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EDITORIAL

"The Faces of Mania: The Legacy of Athanasios Koukopoulos"

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The concept of "Mania" is intimately linked to the evolution of psychiatry itself. The word Mania has two Proto-Indo-European roots, *mn̥yo- and **men*-, meaning "to think" or "to remember"; however, many other Indo-European derivations are more akin to passion and desire [1]. Thinking and memory are central to cognition as passion and desire to motivation, likability, and reward anticipation, the centre of emotional life; their alterations constitute the core of all psychiatric disorders. The above roots gave birth in Greek to a range of words, among which μῆνις, fury, wrath or rage, that was in use since Homer's times (interestingly, in Æolian it was μαῖνις and in Dorian μᾶνις, and referred to the wrath of Gods [2]); μαίνομαι, *i.e.*, to rage, to move back and forth in restlessness and emotional activation, to rampage; μνήμη, memory; and μάντης, diviner, soothsayer or fortune-teller. Hence, the Greek words bound to the *mn̥yo and **men* roots cover a wide emotional and cognitive range. The word μανία refers to persistent rage, unrelenting desire and stubborn goal-directedness; it was used in common Ancient Greek language to refer to madness at least since the times of Æschylus (525-455 b.C.), who in "Prometheus bound" [3] puts in Io's mouth the words "By the fanged insect, with a maniac leap I rushed on to Cenchrea's limpid stream". Further on, in replying to Prometheus, Io states "…καὶ φρενοπληγεῖς μανίαι θάλπουσ'", *i.e.*, "…and mind-striking manias they kindle" [4]. We don't mean to say by this that Æschylus had anticipated Bob Post, but it is astonishing how the words the Ancient Greeks used conveyed emotional meanings and a mentality akin to those of modern people, an interesting match to Julian Jaynes' bicameral mind theory [5]. Socrates (470-469 b.C.–399 b.C.), in Plato's (427 b.C.–347 b.C.) Dialogue "*Phædrus*" initially endorsed Phædrus' presentation of Lysias' view of eros as incurable mania (madness, viewed like an irrational addiction) [6], but later in the Dialogue went on to idealise it and defend it. Around these times, mania often appeared not only in literature and philosophy, but also in Medicine. There several recurrences in Hippocratic writings, not to mention an entire book dedicated to *Περί Μανίας Λόγος*, which however is considered a spurious work [7]. Hippocrates cons all psychological ailments as manias interfering with normal reasoning and imagination

crafting inside the latter two strong beliefs and phantasies, thus elevating mania as the central disease of the soul: "Οἶμαι δὲ ἔγωγε καὶ τὰ τῆς ψυχῆς νουσήματα πάντα μανίας εἶναι σφοδρὰς ἐμποιούσας δόξας τινὰς καὶ φαντασίας τῷ λογισμῷ, ὧν ὸ δι΄ ἀρετῆς ἀποκαθαρθεὶς ὑγιάζεται" (Émile Littré's French translation: "Pour moi, je regarde toutes les maladies de l'âme comme des folies intenses qui créent dans la raison certaines opinions et fantaisies dont on guérit purgé par la vertu", *i.e.*, "For myself, I view all diseases of the soul as intense insanities that create certain opinions and phantasies in the reason from which one recovers purged by virtue") [8]. Hence, during the Classical period, the use of the word Mania was widespread and occupied a central place in the mind and in the language of Ancient Greeks. Marneros and Angst attached to the word context-related meanings, according to whether it referred to a reaction (like the rage of Ajax described by Homer), to a disease (as described by Hippocrates, Aretæus of Cappadocia, Galen and others), to a state of the mind (a divine state towards which Socrates was quite ambivalent, as we detailed above) or to a temperament [9].

Interestingly, μανία was translated from the Greek to Latin as insania [10], which in English is kin to insanity. Other similar terms used to translate mania in Latin-based languages include vesania, follia, folie, folly, furor and fury. In Latin there was not such a root as mania, so people using the term in Greek in the 1st Century, when Roman rule over Greece and other countries and their people was established, was translated quite freely in Latin. For example, the Jewish historian Joseph ben Mattathias (Flavius Josephus de Maccabæis; Jerusalem, 37-Rome, ca.100) who was well-versed in both Greek and Latin, in his "de Rationis imperio liber" used the Greek mania to intend a torment [11].

The trend established by Hippocrates and his followers persisted across the following centuries. However, the consideration of mania and melancholy as aspects of the same disease process or as different, but interconnected disorders to a certain extent, oscillated through the centuries between these two views. It appears that the Methodist Soranus of Ephesus (Σωρανός ο Εφέσιος; ca. 98-ca. 138), considered them the latter way [12], much like the DSM-5, which distinguishes depressive from bipolar disorders, thus abolishing the broader category of mood or affective disorders that had characterised the DSM-III and DSM-IV. Soranus was translated into Latin some centuries later by Cælius Aurelianus (fl. 5th Century), who also brought forth his own ideas. According to Aretæus of Cappadocia (1st-2nd Century), "Μανίης τρόποι εἴδεσι μὲν μυρίοι, γένεϊ δὲ μοῦνος εἷς" ("The modes and species of mania are myriad, but the genus only one") [13]. In fact, mania may have many different clinical presentations. Further on in the same book, Aretæus identified another species of mania (Μανίης εἶδος ἕτερον) that he relates to godly possession: "Τέμνονταί τινες τὰ μέλεα, θεοῖς ἰδίοις, ὡς ἀπαιτοῦσι, χαριζόμενοι εὐσεβεῖ φαντασίῃ· καὶ ἔστι τῆς ὑπολήψιος ἡ μανίη μοῦνον, τὰ δὲ ἄλλα σωφρονέουσι. ἐγείρονται δὲ αὐλῷ καὶ θυμηδίῃ, ἢ μέθῃ, ἢ τῶν παρεόντων προτροπῇ. ἔνθεος ἤδε ἡ μανίη· κἢν ἀπομανῶσι, εὔθυμοι, ἀκηδέες, ὡς τελεσθέντες τῷ θεῷ, ἄχροοι δὲ καὶ ἰσχνοὶ, καὶ ἐς μακρὸν ἀσθενέες πόνοις τῶν τρωμάτων" (Some cut their limbs in a holy phantasy, as if thereby propitiating peculiar divinities. This is a madness of the apprehension solely; for in other respects they are sane. They are roused by the flute, and mirth, or by drinking, or by the admonition of those around them. This madness is of divine origin, and if they recover from the madness, they are cheerful and free of care, as if initiated to the god; but yet they are pale and attenuated, and long remain weak from the pains of the wounds) [14]. Aretæus may be credited with a kind of protoformulation of the primacy of mania concept, in the sense that mania (or madness, as it was intended) engulfed melancholia (that was intended in these times closer to dysphoria than to sadness). In his chapter on melancholia, he stated "…δοκέει τε δέ

μοι μανίης τε ἔμμεναι ἀρχὴ καὶ μέρος ἡ μελαγχολίη." (Latin: Et mihi quidem videtur illa (authors' note: *melancholia*) *insaniæ* principium esse, & pars. English translation: I believe that melancholia is the beginning of mania and a part of it) [13].

Galen (129-216) believed mental illness to be caused by brain imbalances, and viewed manias the same way as he viewed "phrenitides" (frenzy spells), *i.e*., as maliciously combined humours or their dyscrasias upon the brain, distinguishing them according to the co-occurrence of fever (and inflammation), that were present in the latter and absent in the former (…ἐπὶ μοχθηρούς συνίστανται χυμούς ἥ δυσκρασία τῶν κατά τὸν ἐγκέφαλον. ὀνομάζονται δὲ φρενίτιδες μὲν αἱ μετά πυρετῶν, μανία δὲ αἱ χωρίς τούτων,…) [15].

After the split of the Roman Empire, Eastern and Western Romans continued in the groove of the Hippocratic tradition. Cælius Aurelianus in the 5th Century distinguished mania from phrenitis and their relation to hydrophobia similarly to Galen [16]. Paulus Ægineta (625-690) was strictly Hippocratic in stating "When the complaint is occasioned by yellow bile, which, by too much heat, has been turned into black, it will bring on the disease called mania, which occasions ungovernable madness, so that those affected with it will destroy persons who come near them unguardedly" [17]. He also regarded mania to be treatable with measures similar to those adopted for melancholia [17], which may be taken to indicate that ancient people considered the two entities as belonging to the same disease process.

Prognostic, diagnostic, and therapeutic views about mania and melancholia in line with the ideas of the preeminent Greek and Roman physicians (based on the four humours) permeated also Persian-Arab medicine (Ishaq ibn Imran [died ca. 908], Rhazés [854-925], Avicenna [ca. 980-1037], and Constantine the African [ca. 1020-1087]) [18] and persisted into the centuries. For example, in 16th Century Spain [19] and in 17th Century Germany [20], debates on the subject were centred on Galenus' and Hippocrates' views.

In modern times, Heinroth, in reviewing the concept of mania and discussing it according to the ancient masters, he considered it as "the fundamental affection of the psyche" [21]. He attributed the great number of psychiatric clinical pictures to a form of excitement. The title of the first edition of Pinel's Handbook was "*Traité médico-philosophique sur l'aliénation mentale, ou La manie*" [22]. Pinel believed mania to be the most typical and frequent psychiatric disorder.

Wilhelm Griesinger, who introduced the term and the concept of cycle, hypothesised that excitatory phenomena often generate depressive states: "By using the expression 'psychic depressive states' we did not mean to imply that the basic nature of these states is inactivity and weakness and suppression [depression] of the psychic or cerebral processes that underlie them. We have much more reason to assume that very intense states of irritation of the brain and excitation of the psychic processes are very often the cause of such states; but the end result of these [psychic and cerebral] states as far as mood is concerned is a state of depression or psychic pain" [23].

Excitatory phenomena constituted also Kraepelin's focus [24]. He used broad criteria for mania and mixed states, which are basically conditions of excitement (Depressive Mania, Excited Depression, Mania with poverty of thought, Manic stupor, Depression with flight of ideas and Inhibited Mania). He also related excitatory processes to his "Fundamental States", which roughly correspond to the four affective temperaments.

Eugen Bleuler's conceptualisation and his and Kurt Schneider's criteria of schizophrenia [25, 26] are at the basis of the decline of attention to mania during the 20th Century and of the overdiagnosis of schizophrenia at the expense of the diagnosis of manic-depressive illness. In fact, mostly in Europe and considerably more in the US [27], Bleuler's cross-sectional view and the loss of Kraepelin's longitudinal contributed to the inflation of schizophrenia diagnoses, as patients with psychotic mania were classified as schizophrenic, generating a terminological confusion between psychosis and schizophrenia. The motto, "once a schizophrenic always a schizophrenic," dominated the field for decades. The trend for diagnosing schizophrenia in the place of manic-depressive illness was even stronger in post-war United States, where the DSM-I and -II criteria [28, 29] allowed many a patient with psychotic manias to be misdiagnosed as affected by Schizophrenic or Paranoid Reaction.

With the loss of focus on mania, there came a greater emphasis on depression and, consequently, the advent of its disjunction from mania. Clinicians' attention was predominantly focused on the detection and treatment of the depressive phase, dedicating little interest on the manic phase. Incidentally, during these times, antidepressants became available and this prompted much enthusiasm among clinicians. An interesting example of this mania-to-depression transition of clinicians' interest is the following anecdote. In the early fifties, Eliot Slater, a preeminent clinical psychiatrist who was at that time the editor of the *British Journal of Psychiatry*, rejected a paper submitted to this journal that reported a clear antimanic effect of lithium in a double-blind clinical trial because he considered it not sufficiently interesting [30]. Finally, the distinction between unipolar and bipolar disorders [31, 32] led to an overdiagnosis of unipolar depressions (Recurrent Major Depressive Disorder in the DSM system), at the expense of the diagnosis of bipolar disorder; bipolar I disorder was still diagnosed as schizophrenia, while patients with bipolar disorder who had hypomania were diagnosed with major depressive disorder.

It is possible to state that these diagnostic issues are at least in part due to the clinical complexity of manic-depressive illness, and the attempt to oversimplify it. The term "bipolar disorder" itself did not help clinicians and researchers. We fully share Kay Jamison's view: "the word 'bipolar' seems to me to obscure and minimize the illness it is supposed to represent" [33]. We consider the term "bipolar" (literally: with *two* poles) confusing and restrictive, and agree with those who persist in preferring the original Kraepelinian nomenclature "manic-depressive illness" [34].

Today, this complexity is clear in daily clinical practice. Our patients spend long periods of time in acute phases [35], are often suicidal [36], are treated with polypharmacy/combination regimens [37], and other somatic non-pharmacological treatments [38, 39], are often unable to have a normal relational and work life [40]. Because depression is often associated with all these issues, all efforts were put on the treatment of the depressive phases (also because patients with manic-depressive illness are likely to complain about their depressive phase, whereas they tend to like the hypomanic one and to have less insight into their manic phase). The results were, and still are, not totally satisfactory.

In this context, Athanasios Koukopoulos and Daniela Reginaldi had the intuition that the primary force of the whole manic-depressive illness was mania, and that it was possible to prevent the depression and stabilise the course of the illness by suppressing the manic phases [41]. Koukopoulos (misspell as Kukopulos) and Reginaldi suggested that mood disorders

should be viewed from a different perspective, *i.e*., mania should not be considered simply as episodic euphoria plus hyperactivity, but rather reflecting a wide range of excitatory behaviours; contrariwise, depression should be viewed more narrowly (and perhaps redefined, on the ground that its criteria include very contrasting symptoms, such as weight loss and weight gain, increased and decreased appetite, insomnia and hypersomnia and so on).

In this special issue, clinical researchers expert in the field of mood disorders revisited Koukopoulos' hypotheses, addressing the different ways mania may appear. The issue is opened by a personal reflection by prof. Hagop Akiskal, the most renowned worldwide manic-depressive illness expert. Kotzalidis and colleagues reviewed the neurobiological evidence of the primacy of mania hypothesis, testing it with the use of a current neuroimaging paradigm. Tondo and collaborators addressed the hot topic of time spent in illness by patients with bipolar disorders. Perugi and his group investigated in one paper the antimanic and mood stabilizing effect of electro-convulsive therapy, and in another the role of excitatory temperaments in cyclothymic disorder. Faedda's (Mariely Hernandez *et al*.) and Wozniak's (Giulia Serra *et al*.) groups dealt with the delicate problem of the early onset of disease, focusing on the clinical expression of excitement in children and adolescents. Our group (Sani *et al*.) presented data in support of a mania to depression causal relationship in the manic-depressive cycle. Delfina Janiri and her colleagues and Nassir Ghaemi and his collaborators provided important clinical data on patients with mixed states and dual diagnosis. In the paper by Gino Serra's group (Francesca Demontis *et al*.), a neurobiological explanation of the clinical effect of antidepressants is presented. Finally, Rihmer and his collaborators present an innovative hypothesis of a possible theoretical connection between mania and hypertension.

We believe all the contributions presented in this special issue will help clinicians and researchers to better understand the clinical and biological complexity of manic-depressive illness and to seek alternative and more effective treatment strategies. We also hope they will stimulate debate to push forward knowledge about this complex nosographic entity.

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