

# The Clinical Science of Euthymia: A Conceptual Map

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## Keywords

Euthymia · Well-being · Clinimetrics · Dysthymia · Mental pain · Allostasis · Depression · Anxiety · Discomfort · Well-Being Therapy

## Abstract

Euthymia is a trans-diagnostic construct characterized by lack of mood disturbances; presence of positive affect; balance of psychological well-being dimensions, flexibility, consistency, and resistance to stress. The aim of this critical review is to draw a conceptual map of euthymia. Relationships with other constructs, continuum between euthymia and dysthymia with discomfort as an intermediate area, associations with lifestyle, clinimetric assessment, role of psychotherapeutic interventions, establishment of therapeutic targets, and neurobiological mechanisms are discussed. The model is based on the bipolar nature of well-being dimensions. Euthymia means using allostasis optimally and maintaining a healthy balance that promotes positive aspects of brain and body health through health-promoting behaviors. It may provide a framework for a renewed definition of recovery, for measuring treatment outcome and for targeting interventions, including the sequential administration of therapeutic components. Clinical assessment requires a clinimetric approach encompassing a broad range of aspects, such as allostatic load and lifestyle behaviors, all interacting with each other and contributing to the euthymia/dysthy-

mia balance. Clinimetric indices for assessing euthymia (the Clinical Interview for Euthymia and the Euthymia Scale) and related constructs (the Clinical Interview for Dysthymia and the Semi-Structured Interview for the Diagnostic Criteria for Psychosomatic Research) are presented here. Well-Being Therapy, a psychotherapeutic strategy specifically aimed at pursuing euthymia, relies on self-observation of well-being episodes using a structured diary as a distinct therapeutic ingredient. The clinical science of euthymia may unravel innovative approaches to assessment and treatment of psychiatric and medical disorders, according to a unitary conceptual framework.

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## Introduction

For many years, in the psychiatric literature the term euthymia connoted the lack of mood disturbances meeting the threshold for a mental disorder such as depression or mania, as assessed by diagnostic criteria or by cut-off points on dimensional rating scales [1–5]. In bipolar disorders, patients spend about half of their time in depression, (hypo)mania, or mixed states, whereas the remaining periods are defined as euthymic [6]. Similar considerations apply to the use of the term euthymia in unipolar major depressive disorder and persistent depressive disorder [7]. Euthymia was defined essentially in negative

**Table 1.** A conceptual map of euthymia

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Relationships with other constructs
The complex balance between euthymia and dysthymia
Lifestyle and euthymia
The clinimetric approach
Psychotherapeutic interventions geared to euthymia
Euthymia as a target for treatment
Neurobiological mechanisms

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terms, as lack of a certain intensity of mood symptoms, and not as the presence of specific positive features. The term also failed to acknowledge that studies on mood disorders with longitudinal designs have reported considerable fluctuations in psychological distress, suggesting that the illness remained active [8, 9], and that residual symptomatology was exceedingly common in both bipolar and unipolar mood disorders [8].

In 2016, in this journal, Fava and Bech [10] provided a novel definition of euthymia as characterized by both the lack of clinical manifestations of a mood disorder and the presence of features such as positive affect, psychological well-being, flexibility, consistency, and resistance to stress. In 2020, Fava and Guidi [11] further elaborated this concept in a special section of the journal *World Psychiatry* devoted to “the evolving science of euthymia” [12]. In the same year, Guidi and Fava [13] discussed the role of euthymia in psychotherapy research and practice. The aim of this critical review is to draw a conceptual map of euthymia in a clinical setting, with reference to relationships with other constructs, balance between euthymia and dysthymia with discomfort as an intermediate area, associations with lifestyle, clinimetric assessment, role of psychotherapeutic interventions, establishment of therapeutic targets and neurobiological mechanisms (Table 1).

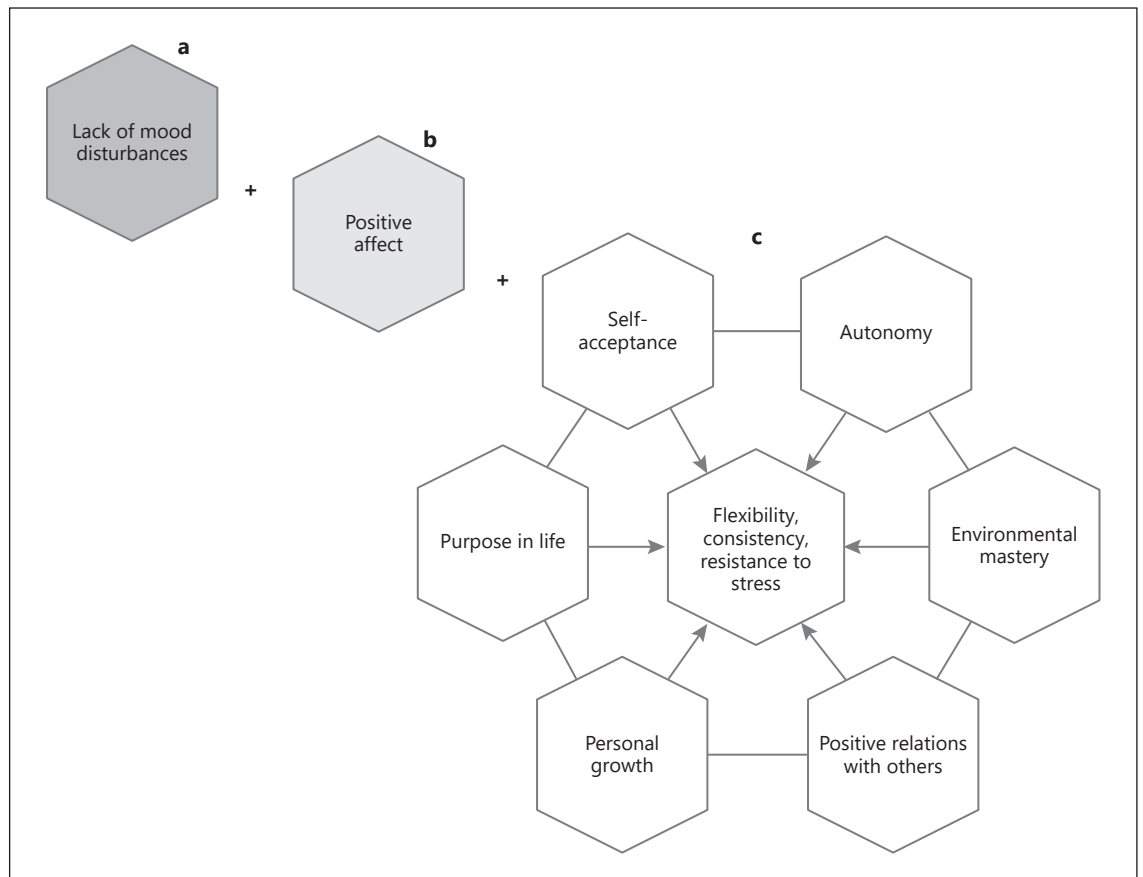
### Relationships with Other Constructs

The importance of psychological well-being achieved growing recognition in the past 2 decades [11]. However, its specific role in the clinical process sparked conflicting views. A major difficulty was that the conceptual frameworks endorsed by investigators were strongly influenced by the prevailing climate of interest and success in the behavioral sciences, with particular reference to positive psychology [14]. These conceptualizations were developed in areas of psychology, such as the general, social,

and developmental, that were quite distant from clinical psychological science. Not surprisingly, the points of observations were often partial, fragmented, and offered a reductionist view of psychological well-being. Further, their interactions with psychological distress were largely ignored [11]. A paradigmatic example is the artificial dichotomy between the hedonic viewpoint, which focuses on subjective well-being, happiness, pain avoidance, and life satisfaction, and the eudaimonic viewpoint, which focuses on meaning and self-realization and defines well-being in terms of degree to which a person is fully functioning or as a set of wellness variables such as self-actualization and vitality [15]. The two viewpoints are inextricably linked in clinical situations, where they also interact with mood fluctuations [11, 13]. The eudaimonic perspective ignores the complex balance of positive and negative affect in psychological disturbances [16] and the longitudinal course of psychiatric disorders [17, 18]. The clinical meaning linked to the presence of dimensions of psychological well-being varies according to the stage of development of a disorder, whether prodromal, acute, residual or chronic. For instance, impairment in environmental mastery may occur in the prodromal phase of an anxiety disorder, persist in its acute phase, and subside in the residual stage. Vice versa, impairment in positive relationships with others may appear only in the acute phase of a depressive disorder and continue in its residual stage. There are thus individual trajectories of interactions between well-being dimensions and symptomatology.

The model of euthymia outlined by Fava and Bech [10] encompassed three different sources of information (Fig. 1):

- (a) Lack of mood disturbances that can be subsumed under diagnostic rubrics; if the subject has a prior history of mood disorder, he/she should be in full remission and not be presenting with residual symptoms judged to be of clinical significance. This does not mean that sadness, anxiety, or irritable mood are not experienced occasionally, but that they tend to be short-lived, related to specific situations, and do not significantly affect everyday life.
- (b) The presence of positive affect, such as the subject feeling cheerful, calm, active, interested in things, and with sleep refreshing or restorative. These characteristics derived from an extensively used questionnaire, the WHO-5 index [19], and from the use of self-rating scales targeted to relaxation, contentment, physical well-being, and friendliness in clinical settings, such as Kellner’s Symptom Questionnaire [20]. There was also



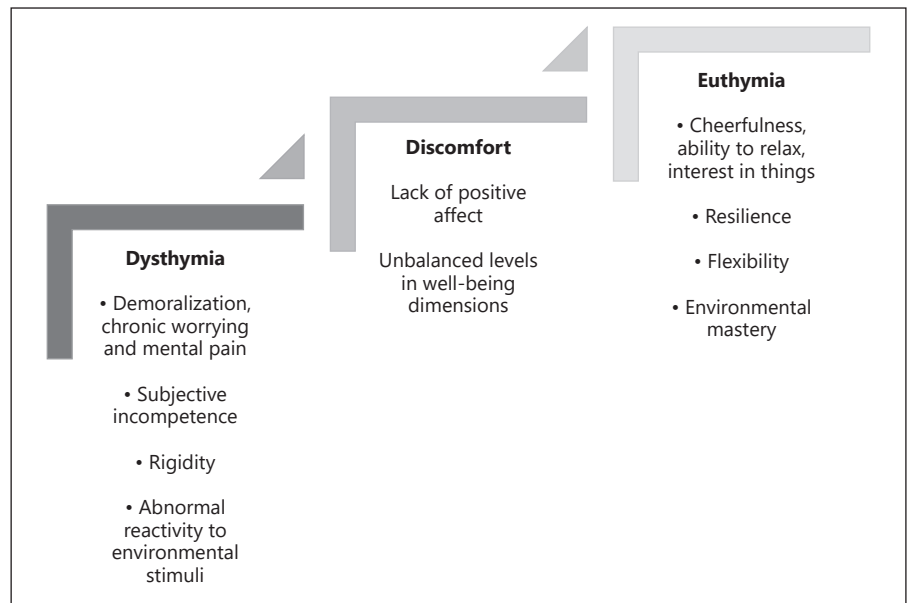
**Fig. 1.** The unifying concept of euthymia.

overlap with the notion of subjective well-being, as the sum of affective and cognitive components [21].

(c) The third component can be ascribed to the work of Marie Jahoda [22] in 1958. Based on a careful inspection of the available literature, she outlined criteria for positive mental health: autonomy, environmental mastery, satisfactory interactions with other people and the milieu, the individual's style and degree of growth, development or self-actualization, the attitudes of an individual toward his/her own self. Such dimensions were translated into a self-rated questionnaire, the Psychological Well-Being scales [23]. Further, Jahoda introduced integration as a criterion for mental health, that is the individual's balance of psychic forces (flexibility), a unifying outlook on life which guides actions and feelings for shaping future accordingly (consistency), and resistance to stress (resilience and anxiety- or frustration-tolerance). The model thus introduces balance and integration of psychological dimensions of well-being according to

changing needs, and not simply a generic effort of avoiding excesses and extremes.

Garamoni et al. [16] suggested that healthy functioning is characterized by an optimal balance of positive and negative cognitions or affects, and that psychopathology is marked by deviations from this optimal balance. As pointed out by Wood and Tarrrier [14], also excessively elevated levels of positive emotions can become detrimental and lead to impaired functioning. The psychological dimensions conceptualized by Jahoda, such as autonomy and environmental mastery, have a bipolar nature, ranging from suboptimal to excessively elevated levels [11], and interact with each other in producing clinical effects. For instance, excessively elevated levels in one dimension (e.g., autonomy) are likely to cause a decrease, whether compensatory or dysfunctional, in another dimension (e.g., positive interpersonal relationships). Indeed, the six dimensions encompassed by the Psychological Well-Being scales were found to be closely correlated [23]. Characteristics of well-being are neither positive nor



**Fig. 2.** The continuum between euthymia and dysthymia, including discomfort as an intermediate area.

negative; they often exist on the same continuum and interact with each other. This optimal-balanced well-being could be different from patient to patient, according to factors such as personality traits, social roles, cultural and social context [11, 13]. The impact of psychological well-being dimensions will depend on the individual's characteristics and on the integration with concurrent distress and other psychological attributes [11, 14]. Similar considerations apply to the interaction between flexibility, consistency, and resistance to stress. Undue emphasis on one component with neglect of the other two is likely to yield a partial and, at times, misleading picture. For instance, the capacity to endure in the face of life adversity (resilience) is definitely affected by flexibility, as the ability to recognize and adapt to various situational demands, to maintaining balance among important life domains, and to display consistency in one's behavior and deeply held values [11]. Clinical consideration of psychological well-being thus requires the integrative and unifying framework of euthymia.

### The Complex Balance between Euthymia and Dysthymia

Euthymia, as defined by Fava and Bech [10], constitutes an example of building a unitary concept that is articulated in heterogeneous components, and yet emphasizes the importance of global judgment [24, 25]. Another

example of unitary concept is subsumed under the rubric of neurosis [26]. Tyrer et al. [27] remarked that what is shared by syndromes such as anxiety, panic, phobic disturbances, and irritability may be as important as the differences between them, and conditions that are apparently comorbid, could be part of the same clinical syndrome. This general neurotic syndrome was shown to be associated with a poor response to treatment, frequency of symptoms throughout the neurotic diagnostic spectrum, and tendency to relapse [28]. Slater and Slater [26] outlined that some people may lack the characteristics that allow to cope with environmental changes, and they are likely to succumb to almost any stress, provided it is sufficient in degree. The absence of flexibility is linked to depression, anxiety, and the general tendency to experience negative emotions more frequently, intensely, and readily, for more enduring periods of time, as in neuroticism [29].

Eysenck [30] referred to neuroticism and introversion by the term of dysthymia. This term then became synonymous of chronic depression, but its original definition [30] provides the conceptual ground for a continuum between euthymia and dysthymia (encompassing liability to demoralization and subjective incompetence, chronic worrying, and mental pain; rigidity; abnormal reactivity to environmental stimuli) (Fig. 2).

Dysthymia is conceptualized at the other end of a continuum with euthymia and does not fall within specific DSM-5 categories [31]. Positive affect is substituted by

the presence of 3 clinical features which take a chronic course. The first is concerned with demoralization, a feeling state characterized by the perception of being unable to cope with some pressing problems and/or of lack of adequate support from others, which can be operationalized with the Diagnostic Criteria for Psychosomatic Research (DCPR) [32]. The concept of subjective incompetence (a feeling of being trapped or blocked because of a sense of inability to plan or start actions toward goals) stands as opposite to that of resilience [33]. Individuals who perceive themselves as incompetent are uncertain and indecisive as to their directions and scopes. The second feature is represented by chronic worrying (also described as anxiety neurosis), a cluster of symptoms based on fear, whose source is often not recognized by the individual [34]; such symptoms do not necessarily reach the diagnostic thresholds of DSM-5 categories [31]. The third clinical manifestation is mental pain, an underappreciated aversive, anguished, or uncomfortable experience characterized by painful tension, feeling of being wounded, emptiness, and loss of meaning of life [35, 36]. In addition, rigidity is a long-standing connotation of neurotic illness [26, 27], that does not allow the individual to cope with situations which need a modification of his/her approach. Such inability becomes critical in the setting of allostatic overload, when environmental challenges exceed the individual ability to cope [32, 37, 38]. Finally, abnormal reactivity to environmental stimuli refers to rapid changes, either improvement or worsening, in mood and symptomatology, which are particularly pronounced in cyclothymic disorder [39, 40] and may also characterize anxiety neurosis [41].

Between euthymia and dysthymia there is an intermediate area with disturbances that are unlikely to fit current diagnostic categories. This area is characterized by lack of positive affect without manifestations of distress, such as demoralization and mental pain. Unbalanced levels in well-being dimensions may be associated (Fig. 2). On the one end, impairments in such dimensions may result in fearing loss of control, having the sensation of being stuck, perceiving lack of meaning in life, overconcern with expectations of others, dissatisfaction with self, and feelings of loneliness [11]. On the other end, excessively elevated levels of psychological well-being may lead to excessive engagement, inability to elaborate negative experiences, unrealistic expectations and hopes, incapacity to ask for help, difficulties admitting own mistakes, tendency to self-sacrifice, and excessive readiness to forgive [11].

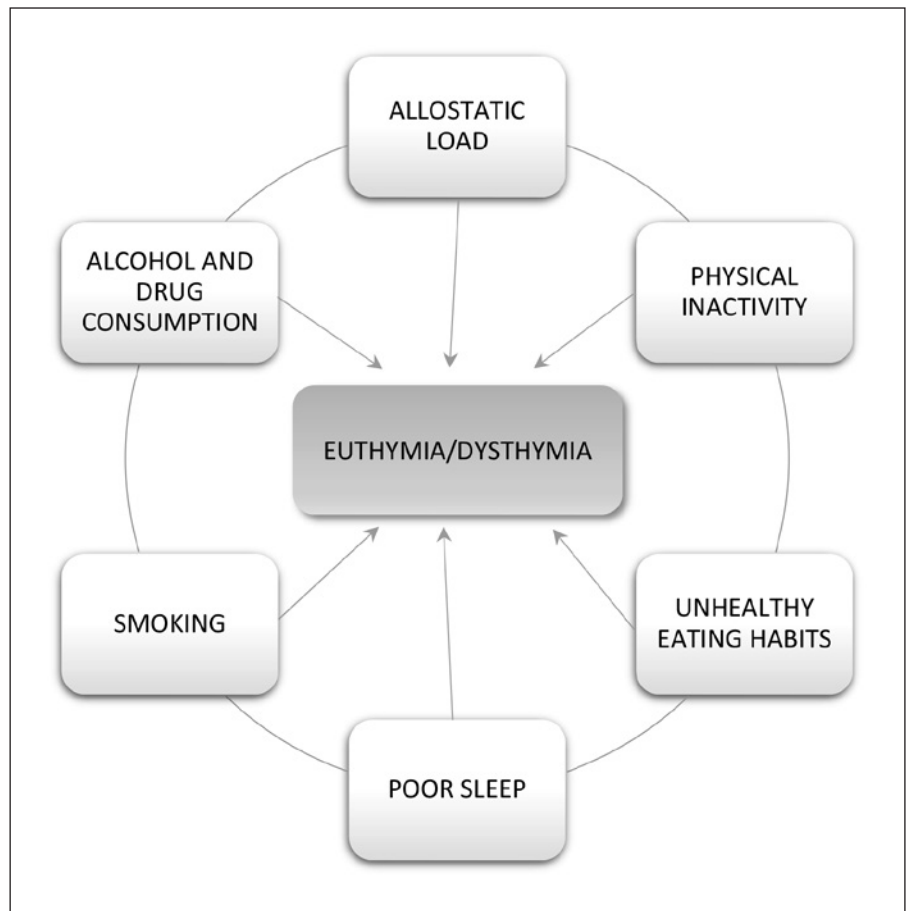
In 1990, in this journal, Per Bech called attention to the differentiation between discomfort, as a dimen-

sion of quality of life, and clinical disability, as the manifestation of an underlying disease process [42]. Discomfort is now used for the definition of the intermediate area between euthymia and dysthymia (Fig. 2). Bech's group found that quality of life measurement, and not symptomatic ratings, could predict recurrence of depression [43]. Much later, Keyes et al. [44] found that "languishing" (an intermediate state between mental health and illness which results in not feeling good and not functioning well) was a strong predictor of mental disorder. The euthymia/dysthymia continuum reflects Engel's conception that "there is no sharp dividing line between health and disease" [45, p. 469] and that "we must also be able to identify the potential for breakdown in the apparently healthy individual" [45, p. 470].

The Clinical Interview for Euthymia (CIE; online suppl. material 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000524279](http://www.karger.com/doi/10.1159/000524279)) provides the clinimetric index for gathering the information related to one side of Figure 2. The questions 6 to 17 of the CIE cover the impaired and excessively elevated expressions of each of the six dimensions of psychological well-being. The yes/no format has been chosen to increase sensitivity. The CIE can be used as an index of change. The Clinical Interview for Dysthymia (CIDys; online suppl. material 2) provides the clinimetric coverage of the other side of Figure 2. It is based on the DCPR for demoralization [32], the Clinical Interview for Depression [46] for worrying and abnormal reactivity to environmental stimuli, the Interview for Mental Pain [47] and the definitions formulated by Tyrer et al. [27, 28] and de Figueiredo et al. [33, 48].

### Lifestyle and Euthymia

An impressive body of evidence has linked the progression of severe medical disorders to specific lifestyle behaviors [32, 49]. A major portion of mortality can be attributed to largely preventable behaviors and exposure, such as physical activity, diet, sleeping, smoking, drinking, and drug consumption [49, 50]. The devastating effects of unhealthy lifestyles and the importance of promoting lifestyle modifications are increasingly recognized in clinical medicine [49]. However, health promotion entails considerable difficulties in its application [49, 51]. Lifestyle modification focused on weight reduction, increased physical activity, and dietary change is advised as first-line therapy in a number of medical dis-



**Fig. 3.** Factors contributing to the dynamic balance between euthymia and dysthymia.

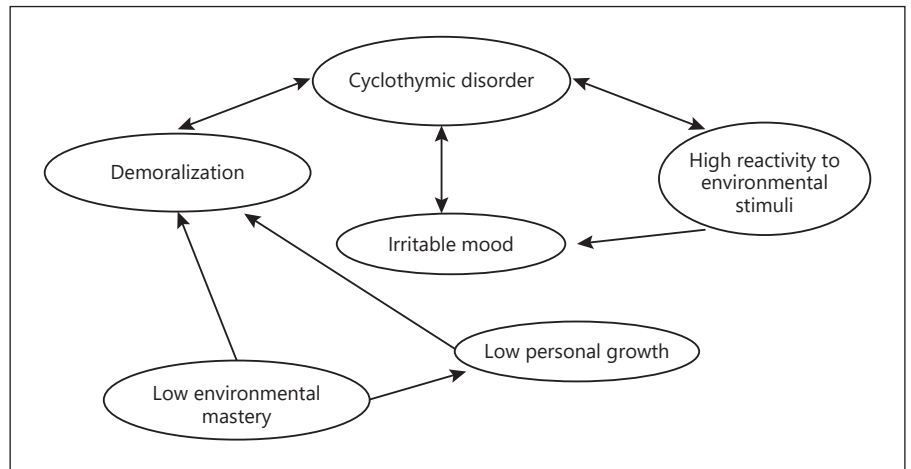
orders, yet the success rate of enduring changes is exceedingly low [51, 52]. Psychological distress and low levels of well-being are commonly observed among patients with chronic conditions and represent important obstacles to behavioral change [52].

Attention to lifestyle, however, has been mainly focused on specific unhealthy behaviors (i.e., physical inactivity, obesity and eating habits, poor sleep, smoking, excessive use of alcohol and drug consumption). Stressful life patterns have not been generally acknowledged as a form of health-damaging behavior [32]. Yet there is growing awareness of the role of allostatic load (the cost of chronic exposure to fluctuating or heightened neural and systemic physiologic responses, possibly exceeding the coping resources of an individual) on the balance between health and disease [37, 38, 53]. The definition of allostatic load provides a synthesis of the cumulative effects of experiences in daily life that involve ordinary events as well as major challenges generally subsumed under the rubric of life events [53]. When environmental challenges exceed the individual ability to cope, then al-

lostatic overload ensues, with major negative health consequences [37, 38].

Diagnostic criteria for the identification of allostatic overload have been developed and validated in a large body of studies [37, 38]. A semi-structured interview for the diagnosis of allostatic overload and related constructs, such as demoralization, according to the DCPR [32] is reported in online supplementary material 3.

The conceptual framework of allostatic load was also extended to work, unemployment, adverse living conditions, social and educational experiences, and income inequality [37, 38, 53] throughout life span development [54]. General population studies indicate that allostatic load is increased by low socioeconomic status, living in impoverished neighborhoods, low educational attainment, ethnicity, and racial discrimination [37, 38, 53]. This comprehensive model also included the physiological consequences of the resulting health-damaging behaviors, including poor sleep and other aspects of circadian disruption, unhealthy diet, smoking, alcohol and drug consumption [37, 38, 53].



**Fig. 4.** Macro-analysis of a patient with cyclothymic disorder.

McEwen [55] observed that “...euthymia means using allostasis optimally and maintaining a healthy balance that promotes positive aspects of brain and body health through health-promoting behaviors. These behaviors involve not only diet, but also adequate and good quality sleep, positive social interactions, as well as a positive physical environment that is safe and includes green space, all of which reduce allostatic load” [55, p. 58]. It has been argued that enduring lifestyle changes can only be achieved with a personalized approach that targets psychological well-being [11, 56]. Indeed, when a psychotherapeutic strategy specifically pursuing euthymia, Well-Being Therapy (WBT) [56–58], was associated with lifestyle interventions [59], enduring behavioral changes were observed. In patients with medical diseases the process of rehabilitation entails the promotion of psychological well-being and lifestyle modification as primary targets of intervention. In a randomized controlled trial on the sequential combination of cognitive-behavioral therapy and WBT, supplemented by lifestyle suggestions, in depressed patients with acute coronary syndrome, significant improvements in depressive symptoms and cardiac biomarkers compared to clinical management were observed, with persistence of treatment gains over a 30-month follow-up [60].

Figure 3 outlines a conceptual model where allostatic load, encompassing both acute and chronic stressful life circumstances, and lifestyle behaviors all interact with each other and contribute, in turn, to the dynamic balance between euthymia and dysthymia. The model emphasizes the relationships among different behaviors. For instance, physical activity was found to be associated with lower allostatic load, whereas poor sleep quality, unhealthy diet and overweight, alcohol consumption, and smoking habits were associated with high allostatic load levels [38, 54].

### The Clinimetric Approach

In most instances of diagnostic reasoning in psychiatry, the process ends with the identification of a disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [31]. Yet, exclusive reliance on diagnostic criteria does not reflect the complex situations that are encountered in clinical practice, since a DSM diagnosis encompasses a wide range of manifestations, comorbidity, seriousness, prognosis, and responses to treatment [24]. It needs to be integrated with an expanded clinical interview, encompassing evaluation of euthymia and dysthymia, allostatic load/overload, and lifestyle according to a longitudinal perspective. Such evaluation requires a clinimetric approach [24, 25, 61], which involves the use of macro-analysis [11, 24, 25, 62, 63]. Macro-analysis has been developed for organizing clinical data as variables according to clinical reasoning (a relationship between co-occurring syndromes and problems is established on the basis of where treatment should commence in the first place). Macro-analysis starts from the assumption that in most cases there are functional relationships with other more or less clearly defined problem areas and strengths, and that the targets of treatment may vary during the course of disturbances. Figure 4 provides a clinical example of this type of assessment in a patient with cyclothymic disorder, displaying high reactivity to environmental stimuli as well as low levels of environmental mastery and personal growth, leading to irritable mood and demoralization.

Macro-analysis can be supplemented by micro-analysis, a detailed analysis of specific symptoms (onset and course of complaints, circumstances that worsen symptoms and consequences), which may consist of dimen-

sional measurements, such as observer- or self-rated scales for assessing euthymia and other related variables [11, 24]. The choice of these instruments is dictated by the clinimetric concept of incremental validity [24]. Each distinct aspect of psychological measurement (whether an index or selected individual items of a scale) should deliver a unique increase in information in order to qualify for inclusion. Such strategy is in sharp contrast with the psychometric model, which calls for homogeneous and redundant items and where severity is essentially determined by the number of symptoms, and not by their quality or intensity [25, 64]. Indices for assessing euthymia according to clinimetric requirements [65] have been developed. The CIE (online suppl. material 1) [11] covers positive affect and both excessive and impaired levels in well-being dimensions, which widely used questionnaires such as the Psychological Well-Being (PWB) scales [23] fail to entail. The Euthymia Scale (ES) [10, 11, 36, 66], an expanded version of the WHO-5 Well-Being Index (WHO-5) [19], allows a self-rated assessment of both positive affect and Jahoda's well-being dimensions [22]. Kellner's Symptom Questionnaire (SQ) [20] encompasses both distress symptoms and well-being. Other clinimetric indices that may be relevant are the PsychoSocial Index (PSI) [67, 68] for evaluating aspects related to allostatic load, and the Mental Pain Questionnaire (MPQ) [35, 36, 57, 69].

### **Psychotherapeutic Interventions Geared to Euthymia**

Self-observation of psychological distress using a structured diary is the basic, and yet neglected, method of cognitive and behavioral strategies. Self-observation paves the ground for cognitive restructuring: schemas can be modified in the course of psychotherapy to achieve a functional role [70]. Self-observation has a major part also in behavioral therapy, such as homework exposure in anxiety disorders [71]. Psychological well-being may ensue with improvement of distress with cognitive-behavioral methods [11] or the individual may enter the neutral zone that is placed between euthymia and dysthymia (Fig. 2). If psychotherapeutic strategies are geared to distress, their effects of psychological well-being can only be indirect. For instance, Mindfulness-Based Cognitive Therapy (MBCT) [72] aims to reduce the impact of potentially distressing thoughts and feelings, and introduces techniques such as mindful, non-judgmental attention and mastery and pleasure tasks that may lead to a good

life. Acceptance and Commitment Therapy (ACT) [73] is another commonly used technique designed to enhance psychological flexibility; it argues that attempts at changing thoughts can be counterproductive and instead it encourages awareness and acceptance through mindfulness practice. Both types of psychotherapy are actually distress-oriented in self-observation, and the good life that is strived for is a state involving detachment and not necessarily euthymia [13].

WBT [56–58] has introduced a clinical revolution in self-observation: patients are encouraged to identify episodes of well-being and to set them into a situational context [13]. Once the instances of well-being are properly recognized, the patient is encouraged to identify negative automatic thoughts (and behaviors) leading to premature interruption of well-being, as is performed in cognitive-behavioral therapy [13, 57, 58]. The therapist may also reinforce and encourage activities that are likely to elicit patient's well-being and optimal experiences. The monitoring of the course of well-being episodes allows the therapist to realize specific impairments or, conversely, excessive levels in well-being dimensions according to Jahoda's conceptual framework [22]. The clinical value of self-observation in WBT is far beyond traditional applications of expressive writing [74], logotherapy [75], or integration of writing techniques within positive interventions for promoting specific well-being aspects (e.g., gratitude, forgiveness). Indeed, self-monitoring of well-being instances occurs within the context of a collaborative therapist/patient relationship, fostered by discussion and interaction. The therapist reviews patient's entries in the well-being diary, but also plays an active role in adding material for reflections, writing specific comments and homework assignments, and completing, with the help of the patient, the sections that are missing or defective. Individuals are not simply encouraged to pursue the highest possible levels of psychological well-being in all dimensions, as is found to be the case in most positive interventions, but to achieve a balanced functioning [13, 57, 58]. WBT thus constitutes a psychotherapeutic strategy specifically aimed at modulating psychological well-being and pursuing euthymia [13].

Disregard of the concept of euthymia may lead to targeting inappropriately elevated levels of positive emotions that can become detrimental [14], and to disruption of the complex balance of well-being and distress [10, 16]. The likelihood of these events is particularly pronounced when the psychotherapeutic intervention is geared to a specific well-being dimension. For instance, forgiveness therapy [76] and compassion therapy [77] may in certain cases pro-



mote excessive empathy, readiness to forgive, and self-sacrifice [57]. Not surprisingly, in a randomized controlled trial of remitted patients with post-traumatic stress disorder presenting with residual symptoms [78], a rehabilitation therapy (inappropriately labeled as WBT [79]) focused exclusively on positive emotions, compassion, and post-traumatic growth did not yield significant advantages compared to treatment as usual, with the exception of those who reported low levels of well-being at baseline [78]. Indeed, the authors failed to use the comprehensive framework of euthymia and overlooked the specific steps and therapeutic ingredients characterizing WBT that may allow an optimal balanced functioning to be obtained [79].

### **Euthymia as a Target for Treatment**

The concept of recovery generally reflects that of “improvement,” which refers to a clinical distance along which the current state of the patient is compared to the pre-treatment position [42]. In this sense, recovery can be expressed either as a categorical variable (present/absent) or as a comparative category (non-recovered, slightly recovered, moderately recovered, greatly recovered). Both expressions require arbitrary cut-offs related to the amount of improvement [42]. Feinstein [61] differentiates between the monadic transition index (devoted exclusively to the rating of change during treatment), the dyadic component index (e.g., before and after treatment ratings), and polyadic component index (when more than two ratings – such as before, during, and after treatment – have been performed). A depressed patient who is asked how he/she feels after 3 weeks of treatment with an antidepressant drug and replies “just fine” (instead of “much better”) uses a self-rated monadic component. The amount of change induced by treatment, however, may make him/her overlook the distance from an intended goal (pre-episode state). The physician may also colude with the patient in this illusion of wellness [80].

The notions of efficacy and effectiveness of pharmacotherapy and psychotherapy in mood disorders essentially reflect the concept of improvement from a pre-treatment position [42], whether a treatment produces a significant change compared to a control condition. Such an assumption, however, may be misleading. Not surprisingly, clinicians treating patients with mood and anxiety disorders often have partial therapeutic targets, neglect residual symptomatology, and equate therapeutic response with full remission [80].

The concept of euthymia may provide an index for targeting treatment that takes into consideration the distance from an expected goal and the complexity and variability of the pre-treatment situation (e.g., a specific effective treatment may produce a substantial improvement in a patient with mild symptomatology and very limited gains in a patient with complex comorbidities). It also provides the conceptual background for the use of pre-planned sequential treatment strategies (e.g., psychotherapy after pharmacotherapy) [81, 82].

Twenty-five years ago, the fact that not meeting syndromal criteria was sufficient to define recovery was criticized, and a comprehensive definition was outlined [80]. It was based on the following points:

- (a) the patient remains in full remission despite discontinuation of treatment (whether pharmacological or psychotherapeutic); an exception is provided by lithium prophylaxis;
- (b) if subclinical or subsyndromal symptoms are present, these are judged to be likely to improve spontaneously over time or not to affect the course of the illness. Residual symptoms which occurred also in the prodromal phase of illness are unlikely to be devoid of clinical implications;
- (c) the patient reports feelings of well-being (relaxation, contentment, physical well-being, friendliness, environmental mastery, sense of autonomy);
- (d) normalization of altered biological markers in the acute phase of illness (if available) should have occurred.

Euthymia allows an updated definition of recovery in the setting of mood and anxiety disorders.

### **Neurobiological Mechanisms**

Euthymia provides a conceptual framework for innovative research on the neurobiological mechanisms of health, with particular reference to allostasis, i.e., “stability through change” [83]. It complements homeostasis, the goal of which is to preserve constancy of the internal milieu by negative feedback regulatory mechanisms. Allostasis suggests that efficient regulation requires anticipating needs and preparing to satisfy them before they arise. It identifies the brain as the fundamental organ for predictive regulation of the internal milieu [83, 84]. The allostasis model defines health as optimal predictive fluctuation to biopsychosocial demands [83, 84]. Euthymia as a therapeutic target means achieving flexibility of the response capacity of the individual, which may entail long-

lasting remission. It is associated with modifications in brain circuits that mobilize resources and govern anticipatory behavior [83, 84]. For instance, it may allow to demarcate major prognostic and therapeutic differences in vulnerability to relapse among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis and treatment [85]. The brain is changing its circuitry and function epigenetically [86]. A key result is structural remodeling of neural architecture, involving many cellular and molecular processes from the cell nucleus to the cell surface, leading to successful adaptation, whereas persistence of these changes when stress ends indicates failed resilience [87].

Current diagnostic definitions of psychiatric disorders based on symptoms collection encompass very heterogeneous populations and are thus likely to yield spurious results when exploring biological correlates of mental disturbances [88]. Exploration of the euthymia/dysthymia continuum may provide the missing link between clinical states such as mental pain and biomarkers, building pathophysiological bridges from clinical manifestations to their neurobiologic counterparts [88].

### The Unifying Concept of Euthymia

Clinical consideration of psychological well-being requires the integrative and comprehensive framework of euthymia [10, 11, 13], and supports an interdisciplinary clinical science unifying contributions that are currently scattered in the literature. Euthymia may provide a framework for a renewed definition of recovery, for measuring treatment outcome, and for targeting interventions, including the sequential administration of therapeutic components, such as pharmacotherapy and psychotherapy [57, 58, 81, 82]. Promoting euthymia may also yield allostatic regulation to biopsychosocial demands and flexibility of the individual response capacity, which may entail long-lasting remission from psychiatric disorders [83, 84] and more successful and enduring results in lifestyle medicine [56–60]. Unlike previous models related to psychological well-being which are exclusively focused on the intraindividual level, euthymia results from interacting mechanisms at the individual, interpersonal, and environmental levels. These latter include work, unemployment, adverse living conditions, social and educational experiences, income inequality, stressful life circumstances, racism, and sexism [89].

Euthymia is a trans-diagnostic construct, which requires a clinical assessment based on clinimetric princi-

ples that goes beyond current reductionistic use of DSM psychiatric criteria [31, 63]. At present, WBT is the only psychotherapeutic approach that specifically aims at a state of euthymia. Systematic monitoring of well-being with the use of a structured diary represents a key, distinct therapeutic ingredient of WBT [11, 13, 57]: it may facilitate the therapist/patient relationship, promote self-awareness of well-being and optimal experiences, and stimulate cognitive restructuring and homework based on the patient's account and material.

Progress can be achieved in psychotherapy research and practice by modifying our clinical approach, still shifted on the side of psychological dysfunction or limited to specific aspects of well-being, and by promoting self-observation of psychological well-being and the pursuit of euthymia. The clinical science of euthymia and the insights gained may unravel innovative approaches to assessment and treatment of both psychiatric and medical disorders.

### Conflict of Interest Statement

Both authors have no conflicts of interests to disclose. Prof. Fava has written a book on Well-Being Therapy, for which he receives no royalties.

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### Author Contributions

Both authors conceived this work and contributed equally to this paper.

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