

The role of Temperament in the etiopathogenesis of bipolar spectrum illness

Running head: Temperament in bipolar spectrum

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word count: 6929

tables: 4

figures: 0

number of references: 166 (EndNote x7)

Acknowledgements

Xenia Gonda is recipient of the Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences.

Disclosures

Role of funding source

None

Abstract

Bipolar disorder constitutes a challenge for clinicians in everyday clinical practice. Our knowledge concerning this clinical entity is incomplete and contemporary classification systems are unable to reflect the complexity of this disorder.. The concept of temperament which for the first time was described during antiquity constitutes a reasonable vehicle to synthesize our knowledge on how the human body works and what determines human behavior. Although it originally included philosophical and sociocultural approaches, today the biomedical model is dominant. It is possible that specific temperaments might constitute vulnerability factors, determine the clinical picture or constitute illness course modifiers and even act as a bridge between genes and clinical manifestations, thus giving birth to the concept of the bipolar spectrum with major implications for all aspects of mental health research and providing of care. More specifically it has been reported that the hyperthymic and the depressive temperaments are related to the more 'classic' bipolar disorder, while cyclothymic, anxious and irritable temperaments are related to more complex manifestations and might predict poor response to treatment, violent or suicidal behavior and high comorbidity. It seems reasonable to assume that the incorporating of the concept of temperament and the bipolar spectrum in the standard training of psychiatric residents might result in an improvement of everyday clinical practice.

Key words: temperaments, bipolar spectrum illness, affective temperaments, etiopathogenesis, affective disorders

1. Introduction

Manic-depressive illness ('bipolar disorder') has been known since the times of Hippocrates and Areteus. Recently accumulated data, however, radically reshaped our view, understanding and definition of this illness¹. Kraepelin, who formulated the prototypical or modern original approach to this disorder differentiated manic-depressive insanity from dementia praecox (schizophrenia) based on the more favourable outcome associated with manic-depression². Today we know that this prototypical bipolar disorder (BD) corresponds only to bipolar type I (BD-I). A summary of BD types and their definitions is shown in table 1³⁻⁵.

Although originally it has been suggested that the prevalence of manic depressive psychosis was approximately 1%, nowadays we are aware that the actual prevalence of the disorder depends on the definition⁶. Bipolar disorder type I (BD-I) and type II (BD-II) are both disabling conditions and show a combined prevalence rate of 3.7%^{7,8}. Data from previous research concerning lifetime prevalence of BD points to a combined rate of 3-6.5%, which includes a wider spectrum of manifestations related to bipolarity compared to what is included in the DSM-IV-TR definition^{7,8}. Research evidence also suggests that in natural patient populations BP-II1/2 might be the most prevalent subtype⁹.

The correct diagnosis is very difficult in patients presenting initially with only depressive episodes. Statistical estimations, however, indicate that more than half of patients originally diagnosed with a depressive episode will eventually turn out to be bipolar in the next 20 years¹⁰. BD in the family history has been established as a strong predictor of bipolarity even in case of children and adolescents¹¹. In spite of some contradictory data¹², there is strong evidence

concerning the association of atypical depression and BD-II¹³, which could also aid early identification of those depressive episodes which are part of a bipolar manifestation. Mixed episodes are another complex part of the BD manifestation spectrum. Recent international research results indicate that DSM-defined mixed episodes (including simultaneous manifestation of full blown mania and depression) are rather the exceptions than the rule¹. Instead, there is usually a combination of manic and depressive symptoms in a clinical manifestation which does not meet the DSM criteria of manic, depressive or mixed episodes, leaving Not-Otherwise-Specified (NOS) mood episode as the only possible diagnosis⁶, which is a clinical picture manifesting with a simultaneous presence of symptoms of depression and mania, and exhibiting a fluctuating course^{14,15}. Manic and especially hypomanic symptoms often remain unrecognised because the mood is irritable instead of hyperthymic. Depressive thought content as well as suicidal ideation often dilute the manic component leading incorrectly to diagnosing anxious or agitated depression or personality disorder and not recognising a mixed or mixed-NOS mood episode^{1,16,17}.

The above manifold features make BD a multi-faceted complex disorder and a problematic entity with respect to diagnosis and differential diagnosis, making it necessary to carefully follow the course of the patient including symptoms, level of functioning and treatment together with internal and external stressors including life events as well as biological stressors. A significant advancement both in the clinical approach and for the understanding of BD is the assessment of temperament in BD patients, which is supposed to provide additional valuable information for the diagnosis and the therapeutic strategic planning. The current article aims to perform a review of the literature on the relationship of temperament to BD.

PubMed was searched using the key words “temperament” and “bipolar” in May 2013. The search retrieved 357 abstracts which were inspected by the authors (KF and XG) for theoretical and clinical relevance. Finally 155 of the identified papers identified were included in the present paper. We included those papers which were clinically and theoretically relevant to the topic of the involvement of affective temperaments in the evolution and emergence or course of bipolar disorder. The discarded papers dealt with psychiatrically healthy subjects, psychiatric disorders other than bipolar disorder, or had no psychopathological relevance at all and were referring to “bipolar” only marginally or in other contexts.

2. The concept of temperament

2.1 Historical perspective

The word ‘temperament’ itself comes from the Latin word ‘temperare’, which means ‘to mix’, while the Greek original word is ‘crasis’ or ‘idiosyncrasia’, standing for ‘mixture’ and ‘unique admixture’ respectively. The concept of temperament can be traced back to antiquity in the theory of humors (which suggests that body humors, and their mixture determine the condition of health). Early versions of this theory might have existed in ancient Egypt or Mesopotamia, but the essence of this approach is ascribed to the school of Cos, and to Polybos who was a pupil and son-in-law to Hippocrates (4th century B.C.) and author of the book ‘Peri physeos anthropou’ (‘On the Nature of Man’). This theory is in fact a microcosmic form of the macrocosmic theory of the four elements (earth, water, air, fire) and the four qualities (dry, wet,

cold, hot) as first proposed by Empedocles (5th century B.C.). Essentially it was a model with two factors: humidity and temperature. The four humors (in Greek 'choli') are fluid substances; a healthy condition is a result of their balanced proportions while discomfort and pain result from either a deficiency or excess of any one or their combination. Four temperamental types (in Greek 'crasis') were described according to the predominance of a given humor: the Choleric (yellow bile from the liver; cyclothymic) the Sanguine (blood from the heart; hyperthymic) the Melancholic (black bile from the kidneys; depressive) and the Phlegmatic (phlegm from the lungs; self-content). The theory was further elaborated by Eristratos, Asclepiades (1st century B.C.) and eventually by Galen (2nd century A.D.) with his treatise 'Peri crasaion' ('De temperamentis'). This approach was the standard until the 16th century, and in India and the Muslim world it constituted the basis of Yunani or Unani medicine (after Yunan meaning Iones-Greeks in eastern languages). Haly Abbas (al-Majusi, 10th century A.D.) believed that some emotions, such as anger, distress, fear, anxiety, and passionate love might be dangerous to health¹⁸. In Avicenna's (980-1037 AD) 'The Canon of Medicine' the theory of temperaments was extended to encompass 'emotion, mental ability, moral attitudes, self-awareness, movement and dreams'. Algazel (al-Ghazali, 1058–1111 AD) stated that in states characterized by well-balanced moderate and harmonious main appetite, anger and intellect give rise to virtues such as justice, wisdom, courage and temperance, however, various vicious features appear when any one of them is excessive or deficient. In English texts, temperament is mentioned in Wycliff's sermons (1380), in the writings of Shakespeare and in Robert Burton's Anatomy of Melancholy.

Temperament theory influenced philosophical thinking as well and played a predominant role in Gnosticism (2nd century A.D). Nicholas Culpeper (1616–1654) disregarded the idea of fluids as defining human behavior and some philosophers dismissed all the materialistic theories. This resulted in Ernst Platner's (1744-1818) *Philosophische Aphorismen* and Immanuel Kant's (1724–1804), *Anthropologie*. In 1795, Friedrich Schiller (1759-1805) conceptualized the Idealist and the Realist types, while Friedrich Wilhelm Nietzsche (1844-1900) described the Apollonian, or rational and the Dionysian, or passionate elements of human nature.

In terms of human physiology, different elements were considered important for temperaments. In 18th century the conflict between Georg Ernst Stahl (1660-1734) with animism/vitalism versus Friedrich Hoffmann (1660-1742) with iatromechanism (hydraulic-based theory) marked a turning point. From then on, the 19th century theories on temperaments followed the modern scientific developments.

Theorists started defining temperament according to the properties of electricity and Friedrich Schelling (1775-1854) in his 'Naturphilosophie' tried to conceptualize a model of human temperament both on philosophical/moral and on materialistic terms. Jacob Henle (1809-1885) was the first to base a theory of temperaments on the tone of the nervous system. During the same period the phrenologistic teachings of Franz Joseph Gall (1758-1828) and Johann Spurzheim (1776-1832) considered the study of temperaments as the first step in the understanding of phrenology.

On the borderline and interface between philosophy, sociology, psychology, anthropology and medicine, Rudolf Steiner (1861–1925), Ernst Kretschmer (1888-1964), and

Erich Fromm (1900-1980) described human types and temperaments, using different nomenclatures and from different approaches. Idealism and idealist philosophers in Germany were particularly involved. Erich Adickes (1866-1928) proposed the 'Four world views' in 1907 ('dogmatic', 'agnostic', 'traditional', and 'innovative'). Alfred Adler (1879–1937) spoke of four mistaken goals ('recognition', 'power', 'service', and 'revenge'). Eduard Spränger (1882-1963) suggested four human values ('religious', 'theoretic', 'economic', and 'artistic') while William James (1842-1910) spoke of tough-minded and tender-minded temperaments. Carl Gustav Jung (1875-1961) suggested an interplay between two axes: sensation-intuition and thinking-feeling which leads to an outer public self and a secret inner self as determining the direction of the libido (extroversion vs. introversion). Thus four types emerge: the 'sensation oriented' (attuned to the external reality), the 'intuitive' (apprehends the overall picture), the 'thinking' (logical principles) and the 'feeling' type (values and relationships). Ernst Kretschmer (1888-1964) described the body types (asthenic/leptosomic, athletic and pyknic) and the related temperaments with the pyknic body type being extrovert and related to manic depression. He also divided personality into two constitutional groups (temperaments): The 'schizothymic' (with the hyperesthetic –sensitive and anesthetic-cold characters) and the 'cyclothymic' (with depressive-melancholic and the hypomanic characters). In 1942, William Sheldon (1898-1977) suggested three body types (endomorph, mesomorph, and ectomorph) and three related groups of temperament traits: 'Viscerotonia' (relaxation, comfort, sociability, gluttony for food, for people, and for affection), 'Somatotonia' (muscular activity and of bodily assertiveness), and 'Cerebratotonia' (restraint, inhibition, concealment). David Keirsey (1921-) combined Kretschmer's, Jung's and Nietzsche's and Spitteler's approaches and suggested four

temperament patterns (Sensing Perceiver, Sensing Judger, Intuitive Thinker, and Intuitive Feeler) and 16 characters.

Following in these footsteps there were several attempts to classify human personality and temperament along dimension using an empirical/statistical method starting from Hans Eysenck (1916-1997) More recently, Robert Cloninger developed a theory of hierarchical temperament and character traits and dimensions, while Hagop Akiskal, unlike his predecessors who were attempting to describe the healthy personality, focused on the affective components of temperament and their relationship to mood disorders and creativity.

In addition to the above description of the historical development of temperamental classifications, It is quite interesting and important to mention that the interest in emotions from an evolutionary perspective was triggered by the 1872 publication of a book by Charles Darwin (1809-1882) titled 'The Expression of the Emotions in Man and Animals', which, unlike prevailing ideas of his age that humans by divine creation uniquely possess muscles to express uniquely human feelings, focused on the idea of common ancestry in humans and animals. Darwin's original suggestion was that emotions evolved via natural selection and therefore have cross-culturally universal counterparts.

A summary of historical hallmarks in the development of the concept of temperament is shown in table 2.

a. 2.2 Empirical studies on Temperament

In a landmark roundtable article experts displayed disagreement about what temperament is ¹⁹. Much of the disagreement comes from the fact that many approaches are theory-driven while others rely more on data collection.

Diamond ²⁰ suggested that when studying adult humans, it is impossible to distinguish between “the essential foundations of individuality and its cultural elaboration”²¹, and in order to separate these two, observationalistic animal studies are needed. On the basis of his observations he suggested the existence of 4 temperamental traits in primates: fearfulness, aggressiveness, affiliativeness, and impulsiveness. These traits reflect and serve the survival of the individual and of the species and the relationship to others. According to Diamond, only knowledge of temperaments described in primates is useful in the study of the human temperament.

Several longitudinal empirical studies were conducted to identify temperamental dimensions, many of which investigated children. The ‘New York Longitudinal Study’ by Alexander Thomas, Stella Chess, Herbert G. Birch, Margaret Hertzog and Sam Korn began in 1956 and followed up more than 100 children from infancy to early adulthood collecting longitudinal data ^{22,23}. The analysis of these data suggested the presence of 9 dimensions of temperament: 1) Activity level 2) Rhythmicity of biological functions 3) Approach /withdrawal 4) Adaptability 5) Threshold of responsiveness 6) Intensity of responses 7) Quality of mood 8) Distractibility and 9) Persistence. On the basis of these 9 dimensions, 3 temperaments were described: the ‘easy children’ (40% of sample, characterized by regularity, ease of approach, mild to moderate mood intensity, adaptability, and a generally positive mood), the ‘difficult children’ (10% of the sample with opposite qualities to the ‘easy’ type) and the ‘slow-to-adapt children’ (15% of the sample;

characterized by slow to warm up, withdrawal from new stimuli, difficulty adapting to change, with mild intensity of reactions and habituating). Approximately one third of the children showed mixed profiles.. Thomas and Chess put an emphasis on 'goodness of fit', that is the extent to which the child's temperament is in accord with the expectations, values, and style of the family and the social environment ²⁴.

Buss and Plomin ^{25,26} followed Diamond's 'phylogenetic' approach and suggested that temperamental traits appear early on during ontogenesis (infancy), are heritable and are predictive of later development. The 4 temperament traits these authors suggested (emotionality, activity, sociability, and impulsivity) are slightly different from Diamond's but essentially they reflect similar concepts.

Goldsmith and Campos considered temperaments as individual differences within primary emotional predispositions, including positive emotions (such as joy, interest, sadness, anger, fear) expressed in intensive and temporal aspects of behavior, manifested as vocal, facial, and motor expressions. They put much emphasis on the basic emotions as being at the core of the concept of temperament. In essence they suggest that temperament is the way people are experiencing and expressing primary emotions (anger, fear, and pleasure), and also the way they regulate these processes. Central to this notion are three characteristics of response: threshold, latency and intensity ²⁷⁻³⁰

Mary Rothbart followed a slightly different approach and emphasized reactivity (meaning biological arousability) and self-regulation (increasing, decreasing, maintaining, or restructuring the pattern of reactivity). In contrast to Goldsmith and Campos, Rothbart emphasized cognitive processes rather than emotions (focus of attention) and identified three

broad dimensions of temperament: 1) surgency-extraversion (positive anticipation, activity level, and sensation seeking), 2) negative affectivity (fear, anger/frustration, and social discomfort), and 3) effortful control (inhibitory control, attentional focusing, and perceptual sensitivity). Important elements in her approach include the link to neurobiology and the issue of effortful control³¹⁻³⁸.

Jerome Kagan described two types of children: the 'inhibited' (cling to their mothers, cry and hesitate with unfamiliar persons or events, are timid and shy and represent about 20%) and the 'uninhibited' (or exuberant; approach new events and persons without hesitation, fearless and sociable and represent about 40%). Kagan's work suggests that these profiles predict later development and are accompanied by physiologic profiles suggesting different levels of CNS reactivity. Kagan suggests that inhibition can be better understood as intolerance of uncertainty and not as a proneness to fear³⁹⁻⁴⁷.

Hans Eysenck (1916–1997) was maybe the first psychologist to analyze personality differences using an empirical/statistical method (factor analysis), and he suggested that temperament is biologically based. He proposed that the basic factors were Neuroticism (tendency to experience negative emotions), Extraversion (tendency to enjoy positive events) and Psychoticism (cognitive style). Eysenck's theory and all subsequent theories that derived from it concern approach/reward, inhibition/punishment, and aggression/flight⁴⁸⁻⁵⁷. His colleague Gray⁵⁸ is well-known for his neural theory which essentially is a 45-degree rotation of the Eysenck system with emphasis on anxiety and suggests the presence of the Behavioral Inhibition System (BIS) which essentially is the system responsible for behavioral avoidance. This Behavioral Inhibition System organizes responses elicited by punishment-related conditioned

stimuli and novel stimuli associated with a frustrating lack of reward simultaneously suppressing ongoing operant behavior, enhancing attention towards the environment coupled with decreasing nonspecific arousal levels and reducing activity of the Behavioral Approach System (BAS). The function of this latter is to organize responses into positive and negative reinforcement-associated conditioned stimuli increasing goal-directed behavior.⁵⁹ A similar approach under different labels (internalizing-externalizing) was proposed later by Krueger and Markon⁶⁰⁻⁶².

A further development of the Eysenck model by McCrae and Costa gave rise to the five-factor model (Big Five)⁶³ which includes neuroticism, extroversion agreeableness, openness and conscientiousness. The older concept of 'psychoticism' is largely substituted by agreeableness and conscientiousness while openness has some degree of overlap with extroversion⁶⁰.

The work of Robert Cloninger is characterized by an attempt to intimately connect temperamental characteristics with individual differences in genetics, neurotransmitter systems, and behavioral conditioning. Cloninger named temperamental dimensions to reflect behaviors stemming from basic emotions: novelty seeking (related to anger), harm avoidance (related to fear), reward dependence (related to attachment) and persistence (related to ambition). His theory suggests a link between novelty seeking and dopamine, harm avoidance and serotonin and reward dependence and noradrenaline^{64,65}. Recent studies from his group suggest that temperamental components can be evaluated from preschool age⁶⁶ and remain moderately stable throughout a person's lifespan except for changes from behavioral conditioning⁶⁷.

The above outlined theoretical and empirical concepts of temperament largely focused on describing healthy personality, therefore the applicability of these temperamental concepts for mental pathology is limited. To fill this void Akiskal developed his model of affective temperaments based on theoretical concepts and observation of affective patients and their healthy first-degree relatives in order to understand the role of temperaments in affective illness, and extrapolated from this to conditions of mental health to describe full spectra of affective temperaments from normal to pathological conditions. In Akiskal's concept, routed in Kraepelin's (1921) theory of fundamental states including manic/hyperthymic, depressive, cyclothymic, irritable and anxious states, temperaments encompass an affective predisposition or basic reactivity. Empirical research has confirmed the hypothesized four-dimensional factor structure and it coincides with those previously identified in clinical populations. In an additional exploratory analysis, a depressive temperament constituted the antipode of hyperthymic temperament and was distinguished from cyclothymic temperament while the irritable temperament appeared somewhat independent. These are close to the classical temperaments put forward by Kraepelin², Kretschmer⁶⁸ and Schneider⁶⁹.

Here has been extensive research to establish the relationship of the affective temperaments and the classical factors of temperament and personality. Recent studies⁷⁰⁻⁷⁴ point to an association between hyperthymic temperament and increased novelty seeking (NS) coupled with lower harm avoidance (HA); cyclothymic temperament and high harm avoidance and high novelty seeking; and depressive temperament with high harm avoidance and low novelty seeking; whereas irritable temperament was associated with increased novelty seeking as well as moderate harm avoidance; and anxious temperament with high harm avoidance and

moderate novelty seeking. There was also a weak correlation reported between the five affective temperaments and the dimensions of reward dependence and persistence.

Recently the 'fear and anger model' has been proposed mainly as a combined approach based on the Cloninger and Akiskal models²⁹, conceptualising temperament as a self-regulated system including six emotional dimensions of anger, control, coping, inhibition, sensitivity and volition. Combining these six dimensions yields 12 affective temperamental types including anxious, apathetic, cyclothymic, depressive, disinhibited, dysphoric, euphoric, euthymic, hyperthymic, irritable, obsessive and volatile temperaments^{30,59,75}. From the new types of affective temperaments in this model disinhibited temperament (originally hyperactive) is associated with moderate novelty seeking and low harm avoidance; labile temperament is associated with low novelty seeking and low harm avoidance; apathetic or passive temperament is associated with low novelty seeking and moderate harm avoidance, and euthymic temperament with both dysphoric and moderate temperament associated with high levels of activation and inhibition, just as cyclothymic temperament²⁹. The authors also included a factor of self-regulation of activation and inhibition, called 'control' and it is similar to 'conscientiousness' in the big five model⁶³ and shares common features with 'persistence' and 'self-directedness' in Cloninger's model⁶⁵ and 'executive functions' and 'effortful control' in Rothbart's concept³³. The "fear and anger" model resembles previous concepts in that it is rooted in the principle that the two major emotional forces are activation (related to anger and drive/pleasure) and inhibition (related to fear and caution), the interaction of which would give rise to a consequential affective trend or prevailing mood.

In line with Darwin's approach, the traits associated with the various temperaments seem to subserve social and evolutionary functions. Cloninger has described the evolution of the brain functions underlying temperament and personality more generally throughout phylogeny in detail.^{76,77} These brain functions are not completely understood in relation to affective temperaments of Hagop Akiskal, however, it seems that the depressive temperament is related to hard working, dependency, sensitivity for the needs and suffering of others, and such persons are good candidates for jobs requiring persistent devotion to meticulous detail⁷⁸. However these persons might carry the burden of existence without experiencing its pleasures. On the contrary, the hyperthymic temperament is related to high levels of energy, extroversion, and humor; hyperthymic people are over-energetic, upbeat, and overconfident, and these characteristics are advantageous with respect to exploratory and territorial behavior as well as leadership. The cyclothymic temperament may contribute to inspiration for love as well as the emotional intensity necessary for creativity embodied in painting, writing poetry, or composing music, while increased tendency for love and love-making has obvious evolutionary advantages⁷⁸. The irritable temperament is associated with fast activation and facing the situation, and may be most suitable for professions like the military or make the person get involved with revolutionary or similar actions. Persons with extreme temperaments might swing too far in either or even both directions, and the use of alcohol or substances might further destabilize them^{79,80}.

The above mentioned empirical studies identify a limited number of temperament dimensions: activity level, adaptability, aggressiveness/anger/cooperativeness, fear/anxiety/harm avoidance, affectivity/emotionality (neuroticism, hyperthymic, cyclothymic,

depressive, irritable, pleasure), impulsivity/inhibition/approach/extraversion/affiliativeness, intensity and threshold of responses, novelty seeking/psychoticism, persistence/distractibility, reward dependence, rhythmicity of biological functions, self-directedness, self-transcendence and control with significant overlapping among them. All the above models have been thoroughly studied. However many limitations still exist, including the difficulty to translate the theoretical concepts into clinical observations, cyclic reasoning among concepts and definitions, too narrow or too broad definitions or non-specific findings. The distinction between temperament and character was initially challenged by factor analysts, but accumulating data about learning mechanisms, inheritance, and developmental patterns indicate that the distinction between temperament and character is fundamental and clinically important⁸¹. Also, the length of psychometric tools as well as copyright issues aggravates the problem.

A summary of empirical studies on temperament and their results is shown in table 3.

b. 2.3 Temperament and personality

While personality refers to goals, motives, identity, self-views, defensive styles, coping styles, and life stories⁸², basic personality traits (e.g. extraversion or neuroticism) are essentially parts of temperament³³.

The concept of temperament is also supported by animal research on the one hand by showing that basic human behavioral traits can also be present in primates⁸³ and on the other hand by the findings of structural and functional differences in the CNS in relationship to temperament in children⁸⁴⁻⁸⁷. Work about temperament in dogs also indicates a shared four-

dimensional structure in humans and dogs corresponding to Cloninger's description⁸⁸. Another work suggests the presence of evolution of 4 factors from reptiles on up phylogenetically⁸⁹.

Another approach could be that the 'trait' and 'state' concepts are not dichotomous but instead most personality features are partially trait-like and partially state-like⁹⁰. If such an approach is accepted, then it serves to bridge clinical, neurobiological and psychodynamic approaches in a flexible way but also predicts that factor solutions produced in various studies will never be identical, because samples are unlikely to be similar or equivalent since the heterogeneity within the normal general population is too great.

The major theories taken together suggest that the seven-factor model of Tellegen⁹¹, Cattell's 16 factor model⁹², the five-factor personality model (operationalised by the NEO-PI)⁹³, the cubical 7-factor model of Cloninger⁹⁴, and the four-temperament model of Akiskal⁹⁵ may in fact represent different levels of a hierarchical structure reflecting both normal as well as pathological personality including a two-superfactor solution on the top representing ego control and ego resiliency^{1,73,96}, a limited number of temperaments in the middle (named under many labels, but significantly overlapping)⁷⁰ and many characters (15 or more) at the bottom¹. 'Temperament' corresponds to the 'higher' levels, while 'personality' and 'character' to the 'lower'.⁹⁷

Several examples may shed more light in this hierarchical organization of personality in action. Cyclothymic traits are reported to associate with anxiety-sleep disturbances, sensitivity to separation, eating disturbances in females and antisocial-aggressive behavior in males⁹⁸. On the other hand, it seems that different professions might prefer distinct temperamental and personality profiles. Thus, dysthymic and obsessional characteristics are markedly present in

physicians and lawyers, cyclothymic traits in artists and architects, hyperthymic temperament is notable in journalists, self-made industrialists, and managers. Cyclothymic and hyperthymic temperaments appear to be moderated by obsessional traits. In this framework, artistic creative imagination seems to be "liberated" by lower levels of obsessive compulsive traits, whereas among architects, their relatively high levels appear to contribute to the execution and fulfilling of their work⁹⁵.

3. Relationship of temperament to bipolar disorder

The relationship of temperament to health involves a strong link to general health and mortality⁹⁹ to future mental health¹⁰⁰ and to anxiety^{42,44,101-106}. Temperamental predispositions are often present in individuals who develop mood disorders, as well as in their relatives, and the pattern of distribution seems to be disorder-specific to a significant extent (e.g. more hyperthymic traits in bipolar I disorder, cyclothymic traits in bipolar II disorder and depressive traits in unipolar depression)^{72-74,107,108}.

3.1 Clinical issues

The 4+1 affective temperaments (depressive, cyclothymic, irritable, hyperthymic plus anxious) have a complex and specific relationship with mental disorders, which goes beyond simple one-to-one correspondence. The anxious temperament has been shown to be a strong and general predictor of several mental illnesses especially within the anxiety and depressive

clusters. On the contrary, the hyperthymic temperament has been shown to have a uniquely protective effect against the majority of psychiatric disorders (with few exceptions including bipolar disorder) ^{109,110}. The dysthymic, cyclothymic and anxious temperaments are related to hopelessness and the irritable temperament to suicidality ¹¹⁰. Besides, several studies described the association of each of these temperaments or specific temperamental constellations with specific mental disorders.

There is a line of research suggesting that temperament assessment might help in differentiating between unipolar and bipolar depression. However it is not absolutely clear that this 'temperament assessment' reflects true 'temperament' (that is basic longstanding characteristics of the patients or traits) rather than subclinical residual features of bipolar disorder (state). To further complicate the picture, the assessment of temperament changes the definition of bipolarity itself, and leads to the concept of the 'bipolar spectrum'. It also increases the prevalence of bipolar cases (especially bipolar II) at the expense of unipolar diagnoses. In spite of the above-mentioned reservations, the presence of an affective temperament presents an additional affirmation of the early occurrence of mood symptoms in early onset forms of both unipolar and bipolar depressions ¹¹¹.

The clinical constellation of 'Euphoric-Grandiose', 'Paranoid-Anxious' and 'Accelerated-Sleepless' symptoms is related to the hyperthymic temperament, while the 'Depressive' constellation is related to the depressive temperament. The cluster of 'Irritable-Agitated' symptoms is related to both temperaments ¹¹². In this frame, the presence of 'hyperthymic' temperament characterizes manic patients with or without psychotic features ¹¹³⁻¹¹⁵. Its

assessment reveals that one third of depressed patients belong to the bipolar spectrum, and especially to BD-II ¹¹⁶.

'Unipolar' patients with hyperthymic temperament (constituting 12.4% of the unipolar cases) are reported to be similar to BD-II patients in terms of gender and bipolar family history ¹¹⁷. BD-II patients (constituting 40% of depressed patients after systematic evaluation) manifest high scores on Hypomania scales and cyclothymic and irritable temperaments. Reversely, 88% of cases assigned to cyclothymic temperament by clinicians were diagnosed as BP-II. Thus, although it has been reported that only cyclothymic temperament is significantly elevated in the bipolar vs. the unipolar depressive group ¹¹⁸ it seems that instead it is a robust clinical marker specifically for BP-II disorder ⁹ and is also higher in patients with a family history of bipolarity ⁷².

Cyclothymic BD-II patients are reported to differ from those without cyclothymic traits as having younger age at onset and age at seeking help, higher scores on HAM-D and more atypical features, longer delay between illness onset and diagnosis of bipolarity, higher rate of psychiatric comorbidity and different axis II profiles (including a higher prevalence of passive-aggressive and histrionic, and lower prevalence of obsessive-compulsive personality disorders). Furthermore, cyclothymic BP-II patients displayed a significantly higher score on irritable-risk-items of hypomania compared to "classic" driven-euphoric items ¹¹⁹. Cyclothymic patients might more frequently be females and manifest a higher number of depressive and hypomanic episodes and suicide attempts, more axis I lifetime co-morbidities (usually panic disorder/agoraphobia and social anxiety disorder), they meet more borderline personality disorder criteria and have higher rates of first-degree family history for both mood and anxiety

disorders when compared to hyperthymic patients who in turn might have more frequent manic episodes and hospitalizations and more antisocial personality disorder features ¹²⁰.

The presence of marked affective temperaments often help to subtype bipolar manifestations marking important distinctions between them with significant pathoplastic consequences.

Marked irritable-explosive traits are observable in 2-3% of young people and ameliorate by middle age. These traits often coexist with the mood-labile cyclothymic type, representing a darker, "borderline" side of this temperament ^{119,121,122}. The type BP-II ½ (patients with cyclothymic temperament developing depressive episodes) manifests early onset, complex temperament structure, and high mood instability, rapid switching, irritable ("dark") hypomania and suicidality and seems to be the most prevalent and severe expression of the bipolar spectrum, accounting for 33% of all depressions ¹²³. BP-III which is associated with antidepressant treatment is reported to arise from depressive temperament and bipolar family history ¹²⁴.

More than half of depressed patients with atypical features are reported to have antecedent cyclothymic or hyperthymic temperaments and often family history for bipolar disorder ¹²⁵. Most of them (78%) could meet the criteria for bipolar spectrum (mainly BD-II). Atypical patients with cyclothymic temperament manifest higher mood reactivity, avoidance of relationships, interpersonal sensitivity, other rejection avoidance, phobic anxiety, paranoid ideation, psychoticism, and functional impairment ^{126,127}. Reversely, as mentioned before, cyclothymic BD-II patients are reported to manifest more atypical features ¹¹⁹.

The psychotic mixed patients seem to be closer to BD-I and are characterized by a hyperthymic temperament with a familial background of psychotic mood disorders, while the

nonpsychotic mixed patients are closer to BD-II, and more often have a cyclothymic temperament and a family background of non-psychotic disorders and substance abuse¹¹⁵. The EPIMAN study in France suggests that the higher prevalence of hyperthymic temperament in males is responsible for the higher frequency of pure mania in men and the higher prevalence of depressive temperament in females is responsible for the more frequent mixed episodes in women¹⁴. Mixed episodes in BD-I women are related to both hyperthymic and depressive temperaments and familial depressive (rather than bipolar) disorders^{114,128}.

A constellation of dysthymic, cyclothymic and anxious temperaments is related to hopelessness (known to be a strong and independent predictor of suicidal behavior) with the irritable temperament related specifically to suicidality¹¹⁰. Lifetime suicide is related (among others) to depressive or mixed polarity of first episode and cyclothymic temperament¹²⁹.

Patients with non-violent suicide attempts in the past have higher depressive, cyclothymic, irritable and anxious temperaments but they do not differ from the general population in terms of hyperthymic temperament^{130,131}.

Patients with high depressive and low hyperthymic temperament seem to be more likely to have higher hopelessness scores, more white matter hyperintensities, higher suicidal risk, and more recent suicide attempts, than the rest. Late-onset mood disorder is characterized by hyperthymic, cyclothymic and irritable temperaments^{132 133}.

In summary, on the clinical level hyperthymic temperament is related to euphoria, grandiose and paranoid thinking, antisocial behavior, psychomotor acceleration and reduced sleep, as well as to a higher frequency of manic episodes and hospitalizations. The cyclothymic temperament is related to the BD-II bipolar type, the presence of panic disorder, agoraphobia

and social anxiety disorder, non-psychotic mixed episodes and suicidality. The depressive temperament is related to depressive symptoms and the irritable to suicidality.

A summary of the relationship of various temperaments and the clinical manifestations of bipolar illness is shown in table 4.

a. 3.2 Gender issues

Although the male:female ratio is 1:1 in classic bipolar disorder, it changes gradually within the bipolar spectrum to eventually become 1:4 in recurrent unipolars. Clinical and epidemiological studies suggest that women carry a higher risk for mood disorders, especially for depression. It has been suggested that this is in part a result of largely genetically determined higher anxious-depressive traits in females¹³⁴, but the differences between genders in personality are actually small except for traits related to attachment. Women are in a much higher for approval (Reward Dependence) and show higher cooperativeness than men¹³⁵. Females manifest less hypomanic and more depressive episodes and more anxiety and somatisation. Gender differences in temperament (higher prevalence of the depressive temperament in women vs. higher hyperthymic temperament in men) might account for the differences in rates between genders¹³⁶.

It has also been proposed that genders are distinguished by the 'ruminative' and the 'active' cognitive response styles. It also seems possible that women are more vulnerable to childhood adversities and to adult stressors especially related to bonding with men as well as

child rearing¹³⁷⁻¹³⁹, which is consistent with gender differences in personality being closely related to traits important for attachment.

The evolutionary significance of these traits is not clear, but it might relate to interactions between harm avoidance and reward dependence in those individuals of the species who are responsible for pregnancy and child birth, as well as for raising children, while the same time are not the physically strongest individuals within the species.

Mixed episodes in bipolar I women are related to lower hyperthymic temperament and familial depressive, rather than bipolar, disorders¹²⁸. Such temperamental dysregulations can be regarded as the intermediate step between familial-genetic factors predisposing to affective illness and gender-related clinical manifestations of mood disorders¹⁴⁰. Differences in clinical manifestations might also include more anxiety-depressive features in females (which is in line with the overrepresentation of females in mixed mania), vs. more social disinhibition in males¹⁴¹.

b. 3.3 Family history/genetics

Unipolar and bipolar depressive patients with hyperthymic temperament are reported to have high rates of bipolar family history^{142,143}. In comparison, patients with depressive temperament are reported to have a higher familial loading for mood disorders in general¹⁴⁰. Cyclothymic patients also have bipolar family history^{72,144}. Monozygotic twins who are discordant for full-blown affective disorders often manifest temperamental features strongly suggesting the presence of a genetic component^{145,146}.

In terms of relatives of patients, the cyclothymic temperament is more frequently present in first-degree relatives of patients with BD-I, followed by persons with family history of mood disorders. This loading was more pronounced in females. In the frame of a spectrum concept of bipolar disorder, cyclothymic temperament is distributed in ascending order in the non-affected relatives of patients from unipolar depression to bipolar disorders, thus possibly constituting a link between molecular and behavioral genetics¹⁴⁷. Although peculiar, it is reported that controls have higher hyperthymic temperament in comparison to relatives of bipolar patients^{107,148}. This is in accord with the above, but in contrast to the results of another study which suggests that BD-I patients and their relatives had a significantly higher frequency of hyperthymic temperament than controls¹⁰⁸. Relatives of bipolar probands showed lower cyclothymic temperament scores compared to bipolar patients but higher scores than controls. Patients and their relatives showed higher anxious temperament scores than controls¹⁴⁸. It seems that the composition of the sample in terms of diagnosis might determine the outcome, by giving weight to depressive, anxious, irritable or cyclothymic temperament, but not hyperthymic which might be higher in controls. The presence of these temperaments might impact on the quality of life of relatives of mood patients¹⁴⁹. Finally it has been shown that personality traits of high Harm Avoidance and low Self-directedness are heritable risk factors for major depression in the never depressed sibs of depressives¹⁵⁰.

Since the genes related to the manifestations of mood disorders seem to be widespread in the general population there must be some kind of a putative evolutionary role if not for specific genes, then at least for affective temperaments. Mood disorders can be viewed as extremes in an oligogenic inheritance model while the constituent traits in their diluted

phenotypes (temperaments) confer adaptive advantages to individuals and their social group. Thus, depressive traits could subserve sensitivity to the suffering peers; anxiety could promote survival; cyclothymia could enhance the pursuit of romantic opportunities thus leading to reproductive success (maybe through creative talent in music, poetry, painting, cooking or even fashion design). Hyperthymic traits may confer distinct advantages concerning territoriality, leadership, exploration, and mating ⁷⁸.

c. 3.4 Personality, temperament and the bipolar spectrum

It is often very difficult to distinguish between 'personality' from one hand and 'bipolar disorder' on the other. Especially if bipolar disorder has a very early onset with complex residual symptoms between episodes.

Many of the subthreshold mood conditions that constitute subaffective disorders were previously subsumed under such rubrics as 'neurotic,' 'characterological,' and 'existential' depressions and more recently personality disorders. It is relevant that measures of Beck's Dysfunctional Attitudes are strongly correlated with low Self-directedness but not with temperament. Any temperament profile as measured by Cloninger may occur in people who are well-adjusted and clinically normal – it is individual differences in character that determine whether a person can self-regulate their emotional drives (temperament) and thereby function in a healthy adaptive manner regardless of stress ^{151,152}.

Cluster B personality disorders are closer to mood disorders in terms of clinical manifestations. Depending on the study population, approximately half to two-thirds of DSM-III

borderline disorders appear to in fact represent subaffective manifestations mainly on the border of bipolar disorder, characterized by dysthymic, irritable, and cyclothymic temperaments or anxious-sensitive temperament lying in continuum with hysteroid dysphoric and atypical depressive disorders¹⁵³. This is particularly true for cyclothymic BD-II patients, who are often misdiagnosed as having borderline personality disorder because of their extreme mood instability¹⁵⁴. Cyclothymic BP-II patients showed more histrionic, passive-aggressive and less obsessive-compulsive characteristics in terms of personality disorders¹¹⁹.

d. 3.5 Child psychiatry

Postpubertal childhood dysthymia evolves into major depressive episodes, a portion of which subsequently switches to bipolar states¹⁵⁵. Almost half of depressed children are reported to be bipolar and this outcome is more common in those with cyclothymic temperament measured at baseline. Bipolar children are characterized by rapid mood shifts with associated conduct disorders, aggressiveness, psychotic symptoms and suicidality¹⁵⁶. More generally, it has been suggested that clinically ascertained juvenile depressions (with onsets typically in late childhood or early adolescence) are part of the bipolar spectrum disorders and are characterized by frequent superposition on affective temperamental dysregulation. Dysthymic, cyclothymic, and hyperthymic temperaments might represent putative developmental pathways to bipolarity¹⁵⁷.

4. Discussion

The complexity of manic-depressive illness with its multiple facets and overlapping forms poses a hard challenge for clinicians in everyday clinical practice. Treatment intervention is also complex with most treatment modalities having proven efficacy only against specific facets of the disorder. Only a few of them have proven efficacy for the prevention of episodes in the long term. In this frame, it is of prime importance for clinicians to be able to understand the nature of the disorder in a more comprehensive way, and also to be able to predict or 'guess' in a more reliable way the nature of future episodes and course. If this can be achieved, then the design of long-term treatment will be substantially improved with profound results on the global outcome of many patients.

Such a prediction is unlikely if clinicians stick to modern classification systems which pay too much attention to the concrete episodes and largely neglect the inter-episode period. Also the disregarding of subthreshold symptoms and conditions by these systems deprive clinicians from a wealth of information which has proven usefulness in clinical practice. Additional problems are neglecting the personality and character background, as well as the wider medical and psychiatric history of the family and the patient.

The concept of temperament has been developed since antiquity to serve the comprehensive understanding of how the human body works, and more importantly what determines human behavior. The many theories on temperament included biological interpretations, philosophical and ethical approaches as well as psychological and sociocultural elements. Therefore, a large amount of information concerning the patient is gathered under

the umbrella of temperament, and thus it is reasonable to assume that by utilizing temperament and related concepts, one can understand mental illness in a more comprehensive way. This has been studied especially for mood disorders with fruitful results, although many areas remain to be further clarified.

Within the area of mood disorders, specific affective temperaments might constitute vulnerability factors, clinical picture and illness course modifiers, residual syndromes or genetically determined variations of mood disorders, or even the source of creativity. Considering the temperament issue in a wider sense, temperaments could constitute all the above in different proportions, but even in the same patient¹⁵⁸⁻¹⁶⁷. Affective temperaments seem to relate also to mood disorders in the family history, thus constituting an endophenotype bridge between genes and mood disorders^{72,140,144,147,148}. Viewing mood disorders under this prism gives birth to the concept of the bipolar spectrum with major implications for all aspects of mental health research and providing of care¹⁶⁸.

Research so far indicates that the hyperthymic and the depressive temperaments are related to the more 'classic' bipolar picture (that is euphoria, grandiose and paranoid thinking, antisocial behavior, psychomotor acceleration and reduced sleep and depressive episodes respectively). On the contrary cyclothymic, anxious and irritable temperaments are related to more complex pictures and might predict poor response to treatment, violent or suicidal behavior and high comorbidity. Coexistence of temperaments or intrusion of a mood episode on a temperament of the opposite polarity also produces complex clinical manifestations and might lead to poor outcome. Often this poor outcome does not reflect inherent properties of the illness, but instead reflects the inability of the therapist to understand the illness and

adequately plan treatment^{72,110-117,123,124,129-131,133}. Temperament assessment could be especially helpful in understanding gender differences and planning treatment accordingly^{128,136,140,141}.

We must mention that the limitations mentioned in the limitation sections of the included papers also apply here. Also, for obvious reasons and space considerations we could not develop ideas on certain parts, such as genetics or the case of pediatric or early onset bipolar disorder, which may in fact be distinct clinical entities and may deserve a paper on their own.

Finally, the widening of our view concerning the information that could be useful for the diagnosis and treatment of bipolar disorder not only radically changes our understanding of the disease but also leads to better treatment and outcome of patients and probably can also lead to saving and better allocation of resources. Future studies could concentrate on how temperamental screening could inform the selection of appropriate pharmaco- and psychotherapies for bipolar patients. Furthermore, the concept of temperament and the temperamental spectrum could be incorporated in further editions of DSM to widen our scope on the complexity and multiple faces of these disorders from the nosological point of view as well as their possible differential response to treatment. Incorporating the concept of temperament and the bipolar spectrum in the standard training of psychiatric residents emerges as a pressing issue but the way this can be achieved remains a challenge.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article

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Legends

Table 1: Bipolar disorder types. From BD-0 to BD-VI according to Hagop S. Akiskal

Table 2: Chronological chart of theoretical elaboration on temperament

Table 3. Summary of the results of empirical studies on temperament

Table 4. Summary of the relationship of bipolar clinical features with various temperaments