Evening Chronotype and Suicide

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A chronotype is generally defined as the variability of the phase angle of entrainment, while the latter reflects the relationship between the timing of a certain rhythm (e.g., the sleep–wake cycle) and the timing of an external temporal cue. Individuals can be placed on a spectrum from "morning types" (M types) to "evening types" (E types). E-chronotype has been proposed as a transdiagnostic risk factor for psychiatric conditions, and it has been associated with psychopathological dimensions. Eveningness seems to be correlated with both suicidal ideation (SI) and suicidal behavior (SB) through several possible mediating factors. Immunological alterations have also been linked to later chronotypes and SI/SB.

Keywords: chronotype ; E-chronotype ; social jet leg ; depression ; suicide ; suicidal ideation ; suicidal behavior ; inflammation ; neuroinflammation

1. Introduction

From an ecological perspective, living organisms exist both in spatial and temporal niches [1]. Within each different spatiotemporal environment, certain regularities can be identified and used by different organisms to develop better forms of adaptation [1]. Therefore, selective pressures have always acted to facilitate the expression of those biological traits that are most associated with the aforementioned adaptive tendency, which also refer to regularities in the temporal architecture of the environment. In this sense, dampened or self-sustained internal biological rhythms represent a refined evolutionary product [1]. Humans, as complex living organisms, express different biological rhythms (ultradian, circadian, infradian) from the level of the individual cell to that of general behavior according to different biological clocks [1]. Specifically, for circadian rhythms, the suprachiasmatic nucleus (SCN) represents a fundamental center of multilevel orchestration within the central nervous system (CNS) in mammals [2].

Within this general and evolutionary framework, the chronotype can be defined as the individual variability in the phase angle of entrainment [3][4]—that is, the relationship between the timing of a certain internal biological clock (with its linked physiological and behavioral manifestations) and the timing of an external temporal cue (i.e., the *zeitgeber*), which is particularly capable of affecting the course of the associated biorhythm. However, chronotypes usually refer to sleep–wake behaviors in humans [5], and light exposure during day–night cycles thus represents the main *zeitgeber* [6][7]. In any case, the expression of behavioral chronotypes is not an exclusively human prerogative [4], which again reflects its importance in evolutionary terms.

When referring to sleep–wake behaviors, the chronotype can be indirectly assessed by checking the so-called mid-sleep point on free days (MSF)—i.e., with no alarm clock. The MSF can be defined, for instance, through questionnaires, such as the Munich ChronoType Questionnaire (MCTQ) [8], and it should subsequently be corrected for oversleeping (MSF-sc). Apparently, chronotype expression estimated in this way takes the form of a near-Gaussian distribution [9]. Consistently and according to circadian typology [10][11], individuals are usually placed on a spectrum ranging from extreme "morning types" (M types) to extreme "evening types" (E types), with most subjects falling into the wide category of "neither type" (N types). The expression of chronotypes as defined above seems to be influenced by a group of constitutive and environmental factors (**Table 1**).

Table 1. Biological, social, and psychological factors possibly influencing the chronotype expression of individual chronotype.

Possible Influencing Factor	Main Findings
Genetics [12][13][14]	Three different genome-wide association studies (GWAS) found that the genes PER2, RGS16, FBXL13, and AK5 are related to the phenotypical expression of chronotype. The gene hPer2 also seems to be involved.
Age [15][16][17][18]	Eveningness is most expressed during adolescence and young adulthood. There is substantial flattening of differences between males and females during the post-menopausal period, suggesting the importance of endocrinological factors.
Light Exposure [19][20][21][22][23]	Light is the strongest *zeitgeber* for the circadian system.
Others [22]	Level of education, religiosity, and cohabiting with small children (possible mediating effect exerted by light exposure).

2. E-Chronotype and Social Jetlag

Jetlag is commonly defined as a transient misalignment between a person's circadian rhythm and the local timing [24]. The researchers specifically refer to social jetlag (SJ) as a condition of misalignment between the preferred and socially required timing of a certain daily activity; for instance, the difference between sleep timing on workdays and the weekend [7]. When chronically experienced, SJ may lead to a condition called "circadian disruption" [7][25][26]. Unlike the notion of SJ, the definition of circadian disruption entails a range of biological effects across several scales of observation (from molecules to cells, tissues, and the organism as a whole), suggesting its possible association with a complex of psychophysical consequences. In line with previous studies [27], the Spanish study conducted by Martinez-Lozano et al. [28] investigated whether E-chronotype was linked with a pattern of psychophysical effects in school-age children. In a sample of 432 children aged 8–12, the chronotype was measured objectively (seven days of wrist temperature, physical activity, and body position) and subjectively (MCTQ). The measure was then integrated into information about sleep rhythms and light exposition, food intake, anthropometric data, metabolic parameters, and academic scores. E-type children, compared to M-type ones, more frequently presented SJ (7% and 3%, respectively; $p = 0.001$), sleep alterations, including, in particular, a lower sleep circadian function index ($p = 0.007$) with decreased relative amplitude and lower interday stability, obesity risk, and as a higher metabolic risk.

3. E-Chronotype and the Expression of Psychopathological Dimensions

E-chronotype may be a predictor of the expression of many psychopathological dimensions both during the prodromal/subacute/chronic disease phases and the overt/acute episodes. For example, eveningness appears to be associated with different aspects of attention deficit hyperactivity disorder (ADHD) symptomatology [29]. More specifically, the link is particularly pronounced for the inattentive dimension, as a correlation with impulsivity–hyperactivity (externalizing behavior) was not found in a sample of 205 adults tested with the Self-Report Scale for ADHD (ASRS) and the Composite Scale of Morningness (CSM) [30]. However, a review of 13 studies by Schlarb et al. [31] illustrates how externalizing behavior could also be chronotype-related because the circadian rhythm seems to be connected to emotional regulation. In fact, eveningness emerged as associated with behavioral problems, such as aggression and impulsivity, in adolescents and children. Social anxiety and emotional dysregulation appeared to be negatively associated with morningness ($p = 0.01$) in a sample of 510 students with no history of psychiatric disorders [32]. Insomnia and sleep problems have been also linked to E-chronotypes [33][34][35][36][37].

Endogenous abnormalities of the circadian rhythm, SJ, and circadian disruption are also hypothesized to be central mechanisms in the pathophysiology of Bipolar Spectrum Disorders (BSDs), as circadian delay may provide a first vulnerability element for BSD onset. Moreover, chronotypes have also been directly associated with manic–depressive symptoms. E-chronotype and circadian delay in BSD patients were particularly associated with the depressive phase [38]. Later chronotypes in BSD patients involved in a 5-year follow-up study (n = 318) led to experiencing fewer hypomania/mania episodes, but these patients were found to be more likely to have mild to more severe depressive symptoms over the follow-up period [39].

Still regarding mood, the available evidence concerns not only correlations between mood swings, depressive, and manic/hypomanic episodes in bipolar patients and E-chronotype, but also between the latter and unipolar depressive manifestations. A metanalysis conducted by Au et al. [40] involving 36 studies (n = 15,734) correlates eveningness to greater depressive symptom intensity both in clinical and subclinical populations, although with an overall small effect size. The association between E-chronotype and a greater likelihood of depression has been observed both in individuals with Major Depressive Disorder (MDD) and even in healthy controls [35][41][42][43]. Because depression is considered a leading cause of SI/SB, it may represent an advanced mediating factor between late chronotype and SI/SB, and it is also possibly linked to other neurobiological correlates, such as systemic or local inflammation (see further).

4. E-Chronotype as a Transdiagnostic Risk Factor for a Group of Psychiatric Conditions

Promoting the individual overexpression of some psychopathological dimensions, the E-chronotype may represent a transdiagnostic risk factor for the emergence of a group of psychiatric conditions, as apparently confirmed by some evidence. A further link between chronotype and depression has been examined in a Finnish study [43] involving 6071 participants; evening types reported depressed mood and loss of interest more frequently than morning types, thus distinguishing themselves as more prone to depression. In other works, the later chronotype has been associated with more hard-to-treat depressive conditions [44] and with a greater likelihood of non-remission of depression (OR 3.36; 95% CI 1.35–8.34; $p < 0.01$), even when controlling for insomnia severity [33]. According to some evidence, people with BD (both type I and II) are more likely to be an E-chronotype than healthy controls [45][46][47][48], even when they are euthymic [49]. Moreover, eveningness appeared to be a relatively stable characteristic irrespective of mood state when assessed longitudinally in BSD subjects [46][50].

5. E-Chronotype and Suicidality

Some interesting studies have chosen to investigate whether chronotype could be considered among the suicide risk factors. In a sample of 1332 Chinese students aged 12 to 13, an association was found (p = 0.005) between E-chronotype and SI/SB (assessed with the Chinese Child Morningness–Eveningness Scale—CMES and with the Child Behavioural Checklist—CBCL, respectively) [51]. In addition, in a population of 89 suicide attempters, E-chronotype, assessed using MEQ, was found to be linked ($p < 0.05$) to impulsiveness, assessed using the Barratt Impulsiveness Scale (BIS), which was also correlated ($p < 0.05$) with more violent suicide attempts (SA) [52]. Despite these findings in both adult and child populations, the univocal and direct association between E-chronotype and suicidality does not seem to be easily demonstrable with enough clarity. However, in line with the above, some possible mediators of the potential correlation could be highlighted. Seasonality and climate changes are well-known characteristics of the epidemiology of suicide [53][54][55][56][57][58][59][60][61], unipolar depressive recurrence [62][63], BD I, BD II, and seasonal affective disorder (SAD) recurrency [64]. As pointed out earlier, mood swings, both in psychiatric and non-psychiatric patients, also occur seasonally and may be further promoted by circadian dysregulation towards eveningness. In addition, late chronotype may facilitate affective destabilizations, though whether this is through biological or psychosocial mechanisms is unclear. In a sample of 120 adult patients affected by MDD, SI scores were higher in patients with seasonality, E-chronotype ($p < 0.001$), and hypomanic personality traits [65], thus illustrating that chronotypes and seasonality [66] may be implicated in the correlation of MDD and SB. A 2018 review taking into account 13 studies with a total sample of 3529 subjects (non-psychiatric, MDD, BPD I-II, schizophrenia, Post-Traumatic Stress Disorder, Borderline Personality Disorder, suicidal) tries to illustrate the complex relationship that seems especially verified in unipolar depression between seasonality, decreased rhythmicity, eveningness, and suicidality [67]. Although chronotype alone did not appear to be significantly associated with suicide (p = 0.139), by considering the indirect effect of the depressive symptoms, the correlation became significant (p = 0.009) in a sample of 5632 university students in which depressive symptoms, chronotype, and suicidality were systematically assessed [68]. In addition to depression, psychological pain, or psychache, also shows a role as a potential mediator between eveningness and suicidality [69].

Importantly, the mediating element between chronotype and SI/SB may also be represented by insomnia [36][37] by leading to poor daytime functioning and negative affectivity outcomes.

Finally, recalling the previous section, the intensities of mood symptoms could also promote the association between chronotype and suicide, which was not found to be direct.

6. E-Chronotypes and Suicidality: Immune Dysregulation as a Further Possible Bridging Factor?

Eveningness seems to be associated with greater local and systemic inflammation. In fact, displaying an E-chronotype is linked to a greater risk for Inflammatory Bowel Disease (IBD) [70], asthma [71], cardiovascular disease [72], metabolic disease [73], and other immune-mediated diseases [74], as well as higher blood levels of inflammatory cytokines without any clinical manifestation [75]. At the same time, neuroinflammation and systemic inflammation are associated with SI/SB both through and independent of the presence of a depressive condition [76]. The complex pathophysiology of suicide is the object of a review by Brundin and colleagues [77], which illustrates how diverse inflammatory conditions (traumatic brain injury, vitamin deficiency, autoimmune disorders, and infection) can lead to the hyperactivation of the hypothalamic–pituitary–adrenal axis and to alterations in the monoamine pathways) by dysregulating the kynurenine pathway of tryptophan metabolism. As it is known, monoamine neurotransmission is involved in the development of depressive symptoms that again appear central as a mediating factor in the suicide–inflammation correlation. Thus, the study contributes to providing a well-structured and valid biological model that could possibly explain how an immunological hyper-activation could be involved in the development of mood symptoms and in suicide risk. Serafini et al. [78] conducted another revisional study underlining a possible association between SB and inflammatory cytokine abnormalities.

A further step in exploring an eventual direct association between inflammation and SI (without any mediating role of depressive symptoms) was made in a cross-sectional study by Bergmans et al. [79] involving four indicators of inflammation: circulating levels of CRP, white blood cell (WBC) count, immunoglobulin-E (Ig-E), and dietary inflammatory potential (measured using the Diet Inflammatory Index (DII)). That study, by assessing SI and MDD with the Patient Health Questionnaire-9 (PHQ-9), distributed participants into four groups (SI with MDD, SI without MDD, MDD without SI, and neither SI nor MDD) and did not find any inflammatory index capable of distinguishing SI in MDD. The most interesting result was a direct association between DII and SI in individuals who did not present MDD. A case-control study by Fernendez-Sevillano et al. [80] showed a similar result. The sample of 96 individuals (20 controls and 76 affected by MDD) was divided into subgroups: MDD patients with a recent suicide attempt, MDD patients with a lifetime history of suicide attempts, MDD non-attempters, and controls. Blood levels of IL-2, IL2-R, IL-4, IL-6, and TNF-α were measured in all of the participants. Significantly, IL-6 concentrations were higher in both recent ($p = 0.04$) and distant ($p = 0.015$) attempters in comparison to MDD non-attempters. Thus, the plasma level of this cytokine appears to be correlated to SB without any association to MDD.

An additional factor that have to be underlined is the possible involvement of chronotype in the determination of inflammatory states, as illustrated in a cross-sectional study conducted by Orsolini and colleagues [81]. Among 133 retrospectively recruited patients with moderate–severe depression (both unipolar and bipolar), higher levels of baseline high-sensitivity CRP were associated with SA ($p = 0.05$), death ($p = 0.018$), and self-harm/self-injury thoughts ($p = 0.011$). In addition, depressive temperament emerging from the TEMPS scale and lower MEQ scores (i.e., eveningness) statistically significantly predicted higher hsCPR blood levels [81]. Thus, inflammation appears to be positively correlated to SI/SB, depressive temperament, and E-chronotype. As underlined by discussing other studies, several biologic theoretical models try to explain the link between inflammation and SI/SB. By considering E-chronotype as a risk factor for numerous inflammatory conditions, we may find one of the possible bridging points between chronotype and suicide.

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