First, sleep in early life has been suggested to play a crucial role in brain development [3]. Being regarded as an ''unconscious'' state to outside stimuli (non-REM sleep) and an ''active'' state of memory consolidation (REM sleep), sleep helps our brain work better by eliminating useless information, updating stored information and reinforcing efficient brain connectivity, to develop a more and more ''personally perfect'' internal representation of the world and a more and more efficient cognitive system. Sleep problems in autistic people, especially the greater fragmentation of sleep, may lead to less efficient brain connectivity in the developing brain, which could furnish a neural substrate for forming such a specificity of information processing (weak central coherence).

Second, abnormal melatonin physiology has been supposed to explain sleep problems in autistic people. Melatonin receptors are detected in a wide spectrum of tissues and cell types of human brain and peripheral structures. Its rhythmic secretion has been suggested to be a major messenger that supports biological rhythm synchronization [4] and modifies the sleep-vigilance states. Interestingly, the secretion of melatonin in autistic subjects has also been reported to be elevated during daytime [5]. Such an abnormal neurotransmitter physiological regulating could probably make a ''functional disconnection effect'' during the day, just like the normal ''fading of consciousness'' effect during the night as reported by Massimini et al. [6] who suppose that the fading of consciousness during certain stages of sleep might be related to a breakdown in cortical effective connectivity. So we suggest that the capacity of the brain to integrate information might be reduced in autistic people given that the regulation of the sleep-vigilance neurotransmitter networks was disturbed.

Thus, sleep problems and abnormal melatonin physiology found in autistic people may play an important role for their specificity in brain connectivity and in information processing.

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Hemodynamic profiles of heart failure patients and ''elementary qualities'' of pre-hippocratic medicine: A hypothesis for a linguistic and epistemological relationship

Clinical assessment is capable of identifying hemodynamic profiles associated with long term outcomes of subjects with heart failure. Simple classification of heart failure patients according to measurements of congestion and perfusion at the time of hospitalization has proved to be useful

and accurate in predicting clinical status and in selecting and titrating pharmacological therapy [1]. The classifying system, detectable through basic physical examination, is based upon the clinical features of hemodynamic profiles, namely wet/cold (congestion and hypoperfusion), wet/warm (congestion and normal clinical perfusion), dry/cold (no clinical congestion and hypoperfusion) and dry/warm (neither clinical congestion nor hypoperfusion). In effect, in recent published research, congestion has been assessed by scientists through the presence of jugular venous distention, rales, orthopnea, peripheral edema and other elementary physical signs, while (deteriorated) perfusion has been evaluated by detecting, among other findings, pulsus alternans, cold extremities and symptomatic hypotension. In patients admitted with heart failure, survival analysis has convincingly shown that wet/warm patients and wet/cold patients have a higher risk of death plus urgent transplantation, as compared with dry/warm and dry/cold individuals. In an era of limited resources, such as the current one, simple, non invasive and inexpensive predictive tools are important for prognostic stratification of problematic patients such as heart failure ones.

The same terms and underlying characteristics were used, however, in other distant eras. Cold, warm, dry and wet were precisely the so-called ''elementary qualities'', whose balanced presence in human bodies was considered by ancient philosophers and physicians to be essential for an optimal health status. According to the philosopher Empedocles (V century B.C.), these elementary qualities were in effect properties of bodies, with their detectable attributes of heat and humidity. To Empedocles is attributable the first identification of a relationship between elementary qualities and health status. His idea was determined by his conviction of the continuous action of natural forces on primordial elements (water, air, earth, fire) [2]. A direct application of this theory to the health context was proposed by Alcmeones, the most representative naturalist philosopher and physician of the pre-hippocratic period, who considered human health status to be the result of a balanced presence of these qualities. In his view, the cause of diseases was to be re-conducted to the relative prevalence of one quality over another (e.g., wet over dry) or to the scarcity of one of them (e.g., the deficiency of dry). The therapy of diseases was consequently based on attempts to re-establish the equilibrium of disarranged qualities, both by means of diet and of appropriate (for the time) drugs. Even if with Hippocrates (V–IV century B.C.) the theory of the four elements lost part of its importance, it was later re-evaluated by distinguished personages, including the philosopher Aristotle (IV century B.C.) and the physician Galen (II century A.D.).

Of course, in present times, the theory of elementary qualities with their medical fall out is no longer considered scientifically valid. It is interesting to note, however, that modern linguistic terminology and epistemological options show some intriguing echoes of it. With regard to linguistic terms, it may be observed that the qualities of Alcmeones are precisely the same ones that identify the clinical characteristics of the hemodynamic profiles of heart failure patients presented in recent research [1]. With regard to the epistemological aspect, just as in ancient Greek medicine importance was attributed to prognosis, so today the current importance of the identification of ''qualities'' lies in its clinical application to the prognosis of heart failure patients. It is pertinent to remember that in classical times the credit and reputation of physicians was essentially determined by their prognostic competence, given the extremely poor effectiveness of therapeutic remedies; the exactness of their prognosis was the only way in which the patient and his/her family could assess technical ability and decide whether to follow the prescriptions [3].

The correct and reliable prediction of the clinical outcome of patients still constitutes a major challenge for modern technological medicine. In the continuous search for economic and easy to implement approaches, based on physical examination, the identification of the clinical aspects of hemodynamic profiles (wet/cold, wet/warm, dry/cold and dry/warm) for heart failure individuals remains a valid prognostic tool, reminding us of the heritage of the past.

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Combined dexamethasone suppression/corticotropin-releasing hormone stimulation test and antidepressants: Different antidepressants may produce different effects

There is a growing interest in the use of the combined dexamethasone suppression/corticotropin-releasing hormone (DEX-CRH) test for psychiatric research around the world [1—3]. The DEX-CRH test has been used to study depression, suicidal behavior, alcoholism, and other psychiatric conditions. In some DEX-CRH studies, patients are maintained on antidepressants, and, in some studies, patients are medication free. How much do antidepressants influence hypothalamic-pituitary-adrenal (HPA) regulation and the DEX-CRH test results? The DEX-CRH test appears to be the most sensitive tool to detect depression-related changes in the HPA axis [1]. Changes in HPA axis reactivity in this test were correlated with changes in depressive symptomatology. Normalization of the DEX-CRH test was shown to anticipate or parallel response to antidepressant treatment [1,4—6]. It has been suggested that antidepressant treatment does not appear to affect test outcome in the absence of clinical response [4]. Kunzel et al. [4] did not find an association of presence or absence of antidepressant treatment, the type of antidepressant treatment or of the number of previous ineffective antidepressant treatment attempts before hospitalization and the results of the DEX-CRH test. However, it has been shown that mirtazapine effectively reduces the overshoot of cortisol and adrenocorticotropic hormone (ACTH) during the DEX-CRH test both in treatment responders and non-responders within 1 week [7]. The authors suggest that mirtazapine rapidly attenuates HPA axis hyperactivity in depressed patients via direct pharmacoendocrinological effects and this amelioration of HPA system dysregulation is not necessarily related to clinical improvement. In another study, both 6- and 12-week fluvoxamine treatments were associated with a significant and robust reduction of ACTH and cortisol response to the DEX-CRH test in patients with borderline personality disorder [8]. These results were independent of psychiatric comorbidity including comorbidity with major depression. It has also been reported that imipramine, clomipramine and desipramine have substantial effects on the HPA axis [9].

The existing body of evidence suggests that antidepressants may affect HPA function and the DEX-CRH test results. Antidepressants may have effects that are independent of their effects on biogenic amine metabolism or receptors and which produce normalization of initial HPA dysregulation. However, it is not clear how much antidepressants affect the HPA axis and the results of the DEX-CRH test in treatment non-responders. It is interesting to hypothesize that different antidepressants produce different effects on the HPA function and the DEX-CRH test results. This intriguing question merits further study.

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