Editorial

Psychotherapy and Psychosomatics

Psychother Psychosom 2017;86:1–4
DOI: 10.1159/000449150

Received: August 12, 2016
Accepted after revision: August 16, 2016
Published online: November 25, 2016

Epigenetic Interactions and the Brain-Body Communication

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There is a saying 'it's all in your head' that is used dismissively to someone complaining about feeling badly but without a clear illness and intended to imply that the problem is not important or 'real'. The article by Fava et al. [1] contradicts this outdated attitude and describes psychosomatic medicine as a vital and growing field. With the recognition that the brain is the master controller of systemic physiology as well as a vulnerable and plastic organ that responds to signals from the body, 'it's all in your head' takes on new meaning. Because of new knowledge from neuroscience and systemic physiology, psychosomatic medicine has taken on new significance and provides particularly important details about the individual personality that can lead to more effective interventions. Indeed, in an era of medicine where silos based on organ systems or disciplines predominate, the individual needs are often overlooked, and interventions on one organ system often do not consider the consequences for other organ systems and for the whole person [2].

In their article 'Current psychosomatic practice', Fava et al. [1] state that 'psychosomatic medicine is a wide interdisciplinary field that is concerned with the interaction of biological, psychological, and social factors in regulating the balance between health and disease. It provides a conceptual framework for (1) scientific investigations on the role of psychosocial factors affecting individual vulnerability, course, and outcome of any type of medical disease; (2) a personalized and holistic approach to the patient, adding psychosocial assessment to the standard medical examination; (3) integration of psychological and psychiatric therapies in the prevention, treatment, and rehabilitation of medical disease, and (4) multidisciplinary organization of health care that overcomes the artificial boundaries of traditional medical specialties'. They note that the concepts of 'allostasis' and 'allostatic load and overload' [3–6] have played a major role in the new version of the practice of psychosomatic medicine. This Editorial discusses the links of psychosomatic medicine to neuroscience and systemic physiology and their growing importance.

A starting point is the ambiguity of the word 'stress', which can refer to 'good stress', 'tolerable stress', or 'toxic stress' (http://developingchild.harvard.edu/science/national-scientific-council-on-the-developing-child/). This 3-part terminology is helpful because it recognizes that the sense of control and mindset [7] determines whether or not the response to experiences can have a successful outcome or may lead to disease. However, this terminology ignores health-damaging and health-promoting behaviors that people adopt in a stressful lifestyle, as well as factors like circadian disruption, loneliness, noise, pollution, and crowding. What is also overlooked in the conventional view of 'stress' is the recognition that the body releases mediators of the neuroendocrine, autonomic, metabolic, and immune systems in response to all experiences in a changing physical and social environment (whether or not we call them 'stress') and that these mediators help us adapt to and survive the changing conditions. Yet the same mediators, when overused or dysregulated amongst themselves, can cause wear and tear on the body called allostatic load, or allostatic overload in its most extreme form, which contributes to disease [5, 6, 8].

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Fava et al. [1] emphasize 'allostatic overload' in table 1 of their article, and, indeed, the concept of allostatic overload can apply to both biology and behavior since loss of control and helplessness have both behavioral and physiological consequences. Moreover, it should be recognized that the neural-behavioral and physiological systems are responding to and affecting the body and brain in all of the behavioral conditions that they described in the other tables on diagnostic criteria in their paper. Thus, allostasis and allostatic load/overload are universal features of coping with daily life, whatever the personality and individual behavioral responses may be. The responses to life events, colored by the personality features and highlighted in those diagnostic tables, are continuously shaping both brain circuitry and systemic physiology, which, in turn, determine reactions to new experiences and lifestyle choices as well as protective or damaging health behaviors.

Indeed, the brain is a plastic and vulnerable organ of the body and shows structural and functional plasticity as the individual adapts to new conditions. The altered architecture is appropriate for the new circumstances, such as enhanced activity of the amygdala in a dangerous environment [9], but when conditions change there must be resilience to adapt to a new state, in which, for example, amygdala activity would be reduced ('reversal' per se never occurs – the expression of genes in the brain is continually changing with experiences over the life course [10]). Moreover, because the mediators of allostasis are affecting all parts of the body and brain simultaneously, and they do so over the entire life course, 'comorbidity' or 'multimorbidity' of disorders is the rule rather than the exception in the case of allostatic overload [11]. Finally, the view that 'biology is destiny' and that genes rule is undergoing major revision as the science of 'epigenetics' develops. Indeed, physical and social experiences are continually changing the brain and body.

Epigenetics and Psychosomatic Medicine and Practice

Epigenetics now refers to events 'above the genome' that regulate the expression of genetic information without altering the DNA sequence. Besides the methylation of cytosine bases in DNA that does not change the genetic code per se, other mechanisms include histone modifications that repress or activate chromatin unfolding [12] and the actions of noncoding RNAs [13] as well as transposons and retrotransposons or 'jumping genes' [14] and RNA editing [15].

For prevention and treatment, in the spirit of psychosomatic medicine, it is important to let the 'wisdom of the body' prevail and to focus upon strategies that center around the use of targeted behavioral therapies along with treatments, including pharmaceutical agents, that 'open up windows of plasticity' in the brain and facilitate the efficacy of the behavioral interventions [16]. This is because a major challenge throughout the life course is to find ways of redirecting future behavior and physiology in more positive and healthy directions [17]. In keeping with the original definition of epigenetics [18] as the emergence of characteristics not previously evident or even predictable from an earlier developmental stage, for example, think about a fertilized frog or human egg which look similar and what happens as each develop! We do not mean 'reversibility' as in 'rolling back the developmental clock' but rather 'redirection' as well as 'resilience', which can be defined as 'achieving a successful outcome in the face of adversity'.

Interventions That Change the Brain and Improve Health

Can the effects of stress, lifestyle, and adverse early life experiences on the brain and body be treated and compensated even though there are no 'magic bullets' like penicillin for stress-related disorders? For psychiatric illnesses such as depression and anxiety disorders, including PTSD, it is necessary to complement and even replace existing drugs and adopt strategies that center around the use of targeted behavioral therapies along with treatments, including pharmaceutical agents, that open up windows of plasticity in the brain and facilitate the efficacy of the behavioral interventions [16, 19, 20]. To that extent, meeting the demands imposed by stressful experiences via various coping resources can lead to growth, adaptation, and learning to promote resilience and improved mental health [21, 22]. Brain-derived neurotrophic factor (BDNF) is a mediator of plasticity, and while it can facilitate beneficial plasticity [23], it should be noted that BDNF also has the ability to promote pathophysiology, as in seizures [24–26].

How the brain gets 'stuck'. Depression and anxiety disorders are examples of a loss of resilience, in the sense that changes in brain circuitry and function caused by the stressors that precipitate the disorder become 'locked' in a particular state and thus need external intervention. Indeed, prolonged depression is associated with shrinkage of the hippocampus [27, 28] and prefrontal cortex [29]. While there appears to be no neuronal loss, there is evidence of glial cell loss and smaller neuronal cell nuclei [30, 31], which is consistent with a shrinking of the dendritic tree described above after chronic stress. Indeed, a few studies indicate that pharmacological treatment may reverse the decreased hippocampal volume in unipolar [32] and bipolar [33] depression, but the possible influence of concurrent cognitive-behavioral therapy in these studies is unclear.

Even in adulthood, gene expression in the brain continually changes with experience [10], and there is loss of resilience of neural architecture with aging [34] that can be redirected by exercise [35] and, to some extent, by pharmacological intervention [36, 37]. More generally, there are new approaches to opening windows of plasticity and redirecting the brain towards a more health-promoting state.

An important concept is 'releasing the brakes' that retard structural and functional plasticity [19]. A prime example is the treatment of amblyopia or 'lazy eye' first done using fluoxetine [38] and caloric restriction [39], in which reducing inhibitory neuronal activity appears to play a key role. This was replicated by putting cortisol in the drinking water instead of caloric restriction [39]. In that connection it is important to note that ultradian fluctuations of cortisol according to a diurnal pattern modulate the turnover of some spine synapses in relation to motor learning and possibly other forms of learning [40, 41].

Related to this is opening windows of plasticity with physical activity. Regular physical activity, which has actions that improve prefrontal and parietal cortex blood flow and enhance executive function [42], increases hippocampal volume in previously sedentary elderly adults [35] and complements work showing that fit individuals have larger hippocampal volumes than sedentary adults of the same age range [43]. Regular physical activity is an effective antidepressant and protects again cardiovascular disease, diabetes, and dementia [44, 45]. Moreover, intensive learning has also been shown to increase the volume of the human hippocampus, based on a study of medical students [46].

In the domain of psychosomatic medicine are cognitive behavioral therapies which are tailored to individual needs. These can produce volumetric changes in the prefrontal cortex (in the case of chronic fatigue) [47], in the amygdala (in the case of chronic anxiety) [48], and in a brainstem area associated with well-being [49]. Mindfulness-based stress reduction practice has been shown to increase regional brain gray matter density in the hippocampus, cerebellum, and prefrontal cortex, brain regions involved in learning and memory processes, emotion regulation, self-referential processing, and perspective taking [50]. Enhancing the self-regulation of mood and emotion appears to be an important outcome [51, 52].

Meditation is another promising strategy and has been reported to enlarge the volume of the hippocampus and to do so differently in men and women, suggesting to the authors that mindfulness practices operate differently in males and females [53].

Conclusion

Fava et al. [1] conclude their article noting that 'the need to include consideration of function in daily life, productivity, performance of social roles, intellectual capacity, emotional stability, and well-being has emerged as a crucial part of clinical investigation and patient care. Such awareness is far from being translated into operational steps in clinical practice, and the traditional outdated way of dealing with health problems still prevails'.

Even 'personalized medicine' is presently cast as genomics-based knowledge and fails to acknowledge the individual person's personality and experiences across the life course [54]. Ignoring this is depersonalizing and may fail to treat the problem. What Fava et al. [1] have presented in this important article is an in-depth view of diagnostic criteria for those individual traits and needs that should be part of a medical approach which recognizes the inseparable, epigenetic interactions between experiences over the life course and the brain-body communication that now has such a strong foundation.

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