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Well-Being: An Important Concept for Psychotherapy and Psychiatric Neuroscience

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The pioneer of psychosocial medicine, George Engel, proposed in his biopsychosocial model that positive and negative psychosocial factors play important roles in any type of diseases, although their relative importance may vary considerably between diseases and even different phases of the same disease [1]. In addition, he elaborated a unified concept of health and disease, suggesting that there is no health and no disease, but only a dynamic balance between health and disease. As a result, health is not just the absence of disease, but also the presence of well-being.

As a young psychiatrist, I was impressed by Carol Ryff's model of psychological well-being [2]. To estimate the subjective relevance of Ryff's proposed well-being dimensions, I developed a treatment outcome measure combining symptom-related items with items on interpersonal goals, existential issues and personal growth [3]. In a naturalistic study, I applied this self-report measure to 84 outpatients 1 year after the end of their integrative psychiatric-psychotherapeutic treatments. The main results of my study were: psychotherapy contributed more to well-being-related outcomes than pharmacotherapy; patient satisfaction was particularly related to reported changes in the interpersonal domain; personal growth was the most important dimension of perceived change in patients with adjustment and personality disorders; ex-

istential issues were crucial in patients with eating disorders, and overall, well-being outcomes were particularly important for women [3, 4].

Recent empirical evidence confirms Engel's assumptions on well-being as an important aspect of health and disease to an extent that I have never dared to imagine. The authors of the World Happiness Report 2016 Update found that positive affect, autonomy, generosity and social support were highly correlated with quality of life and well-being, while there was almost no correlation between negative affect – an important criterion in the definition of psychiatric disorders – and overall happiness [5]. A study including all 3.9 million US personnel who served during the Operation Enduring Freedom or Operation Iraqi Freedom points in the same direction. It demonstrated that the direct involvement in acts of war was not associated with the rate of suicide at all [6]. Instead, socially positive experiences such as marriage, social support, long-term employment and ascending in the military hierarchy were the main drivers of survival. This means that resiliency and quality of life may be better explained by social well-being than by combat trauma.

Unsurprisingly, books about resiliency, personal growth, mindfulness, flow and well-being dominate non-fiction bestseller lists across the world. In contrast, most

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clinical and translational researchers seem to miss a great opportunity by neglecting the concept of well-being in psychosomatic research and psychiatric neuroscience. In 69%, psychological research deals with negative phenomena and in less than 10% with positive ones [7]. As a result, our knowledge about the neurobiology of environmental mastery, social integration and personal growth is minor. When it comes to positive affects, bestseller authors, media-savvy Buddhist monks and Wikipedia are usually referring to Richard Davidson's pioneering work on brain laterality [8]. However, this theory lacks confirmation by an increasing number of studies and is not even mentioned any more in modern textbooks of affective neuroscience. A simple left-right hemisphere model is not qualified to explain the complex dynamic between wellness and disease. In the first part of this editorial, I will try to explain our fascination with pathology that dominates our clinical and scientific understanding of health and disease. In the second part, I will outline a vision for the neurobiological study of positive health.

Professional Negativity Bias

My hypothesis is that psychiatric neuroscience and academic psychology are driven by a strong 'disease bias', comparable to the cognitive and affective negativity bias, which is one of the most consistent risk factors of mood and anxiety disorders. Generally, negativity bias refers to the fact that something negative has more impact on our thoughts, emotions and social interactions than something positive of equal intensity. Losing 10 Euros looms larger than winning 10 Euros. However, as clinical scientists, we have to identify and understand cognitive biases, and not let them command our scientific and clinical work.

Our privileging of the negative, disease-related factors in the balance between health and disease is not just a scientific, but also a clinical problem. As Giovanni Fava pointed out in his recently published treatment manual *Well-Being Therapy* [9], in almost all treatments for prevalent psychiatric and psychosomatic conditions, most attention is dedicated to stress and its consequences. This leads to an involuntary but unavoidable reinforcement of negative aspects of life.

One reason for scientists to see the world predominantly in a negative way may be purely methodological in nature. Humans and animals are more similar in the experience of negative events. Almost no one likes electric foot shocks. In contrast, the processing of rewards shows

important interindividual and interspecies differences. Our preferences for positive things even change considerably across our life spans. Once we liked monster marshmallow cookies, now we go for a sea bass with sizzled ginger and spring onions. As a result, our assessment and experimental methods that allow for comparisons within individuals, between individuals and across species are way better to study the stress system than the reward system. A more fundamental problem in translational research is that negativity might matter more for rodents than for humans. During evolution, the size and the plasticity of the stress system appear to shrink. The relative size and the neuron density of the amygdala, a core structure in learning and expression of fear, is significantly greater in rats than in monkeys, and in monkeys greater than in humans [10]. The brain reward system, in contrast, has increased in relative size from rodents to humans. Neurogenesis is a unique property of the human brain reward pathways [11]. Consistently, the strongest resiliency factor in humans is not a perfectly working stress system but reward-related psychological functions such as experience of meaning and a sense of coherence. The famous Nietzsche quote 'He who has a why to live for can bear almost any how' appears to apply better to humans than to rodents.

Ironically, in the short term, negative aspects in life have more power to create a sense of meaning than the positive ones. This is relevant for us because production of meaning is an important part of our clinical and scientific work. The German philosopher Hegel remarked that the idea of divine life sinks into mere edification and even into insipidity, if pain and the labor of the negative are lacking in it. He also stated that negativity is an immense power to find to yourself, even in absolute disruption. These ideas are corroborated by the concept of posttraumatic growth. Experimental studies confirmed that negative events activate our meaning system more effectively than positive ones [7]. One 'islamic' terrorist gets more mass media attention, news analysis, editorials and commentaries than millions of Muslims contributing to peace and democracy. However, one has to bear in mind that negativity mainly guides our short-term behavior. If Novak Djokovic loses a tennis match – which is rare in these times – he will think more about his strategy for the next game than after winning. Yet, his decision to become the best tennis player in the world is deeply rooted in his early and ongoing positive experiences. Destroying a tennis racket on the court is more dramatic than inner joy, and mass media's food of predilection, but its benefit for the quality of tennis is controversial at best.

Negativity bias may be a response to a lack of felt social connectedness, which is an increasingly important problem in industrial societies. The Banker's Paradox is an evolutionary theory to explain our capacity to engage in long-lasting relationships [12]. A rational banker gives only credit to those who do not need it. Who is in trouble will not get his help since he or she represents a risk for the bank. Early in evolution, many humans such as widows and orphans may have lost their lives due to this rational principle. As a result, there was evolutionary pressure to develop a system to help people in trouble. This system is based on the long-lasting gratitude and relationship to people who help in case of emergency. This means, when we receive help in times of a strong need, we experience a greater change in attitude toward the helper than in other times. We are profoundly moved in such times, find the help deeply memorable and often feel compelled to never forget the helper's assistance. We are compelled to say things like 'Thank you, I will never forget your kindness and help!' and 'I will thank you forever because you have supported me in this difficult situation'. In the short run, talking about negative experiences and vulnerability leads to more interpersonal closeness than the discussion of future perspectives [13]. For us therapists, it makes emergency psychology and the therapeutic focus on past negative events attractive. No field in clinical psychology is as popular as psychotraumatology. My patients with acute stress disorders are the most grateful I have. Given the disappointing and even negative outcomes of debriefing interventions after extreme stress [14], it is crucial that we continuously check whether our interventions are not only attractive for us, but also beneficial to our patients. Even in severely traumatized patients, interpersonal therapy, which is mainly oriented towards the future and the positive, may be more effective and more acceptable than sophisticated trauma exposure treatments [15], particularly for patients with comorbid depression. There is recent evidence that trauma exposure may lead to reconsolidation of trauma memory potentially leading to negative long-term outcomes [16]. The identification with past negative events is another possibly severe side effect of negativity-focused psychotherapy. The survivors of 9/11 who constantly watched the terrorist attacks on television did worse than those who avoided trauma-related cues and got involved in positive activities [17].

There are other social factors to consider. People who talk about the bad are considered more competent and serious than those talking about the good. When George W. Bush came to power, his popularity was modest. Only

his speeches about the axis of evil raised his popularity by 50%. In line, experimental studies demonstrated that subtle reminders of death increased the preference for a charismatic leader and decreased that for a relationship-oriented leader [18]. Just the addition of the sentence 'If you press the control key during installation, the software may damage your computer' to a software installation instruction made the source of the information appear more qualified than the instruction without such a threat-related content [19]. When I tell my students that stress can damage their brain and their body, they are more attentive than when I talk about social integration and personal growth. Have you ever wondered why psychologists and psychiatrists interested in well-being rarely rise on the academic ladder? More importantly, we have to make sure that patients who do not frame their problems in trauma and stress-related narratives get the same attention and empathy as those who do. Finally, sharing of positive emotions leads to more interpersonal symmetry, more well-being and more goal attainment activities than the sharing of negative emotions [20]. Nelson Mandela talked consistently about the good, although he had the best reasons to stir profound emotions in his listeners by pointing them toward the bad he had experienced.

A Neuroscience Vision for Engel's Unified Concept of Health and Disease

I will now propose brain circuitries and neuroscience methods to connect Engel's unified concept of health and disease with neurobiology. With respect to neurocircuitry, the human reward system is the main antagonist of the stress system. As I said above, through evolution, the reward system has become larger and more plastic, whereas the stress system has relatively shrunken and lost some of its plasticity. These developments can be taken as a strong argument to understand health and stress-related disease from a wellness perspective. In his seminal work on the neurobiology of resiliency, my former supervisor Dennis Charney proposed a hypersensitive or resistant brain reward system as an important resiliency factor in the dynamic balance between health and disease [21]. He concluded that such a system would maintain an appropriate hedonic tone even during highly challenging and stressful conditions. Human reward pathways are highly complex, including the mesolimbic dopamine pathways, the prefrontal cortex and the amygdala. Dopaminergic neurons that connect the ventral tegmental area with the ventral striatum have been associated with the experience of plea-

sure and reward expectations, likely representing an important neuronal substrate of hedonic well-being. The prefrontal cortex receives dopaminergic inputs from the ventral tegmental area and sends glutamatergic projections to the striatum and the brainstem. These close connections with the rudimentary reward system allow the prefrontal cortex to set goals, guide behavior, to plan and to make meaning. The amygdala in connection with the ventral striatum and the prefrontal cortex calculates the emotional value of the reward history, which plays an important role in passion and perseverance. Given that the reward neurotransmitter dopamine is one of the most important learning signals in the brain, reward and learning are tightly knotted at a very basic, molecular level. All these dopamine-related functions of the extended reward system importantly contribute to eudaimonic well-being. In two studies, I examined the reward system in fully remitted individuals with a history of depression and, in the second study, of bulimia nervosa. In both studies, we experimentally depleted the neurotransmitter dopamine to reveal subtle reward-processing dysfunctions. In remitted depressive subjects we demonstrated an impaired capacity to anticipate rewards [22]. Conceivably, this impairment contributes to a lack of planfulness and positive health, and therefore increases the risk of relapse. In asymptomatic ex-bulimic women, we showed marked deficits in reward learning [23]. Following Seneca's suggestion that psychological well-being is primarily a learning process, it is plausible to relate this deficit to long-lasting reductions in quality of life and impaired personal growth, which are frequent problems in individuals recovered from severe psychosomatic illness.

The functioning of the reward system shows large interindividual differences, due to genetic, developmental and cultural factors. Given that strong social relationships decrease the likelihood of mortality by 50% [24], the study of social rewards may be particularly relevant to understand the dynamics between health and disease in a large part of the world's population. Studies on sexual desire, social cooperation, social comparison and altruism have demonstrated that social rewards activate the rudimentary reward system similarly to other types of rewards, such as food and money. The social psychologist John Cacioppo demonstrated that gregarious individuals showed a stronger response of the reward system to pleasant pictures of people relative to equally pleasant pictures of objects. In contrast, the activation of the reward pathways of lonely people was stronger to pleasant pictures of objects than of persons [25]. There is increasing evidence that this difference is associated with oxytocin receptor

binding in the ventral striatum, suggesting that oxytocin mediates the rewarding aspects of positive social interactions. This is of particular interest because oxytocin is an antistress hormone [26]. As a result, the elucidation of dopamine-oxytocin interactions will be crucial to understand the molecular mechanisms of social well-being. Simple economic games in combination with functional neuroimaging [27], and the application of hyperscanning will allow for the direct investigation of real social interactions. Hyperscanning refers to experiments in which multiple individuals, each in a separate brain scanner, communicate with one another, while their brains are scanned at the same time. There is preliminary evidence that precise interbrain neural synchronization is necessary for human cooperation [28]. Combining electrophysiological and molecular approaches will provide new insights into social wellness, help-seeking behavior [29] and the health-promoting effects of therapeutic relationships. Momentary assessment will importantly help to understand the real-time dynamics between social interactions and mental states in daily life, and how they influence the balance between wellness and disease. Conditions that trigger upward spirals toward social and emotional well-being are particularly relevant [30, 31]. With wellness consciousness at an all-time high, there will be no shortage of 'citizen scientists' who are eager to contribute time and enthusiasm for large population-based studies.

Epigenetics is the field of genetics that studies modifications of DNA, histones and the three-dimensional chromatin structure that regulate gene expression. These partly stable modifications are determined by genes, age, environment and chance. They are largely responsible for the increasing physical and behavioral differences between identical twins across the life span. Epigenetics lies at the heart of gene-environment interactions, biopsychosocial development and aging. As a consequence, this new field of genetics qualifies for complex investigations into positive health and personal growth. At the gene expression level, the neuroscientist Eric Nestler and his team demonstrated that health is not the absence of disease but an active process that is presumably more complex than the pathogenesis of stress-related disorders. He exposed an inbred population of mice to social defeat [32]. Half of the mice developed social avoidance and other depression-like symptoms, while the other half remained resilient. Unexpectedly, in the ventral tegmental area, 58 genes were differentially upregulated in resilient mice and 36 in susceptible ones, whereas only 9 genes were equally upregulated in both groups. These findings

strongly suggest that positive health is not the absence of disease, but requires complex adaptation to adversity in reward pathways that is vastly unrelated to the development of disease. The psychiatric geneticist Katharina Domschke found that hypomethylation of the promoter region of the monoamine oxidase A gene was associated with the risk of panic disorder [33]. This is plausible since this DNA modification leads to increased monoamine oxidase A expression, contributing to a relative deficiency of monoamines. Interestingly, she also showed that the lack of positive life events rather than the accumulation of negative events explained monoamine oxidase hypomethylation. Recently, she and her team demonstrated that psychotherapy has the power to reverse monoamine oxidase hypomethylation, possibly leading to lasting treatment effects [34]. While these findings are preliminary, they demonstrate the potential of epigenetics to identify environmental factors beyond classical stress models and to elucidate the molecular mechanisms of behavioral change and personal growth.

Because of the important influence of individual and cultural influences on positive health, the measurement of well-being is a huge challenge. In addition, psychometric instruments that are clinically useful may not be appropriate to study the neurobiology of well-being. I doubt that the opposition of hedonic and eudaimonic well-being is a fruitful concept for future research since this differentiation is strongly rooted in culture. Some American authors idealize eudaimonic world views at the expense of hedonic ones, which is consistent with puritan ethics. However, hedonism has been shown to be among the most relevant correlates of well-being in Europe and China [35]. On average, Italians live longer than most of the rest of the world, including Americans. But who can imagine Italian well-being without minestrone, spaghetti alla vongole and saltimbocca alla Romana? Not very surprising to me, an attempt to use epigenetics to devalue pleasure in the pursuit of health and happiness [36] turned out to be the result of erroneous methodology [37]. Both types of well-being are deeply connected within the reward system. The importance attached to the pleasure system by behavioral psychotherapy as well as psychoanalysis is consistent with such an integrative neuroscience perspective that is sensitive to individual and cultural differences. I particularly like the data-driven concept of the British sociologist Paul Dolan of day-to-day well-being being composed of pleasure and purpose [38]. It reflects the fact that we usually do not want to just feel good, but also want to feel that we are doing good. To enhance well-being, we have to balance and combine

these two needs to enhance overall well-being. I also doubt that autonomy is a particularly helpful well-being dimension for neurobiological investigations, given that its value is strongly culture-bound. While high independence correlated with well-being in the USA, high interdependence predicted well-being in Japan [39]. Moreover, individualism is an increasingly important threat to networks of social support and solidarity across the globe. Well-being should be more than individual well-being. That is why I think the study of social reward, social support and social inequality are good starting points to elucidate the neuroscience of positive health. The interplay between psychosocial approaches and neuroscience will provide new insights into how to assess other dimensions of well-being in a way that is consistent with a transcultural biopsychosocial model of health and disease.

There is a huge potential in the connection between Buddhism and psychological well-being research since Buddhism has been rational and nondogmatic from the earliest period of its history and encourages the impartial investigation of human nature. Unsurprisingly, among all positive health-promoting practices, the ones inspired by Buddhism are the best studied by neuroscientists [40]. Recently, a meta-analysis including 15,892 individuals with a broad spectrum of psychiatric conditions including schizophrenia, bipolar disorder, depression, obsessive-compulsive disorder and anxiety disorders found specifically reduced volumes of the anterior cingulate cortex and the anterior insula, suggesting that these two brain regions are part of a common neurobiological substrate for mental illness. Put in Engel's framework, they may – in connection with the brain reward system – represent the neuronal substrate of positive health. Similar to the striatum's capacity for neurogenesis, both regions show specifically human characteristics, including a relatively high content of spindle neurons that allow for high-speed information processing. Both regions are involved in attention, consciousness and resting-state brain activity. One of the more consistent findings from Buddhism-inspired research is that meditation and mindful training increases neuronal activity exactly in these two regions, i.e. the anterior cingulate cortex and the anterior insula. This may explain why mindfulness-based psychotherapies work across diagnostic categories and show high efficacy to reduce the risk of relapse. Taken together, Asian wisdom in combination with modern neuroscience will likely provide important insights and tools toward a better understanding and promotion of health.

Our patients cannot wait for the benefits of neuroscience-informed well-being therapies to arrive in the fu-

ture. In a recent editorial of this journal, Giovanni Fava cites a series of studies that show strong and lasting effects of currently available well-being therapy in severe psychiatric conditions such as major depressive disorder [41]. This is important work that encourages us to implement positive health promotion right now into our clinical work. In addition, clinical trials have the potential to compare various types of treatment methods, including interpersonal therapies, mindfulness training, cognitive and metacognitive approaches, cognitive bias modification and affect-oriented psychotherapies, and to identify markers that predict the individual response to specific interventions. Fava's combination of monitoring well-being in a diary, well-being exposures and the search for a balanced euthymia, which includes gratitude and autonomy [9], appears to do a surprisingly good job in lifting patients out of depression. There is no doubt that current clinical insights and experiences acting in concert with a neurobiological understanding of positive health will provide us with novel and more effective well-being therapy options. I am confident that

our meaning, reward and pleasure system is more powerful and plastic than our academic textbooks have ever dared to imagine.

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