personalized or precision medicine is a relatively new promising concept which is gaining momentum in all branches of medicine including psychiatry and neurology. Psychiatry and neurology are medical specialties dealing with diagnosis, prevention and treatment of brain disorders which are the main causes of years lived with disability worldwide as well as shortened life. Despite a huge progress in clinical psychopharmacology and neuropharmacology, the treatment outcome for many psychiatric disorders and neurologic diseases has remained unsatisfactory. With aging, comorbidities are more the rule, than an exception and may significantly influence on the final treatment outcome. Epigenetic modulation, resilience and life style are key determinants of the health and very important issues for understanding therapeutic mechanisms and responses. There is a hope that epigenetic profiling before treatment could be used in near future to increase the likelihood of good treatment response by selecting the appropriate medication. The aim of this paper is to offer an overview of the main aspects of epigenetic modulation, resilience and comorbidities and their role in developing the concept of personalized medicine. While waiting for more precise and reliable treatment guidelines it is possible to increase treatment effectiveness in psychiatry and neurology by enhancing individual resilience of patients and managing comorbidities properly.

Key words: *treatment outcome – resilience - comorbidity – syndemics – epigenetics - personalized medicine*

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INTRODUCTION

Personalized or precision medicine is an attractive, relatively novel concept which is gaining momentum in all branches of medicine including psychiatry and neurology (Ozomaro et al. 2013, Gotovac et al. 2014, Wium-Andersen et al. 2017). All patients ask for the most effective medication as well as all clinicians would like to offer to their patients the optimal treatment (Sereti 2018), but in everyday clinical practice both sides often do not achieve their desired level of success. Despite the significant progress in understanding etiology and pathogenesis of neurological and psychiatric disorders and availability of a number of new drugs, treatment outcomes of many neurologic diseases and mental disorders in our "century of mind" remain poor in both short term and long term course of the treatment. Huge number of psychiatric and neurologic patients does not respond in satisfactory way with respect to the magnitude of therapeutic response, the persistence of the remission and the length of life. Insufficient treatment response, treatment decrement and treatment resistance are commonly associated with low resilience as well as with comorbidity, syndemics and disease chronification. Major mental and neurologic illnesses are typically chronic disorders with a waxing and waning course and a lot of comorbid problems and illness progression. The high rate of treatment failures, the low effectiveness of psychiatric and neurologic medicines and rigid and mechanistic pharmaco-centric treatment are currently in contention, both outside and within the fields of psychiatry and neurology. Due to non-satisfactory treatment effectiveness related to blockbuster medicines, there has been an increasing concern that clinical psycho- and neuropharmacology have lost their proper way. The philosophy behind personalized medicine is that every patient is a unique person with a unique biology and comorbidity, personality features and environment which may be very important for the choice of medical treatment in order to improve therapeutic effectiveness and efficiency. In other words, personalized medicine is expected to fit individual patient's epigenetics, pathophysiology and comorbidity to enhance resilience and obtain full recovery.

What causes an optimal or good therapeutic outcome and how to achieve it is a fundamental question from the perspective of predictive, preventive, and person-centered medicine (see Jakovljevic 2013a,b,c). The challenge for contemporary thinking about treatment outcome, including therapeutic response, recovery and resistance, arises from the way we understand and treat mental and neurologic disorders. Positive treatment outcome is strongly associated with person-centered approach in therapy, favorable epigenetic mechanisms, level of patient's resilience, creativity of both, doctors and patients, patient-doctor partnership and alliance, and positive therapeutic narratives. In order to increase treatment efficacy and efficiency, including preventing and overcoming treatment resistance, the authors have been trying to develop the concept of creative, person-centered, recovery-oriented pharmacotherapy (Jakovljevic 2010). The key terms of this concept are: the focus on

person in treatment instead of blockbuster and stratified medicine approaches, synergistic drug combinations, enhancing resilience and salutogenesis, not only decreasing illness but also increasing wellness, reconstructing disease and therapeutic narratives, and promoting creativity, therapeutic alliance and partnership.

Epigenetics, resilience and comorbidities are very interesting topics from the perspective of treatment outcome because they incorporate complex interactions between environmental and intrinsic factors both in the development of the disease and its treatment and outcome. Epigenetic alterations are involved in a diverse set of processes and implicated in a variety of mental disorders and somatic diseases. The reversibility of epigenetic defects makes epigenetic disorders and diseases amenable to therapeutics (Shamsi et al. 2017) while the identification of epigenetic dysfunctions gives an opportunity to consider new treatment approaches (Tripathy 2011). The concept of translational medicine implies the application of latest scientific research in diagnostics, prevention and treatment of diseases, all in the spirit of evidence based medicine for the best patients' outcome. It is well known that different patients with the same diagnosis or the same symptoms react differently to same therapy. That's why it is considered that every patient should be treated individually although the use of comprehensive therapeutic protocols is of great benefit and today´s modern clinical approach is increasingly turning to the concept of personalized medicine. Prediction science about the way things will be in future is very important component of personalized or precision medicine. Psychiatry and neurology have strived to understand pathophysiology of mental and brain disorders in order to predict and improve treatment response in their patients and to develop new treatments. In these efforts they can significantly help each other. The best predictions will need to take into account phenomenological features, clinical risk factors and molecular, epigenetic and neuroimaging biomarkers data. Living in the era of variety of omics and big data, interdisciplinary and transdisciplinary studies of mental disorders and neurologic diseases will improve our further understanding, their pathogenesis, comorbidities and opportunities for more successful prevention and treatment enhancing the positive impact of precision medicine.

The aim of this paper is to offer an overview of the main aspects of epigenetic modulation, resilience and comorbidities and their role in developing the concept of personalized medicine. While waiting for more precise and reliable treatment guidelines it is possible to increase treatment effectiveness in psychiatry and neurology by enhancing individual resilience of patients and managing comorbidities properly.

RECOVERY ORIENTED TREATMENT OUTCOME

Treatment outcome refers to a range of end points, including response, remission, recovery, relapse, and recurrence. However, these terms have been used inconsistently with different meanings (see McMahon 2014, Carbon & Correl 2014). Response is a relative term referring to a clinical improvement of a patient's overall pathology, even though he may have specific symptoms (patient may be minimally, moderately, much and fully improved). Remission is an absolute term meaning the sustained absence of significant, but not necessarily all, clinical signs and symptoms. Recovery is an outcome domain that combines symptomatic remission with achieving premorbid or optimal functional level and quality of life. According to some proposals, relapse should be defined as deterioration in patient's health after a temporary improving, and recurrence as the return of disease or disorder after a remission, which in psychiatry means appearance of a new episode of mental disorder.

Recently, the concept of personal recovery has become a common thread in psychiatry as well as in other branches of medicine. It involves new thinking approach, more positive attitudes and refined communication and therapeutic skills (Slade 2009, Rufener et al. 2015). This concept is based on resilience phenomenon and ideas of patient's self-determination and self-management. It includes set of values about patients' right to create a meaningful life for themselves with or without the presence of mental disorder or somatic/neurologic disease. The concept of recovery oriented treatment is essential in the context of creative psycho/neuropharmacology. Guiding principles of recovery oriented treatment are presented on table 1.

Table 1. Guiding principles of recovery oriented treatment (Slade 2009, Rufener et al. 2015, Vaillant 2015, Blackburn & Epel 2018)

1. There are many pathways to recovery
2. Recovery exists on a continuum of improved health and full wellness/well-being
3. Recovery is strongly related to the concept of positive mental health
4. Recovery is predicated on resilience
5. Recovery involves a process of healing, self-redefinition and self-directedness (life script change)
6. Recovery involves resilient thinking, mindfulness training and new purpose in life
7. Recovery involves re/joining and re/building a creative life in the community
8. Recovery involves authentic self-actualization
9. Recovery involves supportive environment, family, peers and allies
10. Recovery involves physical activity and eating for optimal cell health against oxidative stress, inflammation and insulin resistance.

In spite of varieties in measuring recovery-oriented outcomes, the fore-mentioned principles illustrate efficient guidelines for recovery oriented treatment. Recovery oriented treatment approach is predicated on the fact that patients with any type of mental disorder or somatic disease have, more or less. a capacity to live a fulfilling and meaningful life when provided with proper and efficient support and resources.

RESILENCE AND TREATMENT OUTCOME/RECOVERY

Resilience is a relatively new multidimensional psychobiological concept, essential for understanding of salutogenesis and pathogenesis as well as therapeutic and healing mechanisms and responses. It may be defined as a collection of protective and salutogenic factors that modulate the relationship between a stressful event, adversity or disease, and positive outcomes. Resilience is about the whole person, it includes biological, psychological, social and spiritual dimension of human existence. It enables individuals and communities not only to survive and adapt to challenges and adversities but also to be better off and to grow and thrive (post-traumatic growth) in addition to overcoming a specific adversity. Resilience is a very complex process ranging from surviving to thriving. It includes positive transformation and personal growth, an indivisible part of mental health and health in general, well-being and quality of life as well as recovery and treatment outcome. It is very important to note that "some resilience factors contribute to the development of other resilience factors, and, in consistency with a cascade model, together they contribute to predict personal recovery (Echezarraga et al. 2018). *Primary resilience* is related to maintaining equilibrium, balance and mental health. The level of primary resilience has been regarded as a protective factor against developing illness what means that lack of resilience carries a risk for the appearance of mental disorders and somatic/neurologic diseases. It can be described as "bouncing back" and "rebounding after adversity" and as such it is related to disease prevention. The concept of primary resilience explains why many people do not become ill or do not develop a particular disorder although they are subject to the same kind of adversary events, even after a prolonged period of adversity, with psychological and physical burdens, that cause the disorder in other people (Kalisch et al. 2015). *Secondary resilience* refers to the capability of individuals to cope with illness/disease and successfully recover. It is aimed to regain mental equilibrium and somatic balance after allostatic load and illness. The capability to achieve clinical, functional/social and personal recovery implies the presence of secondary resilience. Placebo response may be an expression of psychological and spiritual resilience (Jakovljevic 2017). In addition to clinical remission, secondary resilience may lead to personal growth and developing a meaningful life after mental illness. On the opposite side, lack of resilience determines onset, course, outcome, distress and burden of mental illness (see Shrivastava et al. 2016). *Tertiary resilience* enables patients to develop a healthy and productive way to live with their illness, helps them to adapt to limitations in life associated with illness and have positive and creative life attitudes. Proactive and more efficacious participation of patients with chronic illness and residual symptoms in their medical treatment is also an expression of tertiary resilience.

The model of primary, secondary and tertiary resilience explains how appropriate resilience enhancing interventions may help in obtaining favorable therapeutic response. The level of and pace by which personal recovery is established is a function of brain resilience, external resources like support, nature of illness and chosen drug treatment. However, resiliency as a treatment target has been largely neglected in the field of therapeutics (Davidson et al. 2005) so the lack of favorable treatment outcome may be commonly related to the treatment focus only on symptoms and illness. The route of clinical, functional and personal recovery lies not only in decreasing illness, but also in enhancing resilience and increasing wellness (Jakovljevic 2017). Full personal recovery does not mean only the absence of symptoms of mental illness, but also the presence of resilience, quality of life and wellness. The concept of resilience enhancement promotes strengths and potentials for wellness which are present in patients instead focusing only on their weakness and pathology. Each patient is unique, responsive and responsible person and within every person there is a force that drives them to strive to self-realization, self-understanding, self-transcendence, and a sense of coherence and control over their own life. Enhancing patients' resilience by emphasizing their strength and opportunities and covering up weakness is an ambitious goal that aims to promote positive mental health in spite of the presence of symptoms (Bolos 2015) and drug treatment failure. Good news is that resilience can be enhanced through learning and training. Resilience training can result in augmented neuroplasticity and balance of neural circuits that modulate reward and motivation, emotion regulation, cognitive reappraisal and executive function, novelty seeking, harm avoidance and fear response, self-directedness, cooperativeness and adaptive social behavior, and self-transcendence. Our five steps model of resilience-enhancing approach includes: 1. SWOT (strength, weakness, opportunities, threats) analysis; 2. Re-construct of disease and therapeutic narratives (DTN); 3. Construct of personal model of individual and family resilience (PMIFR); and 4. Put the PMIFR into operation and practice resilience; 5. Practice personal recovery and creativity.

COMORBIDITY, SYNDEMICS AND TREATMENT OUTCOME/RECOVERY

It is well known fact that some mental disorders and some somatic diseases occur together or following one

another more commonly (comorbidity, hyper-comorbidity) or rarely (anti-comorbidity, hypo-comorbidity) than it would be expected by chance. Generally speaking, one can say the more comorbidity, the poorer the outcome and the less recovery. The comorbid presence of a mental disorder may hinder alleviation of symptoms of a somatic/neurologic disease and process of recovery. Likewise, the presence of a neurologic/somatic disease may hinder remission and recovery from a mental disorder. With aging, the simultaneous presence of multiple pathological conditions is more a rule than an exception, but this problem is not limited to the elderly population (Starfield 2006, Jakovljevic 2009). According to some data disease comorbidity is becoming omnipresent counting for 35-80% of case reports among 20 to 75 year-old patients (Pouladi et al. 2016). Pattern of comorbidities may significantly influence the choice of medication, medication tapering, appearance of unwanted side effects, follow up treatment and achieving optimal therapeutic outcome and full recovery. As comorbidities are indifferent to professional specialties and ever growing sub-specialization in medicine and psychiatry, preventing, treating and managing comorbid or multi-morbid conditions is one of the major aspects of personalized medicine. Here it would be useful to have more precise definition of terms like comorbidity, multi-morbidity and syndemics. According to some proposals the term multi-morbidity should refer to the simultaneous presence of two or more chronic illnesses without any single predominant condition while the term comorbidity should be related to co-existence of two or more pathological conditions when one is predominant (Grumbach 2003). According to Merrill Singer et al. (2017) syndemics represents two or more concurrent or sequential diseases in a population with pathophysiologic interactions, which exacerbate the prognosis and the burden of disease. The presence of comorbidity and syndemics, the social, psychological, and biological reasons that diseases appear together, the ways comorbid diseases affect each other, the pathways of disease interaction, and the way in which the prognosis is affected by the comorbidity are crucial questions from treatment perspective. Mental disorders of all types are more common in patients with somatic illness compared to general population, and to turn around, somatic illnesses of all sorts are more common in psychiatric patients than in general population. Patients with comorbid mental disorders and somatic diseases experience a lot of difficulties in adequate health care. Psychiatrists often fail to recognize and treat somatic disease in their patients, similarly as specialists in other medical disciplines often do not recognize mental disorders in their patients and do not provide appropriate treatment for them.

The conceptual basis of comorbidity rests on theories about interconnections of mind, brain and body, health and disease, wellness and illness (see Jakovljević 2007, 2008). The presence of mental disorders and somatic disease in the same time in the same patient may be understood as a synchronicity as well as causal chains (Table 2,3). Mind impacts the brain and body as well as the body always impacts the brain and mind through very complex brain-heart-gut communications. The state of human mind, that associates psychosocial factors with emotional states such as depression and with behavioral dispositions which include hostility and psychosocial lifestyle stresses, can directly and significantly influence human physiology and health outcomes (Vitetta et al. 2005). The human body is more than just a physical organism or functioning machine that fluctuates between health and illness. It is also the focus of very different beliefs about its social and psychological significance, its structure and its function (Helman 2007). The body image and illness/disease perceptions, which includes all the ways that an individual conceptualizes and experiences her or his body and illness/disease, consciously or unconsciously, is acquired as a part of growing up in particular family, culture and society. The mind-body dualism that dominated in medicine and psychiatry for a long time has been transformed to a more holistic and integrated conceptualization of disease and health (Jakovljević 2008). Its basic view is that mind, brain and body interact and influence each other in health and illness such that comorbidity (see table 2) and syndemics represent result of their complex interactions and processes. Epigenetic mechanisms, oxidative stress, inflammation, insulin resistance and metabolic disorders show very important roles in behavioral pathology and mental disorders as well in many somatic/neurologic diseases like cardiovascular disease, diabetes and cancer (Miller et al. 2008, Del Campo et al. 2018). Some comorbidity between schizophrenia and cardiac disease can be explained by overlapping but not identical mechanisms through which subtle single-nucleotide polimorphisms (SNPs) of ion-channel (Na+, K+, Ca2+) and calcium-transporter-encoding genes modulate the intrinsic excitability of neurons and heart cells (Maeki-Marttunen et al. 2017).

Table 2. Types of comorbidity (Jakovljevic & Ostojic 2013 modified)

Etiological and non-etiological comorbidity
Primary and secondary disease comorbidity
Concurrent (co-occuring, simultaneous) and successive (sequential) comorbidity
Casual (conjugated) and random (non-conjugated) comorbidity
Iatrogenic (complicated) and non-iatrogenic comorbidity
Undirectional and bidirectional comorbidity
Trans-syndromal and trans-nosological comorbidity
Diagnostic and prognostic comorbidity
Homotypic and heterotypic comorbidity
Concordant and discordant comorbidity
Organic and non-organic comorbidity

Table 3. Somatic disease-Mental disorder Comorbidity (Jakovljevic 2009, Jakovljevic et al. 2010)

- Mental disorders with preexisting somatic diseases: The development of comorbid mental disorder that occurs in relation with a somatic disease might be the result of the distress attributable to the disease or it may be secondary to psychosocial stress associated with it (Anisman et al. 2008).
  - *Somatic disease predisposes to the development of mental disorder*
  - *Somatic disease causes mental disorder (organic or symptomatic mental disorders)*
  - *Mental disorder is a reaction to somatic disease (adjustment disorders, reactive mental disorders) related to negative or auto-destructive emotional response to diagnosis, treatment and loss of future life prospects*
- Somatic diseases with preexisting mental disorder
  - *Mental disorder predisposes to the development of somatic disease (*e.g. depression contributes to the etiology and progression of somatic illness and this relationship may be mediated by immune, neuroendocrine and inflammatory factors as well as by behavioral factors like smoking, low physical activity, alcohol or drug abuse, diet, etc. (see Steptoe 2007).
  - *Somatic diseases caused by the psychopharmacotherapy – iatrogenic comorbidity*
  - *Mental disorder causes somatic disease (psychosomatic disease as a nocebo response)*
- Shared determinants model: Somatic disease and mental disorder are induced or caused by the same predisposing or casual factor („pathogenic interplay" with overlapping signs and symptoms)
  - *shared predisposition and vulnerability (risky personality traits and types; joint genetic abnormalities)*
  - *shared risk factors (low social status, stress, psychotrauma, food intolerance, unhealthy life styles, lack of social support*
  - *shared mechanisms (low resilience, epigenetic dysfunctions, failed or unsuccessful coping or defense mechanisms, oxidative stress, endocrine and immune disruption, inflammation, vital exhaustion, dysfunction of internal healing system, etc.).*

Understanding the specific pathways and brain-heart-gut communications through which mental disorders and somatic/neurologic diseases interact in individual mind-body system and within populations and so increase and multiply adverse health effects and negatively influence treatment outcome is very important from the perspective of personalized medicine. Here arises the question what is the best course of medical treatment for comorbidity and syndemic disorders and how iatrogenic syndemics can be avoided (Singer et al. 2017). Shifting the paradigm from vertical and monomorbid interventions to multi-morbidity, comorbidity and syndemic approach facilitates the association between the successful treatment of mental disorders with the successful treatment for comorbid somatic/neurologic disease, and vice versa.

EPIGENETICS OF RESILIENCE, COMORBIDITY, AND TREATMENT OUTCOME

The etiology as well as the outcome of most psychiatric and somatic/neurologic disorders is multidimensional and predicated on complex interactions between genes and environmental factors. Aberrations of epigenetic mechanisms are critical factors in the initiation and progression of many disorders and diseases (Shamsi et al. 2017). It is well confirmed that many psychiatric disorders (schizophrenia, bipolar disorder, recurrent depression) and neurologic (Parkinson's disease, Alzheimer's disease and other dementias, multiple sclerosis) are associated with aging, epigenetic alterations (see table 4), a loss of neurons and glial cells, and neurodegeneration. Epigenetics suggests a novel pathophysiology and entirely new approach to prevention and treatment in the neurology and psychiatry, but the field is still in its infancy. Epigenetic regulation encompasses multiple levels of gene expression; from direct DNA and histone modifications, which regulate the level of transcription, to interactions with messenger RNAs, regulating the level of translation (Lardenoije et al. 2015). We are not always victims of our genes, in many cases our genes are victims of us. The concept of epigenetic changes has added a new dimension to our understanding of resilience (see table 5), comorbidity, treatment outcome and recovery.

The enormous variation in treatment outcome as well as in resilience and comorbidities may be due to epigenetic influences not only from actual events, but also those that happened many years ago. Treatment outcome may be seen as a result of complex epigenetic interplay involved in treatment, resilience and comorbidity. It seems that aging is accompanied by a substantial shift in epigenetic mechanisms, implying that diseases associated with aging, such as diabetes, coronary heart disease, depression, dementia, Parkinson's disease, etc. might be related to changes in epigenetic regulatory processes. Epigenetic regulation influences on many important neural processes like mitochondrial function, protein folding in the endoplasmic reticulum, nuclear processes such as telomere length and DNA repair, neurogenesis, resilience, learning and memory (del Campo et al. 2018). Epigenetic dysregulation currently attracts great attention as an important protagonist in aging, age-related neurodegenerative disorders, comorbidities and syndemics where it may mediate interactions between

Tablica 4. Epigenetic alterations in some psychiatric and neurologic disorders (Maric & Svrakic 2012, Lovrečić et al. 2013, Vialou et al. 2013, Swathy & Benerjee 2017, Chen et al. 2017, Chuang et al. 2017, Pavlou & Outeiro 2017, Bassi et al. 2017, Huihui et al. 2017, Vitale et al. 2017, Zhang et al. 2018)

Schizophrenia
- *DNA methylation:* Differential global and gene-specific changes in DNA methylation (e.g. for hypomethyleted genes: PSMD5, AEN, FAM20B, LRRN4, and one hypermethylated gene ID2) have been reported with contradictions
- *Histone modifications:* increased expressions of histone methyl-transferases was reported as a significant predictor for diagnosis; histone modifications in few candidate genes may contribute to pathogenesis of prefrontal dysfunction
- *MicroRNA regulation:* Aberrant expression of serum miRNA and postmortem brain indicate disease status

Bipolar disorder
- *DNA methylation:* COMT and PPIELgene methylation increased

Major depression
- *DNA methylation:*Most studies showed BDNF and NR3C1 gene methylation levels were correlated with depression
- *Histone modifications:* increased H3 acetylation and decreased HDAC2 levels in the NAc of depressed humans; HDAC inhibitors show some potential as novel antidepressant agents

Alzheimer's disease
- *DNA methylation:* reduced DNA methylation in the anterior temporal neocortex neuronal nuclei; hyper-methylation of HTERT gene; hypo-methylation of inflammatory genes iNOS, IL-1, and TBF-alfa in the AD cortex
- *Histone modifications:* increased phosphorylated histone H3 in hippocampus, modulation of histone acetylation by HDAC inhibitors improved learning and memories in mouse models, increased acetylation of H3 on BACE1 promoter
- *MicroRNA regulation:* dys-regulation of several miRNAs in brain

Parkinson's disease
- *DNA methylation:* overall reduction of methylation potential; hypo-methylation of SNCA gene in brain, hypo-methylation of CpG islands in the promoter of the SNCA in DNA isolated from peripheral blood leukocytes, alpha-synuclein related reduction of DNMT1 methyl-transferase availability, differential methylation of ARK16, GPNMB, STX1B and CYP2E1, hypo-methylation of TNF-α promoters in substantia nigra pars compacta (SNpc) compared to cortex
- *Histone modifications:* Positive response to HDAC inhibitors in disease models; alpha-synuclein related reduction in histone acetylation and histone gene expression
- *MicroRNA regulation:* differential expression of dopaminergic neuron specific miRNA miR-133b

Huntington's disease
- *DNA methylation:* Increased variability at HTT gene locus
- *Histone modifications:* Beneficial effects of HDACs in disease models, sequestration of proteins with HDAC activity (CBP); increase of histone proteins carrying H3K9 marks in brain and blood tissues
- *MicroRNA regulation:* down-regulation of several miRNS in animal models of disease (AC128, R6/2), high 3'terminal sequence variability of miRNAs, miR-34-b unregulated in plasma of pre-manifest disease patients, miR-9 and miR-9* down-regulated early in the HD cortex, miR-124 down-regulated in both caudate and motor cortex of HD patients, Polycomb repressive complex 2 regulation correlated to a significant up-regulation of five mRNAs (miR-10b-5p, miR-196a-5p, miR-196b-5p, and miR-615-3p) in prefrontal cortexes of HD brains

genetic and environmental risk factors (Lardenoije et al. 2015). Although there are several mechanisms of epigenetic control the strongest connection with aging was found with DNA methylation. As aging is the prime risk-factor of most neurodegenerative diseases and multimorbidities, it is plausible that age-related processes facilitate the development of these illnesses and their comorbidities (Lardenoije et al. 2015).

There are three basic molecular epigenetic mechanisms: DNA methylation, histone modification and microRNA dysregulation. Age-related DNA methylation alterations include epigenetic drift and epigenetic clock phenomena. Epigenetic drift is defined as a global change of DNA methylation caused by random and environmental individual specific factors while the epigenetic clock is defined as a group of progressive epigenetic changes associated with aging at specific genomic sites that are common among individuals and occasional across different tissue types (Jones et al. 2015, Horvath 2013). In simple terms, epigenetic drift represents the tendency of increasing discordance between epigenomes over time, and the epigenetic clock describes age-related similarities (Jones et al. 2015). In 2013 Horvath defined some age-dependent CpG signatures regardless of gender, tissue type, and related diseases, suggesting that methylation is a promising marker for studying human development, aging, and cancer (Horvath 2013). He derived a multitissue age predictor consisting of 353 CpGs called 'DNAm age' (Horvath 2013).

Epigenetic dysregulation currently attracts great attention as an important protagonist in aging and age-related neurodegenerative disorders where it may mediate interactions between genetic and environmental risk factors (Lardenoije et al. 2015). As already said epigenetic clock is an indicator of the true 'biological' age of a tissue including the function of additional endogenous

Table 5. Epigenetic regulation of the hypothalamus-hypophysis-adrenal (HPA) axis and resilience programming by epigenetic modifications (del Campo et al. 2018a)

Location	Resilience programming by epigenetic modifications	Stress risk by epigenetic modifications
Hippocampus	Methylation of NR3C1 ↓	Methylation of NR3C1 ↑
	Histone 3 acetylation ↑	Histone 3 acetylation ↓
Paraventricular nucleus	Methylation of CRF ↑	Methylation of CRF ↑
		Methylation of AVP ↓
		Phosphorylation of MeCP2 at ser421 ↑
Adrenal gland		
Limbic brain (MR, GR)		Methylation of FKBP5 ↓

NR3C1: steroid receptor gene; pMeCP2: phosphorylated protein related to methylation of histones; CRF: corticotrophin releasing factor gene; AVP: arginine vasopressin gene; FKBP5: gene coding for chaperons for the expression of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). Increasing the activity or expression of brain MR may prevent or reverse symptoms of stress-related states and may participate in the prevention and treatment of other psychiatric disorders

and exogenous factors in consideration (Zheng et al. 2016). This is especially important in some neurodegenerative disorders in psychiatry and neurology (Table 4). For instance, it is known that blood tissue of patients with Parkinson's disease (PD) may exhibit signs of accelerated aging (Horvath & Ritz 2015). The exact etiology of most neurodegenerative diseases is unknown. In some cases it is clear that the origin of the disease is predominantly genetic, for others, including sporadic Alzheimer's and Parkinson's disease, the link between genetics and disease development is much more complex. A large number of studies have been conducted to identify causal factors and molecular markers of Parkinson's disease. Several studies have pointed out the role of different genetic pathways in the development of this disease. Understanding epigenetic changes leads to the recognition of changes in gene expression responses to disease progression (Chatterjee et al. 2017). Systematic research on epigenetic signs of Parkinson's disease has led to the recognition of the most consistent epigenetically-modified genes associated with Parkinson's disease (Wen et al. 2016). Several lines of evidence point to a gene-dosage effect of SNCA in PD pathogenesis. Studies have shown hypomethylation of intron 1 SNCA gene in brains of patients with PD. Significantly decreased levels of methylation of CpG island in the promoter of the SNCA patients compared to healthy subjects have also been demonstrated in DNA isolated from peripheral blood leukocytes (Tan et al. 2014). It is also interesting that studies in individuals with alcoholism (Bönsch et al. 2005) and in anorexia patients (Frieling et al. 2007) revealed hypermethylation of the SNCA promoter confirming that the gene could be epigenetically regulated. It is shown that alpha-synuclein sequesters DNA methyltransferase 1 (DNMT1) leading to global DNA hypomethylation in human and mouse brain, including CpG islands upstream of SNCA and other genes. There was also a reduction in the level of nuclear DNMT1 in human postmortal brain patterns from PD and Lewy body dementia patients (DLBs), as well as in the brain of alpha-sinuklein transgenic mice model suggesting that the association of DNMT1 and alpha-sinukleins might result in epigenetic modifications in the brain (Desplats et al. 2011). In addition to SCNA, Parkinson's disease is associated with several other genes that are also regulated by DNA methylation of promoters or RNA-mediated mechanisms. For example, the reduction of DJ1 and parkin expression may result from microRNA mediated mechanisms in PD brains, resulting in mitochondrial disorders such as those caused by Parkin or DJ-1 gene mutations (Miñones-Moyano et al. 2011).

Progression of Alzheimer's disease (AD) is associated with changes in epigenetic markers over the life span. Epigenome-wide analysis studies identified that several genes are regulated by DNA methylation in human brain samples of AD patients. Studies have shown that AD, as well as other types of dementia, generally have a specific epigenetic signature. Expression of the APP gene is shown as partially regulated by the methylation of the multiple CpG sites of its promoter, and hypometilation events were described in AD patients aged over 70 years (Iwata et al. 2014). In addition, PSEN1 gene also showed aberrant methylation status in AD. And finally, the most important protein accumulated in brains of AD patients, amyloid β itself acts as an epigenetic modulator that induces global DNA hypometilation and specific hypermetilation of enzymes associated with its degradation thereby decreasing its expression (Chen et al. 2009). In addition to DNA methylation, the role of histone modifications is also associated with AD. One example is reduced histone acetylation found both in human brain tissue of AD patients as well as in AD mice models (Graff et al. 2012). Gene transcription activity of genes associated with AD has been associated with certain histone markers, such as increased acetylation of H3 on BACE1 promoter (Marques et al. 2012). Although epigenomic changes in AD are potentially suitable targets for therapeutic intervention, so far only histone changes have

been studied in pharmacoepigenomic studies (Delgado-Morales et al. 2017). Today's therapeutic capabilities in almost all neurodegenerative diseases are primarily symptomatic and do not slow down the progression of the disease. Therefore, there is a critical need to develop new drugs and drug targets to protect neurons from degeneration. Further research is needed to detect biomarkers in order to detect the disease as early as possible to allow appropriate preventive treatment. The next step is a comprehensive approach for targeted drug treatment and prevention called precision medicine. Also there is the clinical problem of overlapping of symptoms. For instance, depression in elder is frequently associated with cognitive impairment (Leyhe et al. 2017). Identification of biomarkers of preclinical depression and preclinical dementia, and their response to drug treatment, will be crucial in the development of precision medicine (Trivedi 2016). Additionally, the integration of these biomarkers with neurological, cognitive and psychological assessments will allow easier differentiation of dementia and depression, leading consequently to more successful therapy (Trivedi 2016). Combined with the sporadic and complex nature of neurodegenerative and psychiatric diseases, it is considered that minor aberrancies in the epigenetic machinery can have widespread consequences on gene expression and lead to the development of late-onset neurodegenerative diseases (Lahiri et al. 2009, Mastroeni et al. 2011, Lardenoije et al. 2015).

According to del Campo et al. (2018a) the common origin of risk/resilience to somatic diseases, e.g. cardiovascular diseases and stress related or mental disorders could involve: 1.common anatomical brain structures participating in somatic (e.g. cardiovascular) and behavioral responses; 2.common mechanism at subcellular structures (mitochondria, endoplasmatic reticulum, telomere length) which are regulated by reactive oxygen species (ROS), inflammation, and intracellular calcium in myocytes and neural cells; 3.microbiome effects on the brain, cardiovascular and other somatic systems; and 4. common chemical mediators. The link between somatic diseases and psychiatric disorders is bidirectional and predicated on neuroimmunoendocrine mediators. In spite the fact that studies on epigenetics of the comorbidity are absent for the time being, there are enough data on the epigenetics of mental disorders and somatic diseases that occur together more frequently than it would be expected by chance. Comorbid cardiometabolic and neuropsychiatric disorders may be the result of the anatomical and functional connections between the HPA (CRF, ACTH, cortisol) and the Bad nucleus of stria terminalis – BNST (natriuretic peptides, oxytocin, vasopressin) – (del Campo 2018a). Oxytocin exerts anti-inflammatory and anti-oxidative properties, improves vascular and metabolic functions and might favor resilience. Important brain mechanisms of neurotransmitter metabolism, neuroendocrine functions, synaptic plasticity, and the neural circuity of mood are influenced by cytokine signaling in the brain. Intestinal microbial steady-state imbalances may case a range of metabolic disorders and influencing the gut microbiome through diet consuming psychobiotics may serve to ameliorate some psychiatric disorders. Mechanisms controlling mitochondrial function, protein folding in the endoplasmic reticulum and nuclear processes such as telomere length and DNA repair may be partly the basis of the common susceptibility or resilience to develop cardiometabolic and neuropsychiatric disorders during adulthood (del Campo et al. 2018b). DNA modifications might function as novel biomarkers of exposure, risk or progression of disease. Neuro-imunno-endocrine mediators of comorbidity might be programmed and reprogrammed and epigenetics is already considered as a novel therapeutic area (del Campo et al. 2018a)

Epigenetic regulation of comorbidity is not always linked directly with methylation of specific promoters, but rather to other genetic mechanisms influencing epigenetic changes indirectly. Namely, studies analyzing the promoter methylation status of the angiotensin converting enzyme (ACE), a key regulator of the stress response, showed no association between ACE promoter methylation and depression (Lam et al. 2018). Rather, ACE genetic variants were shown to influence methylation itself and modified the association between depression and methylation. Therefore, the study of genetic variants should not be fully dismissed and may provide the missing link between genetic variation, epigenetic mechanisms, environmental influence and comorbidity in complex diseases. We are still trying to fully elucidate the effects of genetic variation on the epigenetic profile and the resulting phenotype. Genetic epistasis, synergistic heterozygosity, existence of phenotype modifying genes and the principle of the rare variant load could explain colex disease inheritance patterns and the multigenic disease landscape (Chakravorty & Hedge 2018). This vital evidence represents the foundation for understanding disorders with overlapping phenotypes and may provide the basis for understanding the epigenetic regulatory processes, facilitating the discovery of new disease-causing biological mechanisms, their therapeutic targets, and design of novel drugs.

Since the fact that many psychiatric disorders and neurologic diseases do not have satisfactory therapy, the solution to prevention and successful treatment might be hidden in a personalized approach using reliable biomarkers. Putative biomarkers could be indicative of illness vulnerability and probability of comorbidity as well as of effectiveness of particular treatment strategies and prediction of illness recurrence (Anisman & Hayley 2012). Biomarkers are measurable characteristics of biologic function or dysfunction which indicate diagnosis, treatment response, or natural course of disease. Implementation of multifaceted biomarkers, capable of diagnostics, response to therapy monitoring and predicting disease progression seems to be a farfetched proposition. In its place, a combination of different biomarkers specific for each described aspect seems to be a more viable approach.

Table 6. Pharmacoepigenetics in psychiatry and neurology (Stahl 2010, Beaulieu et al. 2011, Vialou et al. 2013, Södersten et al. 2014, Schmitt et al. 2015, Swathy & Banerjee 2017, Figge & Standaert 2017, Lockwood & Youssef 2017, Mythri et al. 2017, Simchovitz et al. 2017, Ji et al. 2017, Kular & Kular 2018)

Antipsychotics
- *Haloperidol:* induces changes in DNA methylation, histone modifications and miRNA expressions
- *Clozapine:* alters expression of histone modifier genes, gene-specific methylation and miRNA expressions; activates brain DNA methylation
- *Sulpiride:* activates brain DNA methylation
- *Olanzapine:* increases methylation in hippocampus
- *Quetiapine:* increases methylation levels (RELN, SLC1A2, MTNR1A, IGF2, H19, BDNF, SLC6A4, and GAD investigated)

Mood stabilizers
- *Lithium:* a negative correlation was reported between the improvement of depressive symptoms after lithium treatment and telomerase activity; decreases BDNF levels, but not statistically significant
- *Valproic acid:* inhibits histone deacethylase (HDAC), increased methylation levels
- *Topiramate:* inhibits HDAC

Antidepressants
- *Imipramine:* reduces *Crf*mRNA lebel and increase DNA methylation at the *Crf* promoter in socially defeated mice
- *Amytriptiline:* reduces DNA methylation, but not by HDAC inhibition
- *Fluoxetine:* increases level of miRNA-16 which targets serotonin transporter (SERT) transcript in 5-HT neurons and decreases SERT expression
- *Escitalopram:* reduces elevated DNA methylation at the P11 promoter leading to an increase in P11 and a decrease in DNMTs in prefrontal cortex
- *S-adenosylmethionine (SAMe)*
- *L-methyfolate:* restores epigenetic balance

Antiparkinsonian drugs
- *Levodopa:* induces an increase in H3K27me3S28 phosphorylation, increased histone H3 phosphorylation at the fosB promoter, increased alpha-synuclein DNA methylation, increased expression of bromodomain and extraterminal proteins

Antidementives
- *Donepezil:* decreases H3-K27 acetylation occupancy of the Fmr1 gene in hippocampus

More precisely, biomarkers may in the end have to be quite particular, relating to specific processes or endophenotypes involved in the disease in question or a biological mechanism (Gotovac et al. 2016). There is an interesting idea that illness comorbidity could be also used as a biomarker (Anisman & Hayley 2012). Biomarkers should direct the physician to the best medicine for a specific patient with personal history, clinical picture, diagnosis and comorbidity that are unique to them. Individualized and person-centered approach with claim "the right treatment for the right person at the right time" is a cornerstone of the personalized medicine. An individual's unique epigenetic and resilience characteristics play a significant role in disease vulnerability, tailoring their therapies and in individual response to specific therapies and treatment outcome. Epigenetics of resilience, comorbidity and treatment outcome is an extremely important issue from the perspective of personalized medicine and creative neuro- and psychopharmacology. According to some reports DNA methylation at the IL6 locus predicted response to classical antidepressant treatment in the Genome-Based Therapeutic Drugs for Depression (see Klenger & Binder 2015). Selective HDAC inhibitors seem to have antidepressant actions, increase levels of the brain-derived neurotrophic factor (BDNF) and show neuroprotective effects in models of stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, etc. (Stahl 2010). Several medications already used in psychiatry and neurology show HDAC inhibitory properties (Table 6). Providing precision medication requires more sophisticated treatment guidelines. Unfortunately, personalized or precision medicine for psychiatric and neurologic disorders is in an early phase of development.

CONCLUSION

Person-centered, personalized or precision medicine is an ideal in psychiatry and neurology. Good news is that in some cases this ideal might become reality. Epigenetics of resilience and comorbidity are very interesting topics from the perspective of predictive, preventive and person-centered medicine. They incorporate complex interactions between environmental and intrinsic factors in the development of the diseases and disorders and their comorbidities as well as in their treatment and outcome. Patients should be evaluated by their total multi-morbidity burden and the pattern of comorbidity that appears with time. Epigenetic mechanisms are accessible therapeutic targets which are already in experimental phase for some significant diseases like cancer, diabetes mellitus, coronary heart

disease, schizophrenia, bipolar disorder, Hungtington's disease, Parkinson's disease, Alzheimer disease etc. There is a hope that epigenetic profiling before treatment could be used to increase the likelihood of good treatment response by selecting the appropriate medication and resilience enhancing treatment.

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Miro Jakovljevic conceived and wrote major sections of this paper.

Fran Borovecki wrote text about epigenetics and provided suggests for changes in paper.

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