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Perspectives in affective disorders: Clocks and sleep

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Abstract

Mood disorders are often characterised by alterations in circadian rhythms, sleep disturbances and seasonal exacerbation. Conversely, chronobiological treatments utilise zeitgebers for circadian rhythms such as light to improve mood and stabilise sleep, and manipulations of sleep timing and duration as rapid antidepressant modalities. Although sleep deprivation ("wake therapy") can act within hours, and its mood-elevating effects be maintained by regular morning light administration/medication/earlier sleep, it has not entered the regular guidelines for treating affective disorders as a first-line treatment. The hindrances to using chronotherapeutics may lie in their lack of patentability, few sponsors to carry out large multi-centre trials, non-reimbursement by medical insurance and their perceived difficulty or exotic "alternative" nature. Future use can be promoted by new technology (single-sample phase measurements, phone apps, movement and sleep trackers) that provides ambulatory documentation over long periods and feedback to therapist and patient. Light combinations with cognitive behavioural therapy and sleep hygiene practice may speed up and also maintain response. The urgent need for new antidepressants should hopefully lead to reconsideration and implementation of these non-pharmacological methods, as well as further clinical trials. We review the putative neurochemical mechanisms underlying the antidepressant effect of sleep deprivation and light therapy, and current knowledge linking clocks and sleep with affective disorders: neurotransmitter switching, stress and cortico-limbic reactivity, clock genes, cortical neuroplasticity, connectomics and neuroinflammation. Despite the complexity of multi-system mechanisms, more insight will lead to fine tuning and better application of circadian and sleep-related treatments of depression.

KEYWORDS

circadian rhythms, clock genes, connectomics, cortical neuroplasticity, neuroinflammation, sleep homeostasis

Abbreviations: 5-HT, serotonin; ACC, anterior cingulate cortex; CBT, cognitive behavioural therapy; COMT, catechol-O-methyltransferase; DA, dopamine; DLMO, dim light melatonin onset; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; GWAS, genomewide association studies; ipRGCs, intrinsically photoreceptive retinal ganglion cells; LT, light therapy; MEQ, Morningness-Eveningness Questionnaire; MHPG, 3-methoxy-4-hydroxyphenylglycol; NA, noradrenaline; SAD, seasonal affective disorder; SCN, suprachiasmatic nuclei; SD, sleep deprivation; TMS, transcranial magnetic stimulation.

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1 | INTRODUCTION

The psychiatrists of yore, well versed in observation if not in ways to cure their patients, described in detail the rhythms of mood across the day and seasons (Menninger-Lerchenthal, 1960), and even the recurrent patterns of depression and mania sometimes seemingly linked to lunar phase, a phenomenon that has now actually been documented in certain rapid cycling patients (Wehr, 2018). Rhythms have been found in a variety of periodic illnesses (Gjessing & Gjessing, 1961; Richter, 1965), but most clearly in mood disorders (Papousek, 1975). Abnormal timing, amplitude, or stability of daily rhythms characterise major depression and particularly bipolar illness; clinically, diurnal mood variation and early morning awakening, and often seasonal recurrence, are part of the diagnostic check list. Sleep disturbances are ubiquitous and not necessarily specific, but specific sleep manipulations have powerful effects on clinical state. Altered sleep–wake cycles may precede a psychotic episode (Wirz-Justice, 1995).

2 | WHERE HAVE WE COME FROM?

Historically, the non-pharmacological treatments for depression have been developed by chance and by hypothesis. Without being a comprehensive review, we summarise the evidence for circadian and sleep therapies, which have a longer tradition than basic neuroscientists usually recognise.

In the late sixties, observation of a depressed patient who improved after biking through the night led to a series of studies replicating the remarkable and rapid antidepressant effect of a night without sleep (not necessarily with biking). The difficulty of carrying out double-blind placebo-controlled trials of sleep deprivation (SD) is obvious; however, the accumulated evidence for this overnight response in severe depression is incontrovertible (Boland et al., 2017; Dallaspezia & Benedetti, 2015).

Because it seemed unfair to demand a sleepless night in sleep disturbed patients, the name was changed from sleep deprivation to "wake therapy." Furthermore, to diminish the perceived load, comparisons were made with partial sleep deprivation in the first or second half of the night to see whether this shorter wake period would suffice (the latter was efficacious). Finally, a paradigm of shifting sleep earlier, that is, not a sleep deprivation but a modification of the timing of sleep, was postulated, under the assumption that the second half of the night was the vulnerable phase for depression when asleep (the "internal coincidence" hypothesis [Wehr & Wirz-Justice, 1981]). Phase advance of the sleep–wake cycle led to more gradual, but longer-lasting mood improvement (Wehr & Wirz-Justice, 1981).

Thus, even though SD has been known to be antidepressant for nearly fifty years, these procedures have not entered treatment guidelines or everyday practice (Kuiper, McLean, Fritz, Lampe, & Malhi, 2013; Wirz-Justice, 1998). In this respect, the paradoxical finding of a questionnaire study in all psychiatric hospitals in Austria, Germany and Switzerland is instructive (Winkler et al., 2018). Although sleep deprivation was known and recommended by 61% of all hospitals, nearly two-thirds of them had not treated a patient with it during the last 12 months. The gap between theory and practice is enormous, probably due to the perceived burden of managing the night shift to keep patients awake.

The use of light as a therapeutic modality developed out of key discoveries in basic circadian rhythm research in the early eighties. First, that daylength (photoperiod) was coded by the biological clock in the suprachiasmatic nuclei (SCN) into the duration signal of nocturnal melatonin secretion, as a mechanism for seasonal initiation of behaviours such as hibernation and reproduction (Kripke, Elliott, Welsh, & Youngstedt, 2015). Second, that melatonin secretion could be suppressed by bright light in humans, which provided a tool for manipulating circadian timing as well as seasonal behaviour (Lewy, Wehr, Goodwin, Newsome, & Markey, 1980). This led to the (re)discovery of seasonal affective disorder (SAD; Rosenthal et al., 1984) and a worldwide series of clinical trials of light therapy that established light as the treatment of choice for these patients (Partonen & Pandi-Perumal, 2010). Over the years, several trials have extended the use of light to non-seasonal depression (e.g., Lam et al., 2016): response usually required longer treatment than in SAD, but the effect size was equal to, if not better, than for antidepressant drugs (Al-Karawi & Jubair, 2016; Penders et al., 2016; Perera et al., 2016). In addition, light therapy became established in sleep medicine for circadian sleep–wake cycle disorders (Campbell et al., 1995).

The physiological meaning of melatonin for human sleep and the circadian system is still a matter of controversy (Li et al., 2019). Melatonin is of interest, not only as the gold standard biological marker of internal time, but, exogenously applied, as a putative zeitgeber, shifting rhythms earlier when ingested in the early evening. Melatonin is the hormonal signal of darkness and directly induces distal vasodilatation and heat loss, the physiological gate to sleep onset (Kräuchi, Cajochen, Pache, Flammer, & Wirz-Justice, 2006). Thus, in addition to its use to speed up re-entrainment in jet lag and shift work, melatonin could be a mild soporific for many psychiatric sleep problems (Wirz-Justice & Armstrong, 1996). There have been but few studies. Investigations of a putative antidepressant effect have been negative (the improvement being rather in the sleep than mood domain; Hansen, Danielsen, Hageman, Rosenberg, & Gogenur, 2014).

3 | WHERE ARE WE TODAY?

Sleep deprivation continues to be used in individual clinics, but interest in further research is lacking (Winkler et al., 2018). Our research unit in Milano appears to be one of the very few which has consistently studied the clinical and neurobiological effects of sleep deprivation, now for over twenty years (Benedetti, Barbini, Colombo, & Smeraldi, 2007). Our present knowledge combines information about clock gene variants, correlations with symptoms, neurotransmission and brain imaging.

In animal models, all the neurotransmitters that have been involved in the pathogenetic models of depression are influenced by SD in the same direction as antidepressant drugs. (a) SD increases serotonin (5-HT) neurotransmission (Adrien, 2002) and the behavioural responsiveness to 5-HT precursors (Santos & Carlini, 1983); it enhances the activity of 5-HT neurons (Gardner, Fornal, & Jacobs, 1997); it increases extracellular 5-HT (Lopez-Rodriguez, Wilson, Maidment, Poland, & Engel, 2003) and 5-HT turnover (Asikainen, Deboer, Porkka-Heiskanen, Stenberg, & Tobler, 1995; Cramer, Tagliamonte, Tagliamonte, Perez-Cruet, & Gessa, 1973; Hery, Pujol, Lopez, Macon, & Glowinski, 1970); and it reduces the sensitivity of 5-HT-1_A inhibitory autoreceptors (Gardner et al., 1997; Maudhuit, Jolas, Chastanet, Hamon, & Adrien, 1996). (b) SD also increases synaptic levels of noradrenaline (NA) (Hipolide et al., 2005), tyrosine hydroxylase and NA transporter mRNA in the locus coeruleus (Basheer, Magner, McCarley, & Shiromani, 1998). (c) SD increases dopamine (DA) activity and behavioural response to DA agonists (Mogilnicka, 1981; Tufik, Lindsey, & Carlini, 1978), with an increase of DA receptor binding sites during the early stages of SD (following 12–24 hr awake; Wirz-Justice et al., 1981) and a subsequent subsensitivity after more prolonged wake (Zwicker & Calil, 1986), suggesting downregulation after prolonged stimulation. (d) Following a similar pattern, SD first increases glutamate release and then downregulates it (Dash, Douglas, Vyazovskiy, Cirelli, & Tononi, 2009), an effect paralleled by a reduction of NMDA receptor sensitivity (Novati, Hulshof, Granic, & Meerlo, 2012), possibly due to a change in the expression of its subunits (Park, Kang, Paik, & Kim, 2012). (e) SD downregulates the expression of several clock genes, including Ciart, Per2, Npas4, Dbp and Rorb, in the anterior cingulate cortex (ACC; Orozco-Solis et al., 2017).

In depressed patients, clinical psychobiology has linked these effects with the efficacy of chronotherapeutics. (a) Concerning 5-HT, SD increased the prolactin response to intravenous tryptophan infusion, a challenge for 5-HT function (Salomon et al., 1994); its clinical effects are influenced by genotypes influencing the density of the 5-HT transporter (Benedetti, Barbini, Bernasconi, Fulgosi, Campori, et al., 2008; Benedetti, Colombo, et al., 2003; Benedetti, Serretti, et al., 1999) and of the 5-HT_{2A} receptor (Benedetti, Barbini, Bernasconi, Fulgosi, Colombo, et al., 2008), with effect sizes similar to those observed for antidepressant drugs (Serretti, Benedetti, Zanardi, & Smeraldi, 2005); (b) Concerning NA, its metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG) and MHPG sulphate (Muller, Riemann, Berger, & Muller, 1993) increased after SD proportionally to severity of depression (Amin, Khalid, & Khan, 1980) and clinical response to treatment (Matussek, Romisch, & Ackenheil, 1977). (c) Concerning DA, SD decreased plasma levels of prolactin, which is inhibited by DA agonists (Baumgartner, Riemann, & Berger, 1990; Kasper et al., 1988); it decreased D2 receptor occupancy by a radioligand proportional to antidepressant response, thus suggesting an enhanced DA release in responders displacing the radioligand (Ebert, Feistel, Kaschka, Barocka, & Pirner, 1994); its clinical effects are predicted by levels of homovanillic acid in the spinal fluid (Gerner, Post, Gillin, & Bunney, 1979); it increases eye-blink rate, suggesting DA activation in responders (Ebert et al., 1996). Moreover, the clinical effects of SD are influenced by gene variants affecting the efficiency of catechol-O-methyltransferase (COMT) in clearing NA and DA from the synapse (Benedetti, Barbini, et al., 2010), again with effect sizes comparable to those observed for response to antidepressant drugs (Benedetti, Colombo, Pirovano, Marino, & Smeraldi, 2009; Benedetti, Dallaspezia, et al., 2010). (d) Concerning glutamate, the decrease of glutamate/glutamine levels in the ACC after repeated SD is proportional to the antidepressant response (Benedetti, Calabrese, et al., 2009), and gene variants affecting post-synaptic scaffolding proteins for glutamate-mediated synaptic plasticity influence its efficacy (Benedetti et al., 2018). (e) Concerning clock genes, variants of hPER3 affect efficacy (Dallaspezia et al., 2016).

Light therapy (LT) has expanded in application to other neuropsychiatric domains—some examples are to be found in studies of bipolar disorder (Benedetti, 2018), borderline personality disorder (Bromundt et al., 2013), Parkinson's disease (Martino, Freelance, & Willis, 2018; Videnovic et al., 2017), fibromyalgia (Burgess et al., 2017)—and even to internal medicine, for example, insomnia in cirrhosis (De Rui et al., 2015) or post-kidney transplantation (Burkhalter et al., 2015), depression in cystic fibrosis patients (Kopp et al., 2016), post-stroke (Sondergaard, Jarden, Martiny, Andersen, & Bech, 2006) and cancer (Dallaspezia, Cantamessa, & Benedetti, 2018). Light probably does not treat the illness *per se*, but it can aid in reducing concomitant symptoms of poor sleep and daytime alertness. Important are the stabilising and entraining properties of light, as well as direct activating and mood enhancing effects.

The discovery of a novel photoreceptor in retinal ganglion cells (ipRGCs), containing the photopigment melanopsin sensitive to blue wavelength light (Schmidt et al., 2011), initiated exciting basic research on the non-visual and emotional

effects of light, but also immediately impacted on the design of light therapy devices. The original broad-spectrum white light boxes were followed by development and sale of blue LED devices without sufficient evidence for greater efficacy (with additional "blue cone danger"). The ipRGCs have initiated a veritable revolution in the lighting industry and led to complex questions as to what kind of light and how much should be given to whom when—to which research is not yet able to provide recipe-like answers. However, the norms of indoor lighting are being broadened beyond the visual system (Lucas et al., 2014), somewhat simplified in the formula "human centric lighting." Today, the flexibility of programming LEDs allows artificial lighting to follow the arc of changes in daylight, indeed, to develop lighting patterns tailored to the inhabitants of a given building. This has enormous implications also for architecture itself, demanding more daylight and more naturalistic artificial lighting in a still-to-be-defined "healthy" combination. Already we know that higher daylight availability for hospitalised patients, as observed in east-facing rooms, or with bigger windows, or with hospital beds nearer to windows, has been shown to act indirectly as "light therapy" and to consistently speed up recovery from depression (Beauchemin & Hays, 1996; Benedetti, Colombo, Barbini, Campori, & Smeraldi, 2001; Canellas et al., 2016; Gbyl et al., 2016). More generally, sunny rooms improve outcomes after a first attack of myocardial infarction (Beauchemin & Hays, 1998); improve sleep in medical wards (Bano et al., 2014); and reduce the need of painkillers after spinal surgery (Walch et al., 2005). Architects are now constructing psychiatric wards or retirement homes using the new technology and chronotherapeutic principles (Kallestad, Morken, & Langsrud, 2016; Münch et al., 2017). Conversely, there is growing awareness of the potential influence of LED lighting on mental illness (Bauer et al., 2018).

As found for SD, the antidepressant effects of LT have been associated with changes in monoaminergic neurotransmission. In patients with non-seasonal depression and in healthy subjects, light augmented blood 5-HT throughout the day (Rao et al., 1990), with platelet paroxetine and imipramine binding decreasing significantly after treatment (Mellerup, Errebo, Molin, Plenge, & Dam, 1993). Light therapy decreased 5-HT transporter binding by a radioligand in anterior cingulate and prefrontal cortex (Tyrer et al., 2016b), thus counteracting its excessive winter seasonal increase in patients with SAD (Tyrer et al., 2016a). These mechanisms are necessary for the antidepressant effect, because both rapid tryptophan/5-HT depletion and catecholamine depletion reverse the antidepressant effect of LT in SAD (Lam et al., 1996; Neumeister et al., 1998).

Melatonin, the ideal "natural" soporific (Wirz-Justice & Armstrong, 1996), has only been commercially developed for age-related insomnia (in a patented slow release formulation, Circadin®); otherwise, it is available over the counter in many countries without regard to dosage, formulation, information as to appropriate timing, or control over purity or content. The evidence for melatonin as a treatment for circadian sleep–wake cycle disturbances in blind persons is strong (Quera Salva, Hartley, Leger, & Dauvilliers, 2017; Uchiyama & Lockley, 2015); also for other visually impaired individuals where light input is diminished, melatonin can provide the evening zeitgeber signal for sleep onset. Not surprisingly, patented melatonin agonists (Tasimelteon® and Ramelteon®) have been more stringently studied and approved for treating sleep disorders in the blind than melatonin itself. Agomelatine, which acts not only on melatonin receptors but also as a $5HT_{2C}$ antagonist, is available as an antidepressant (Williams, McLin, Dressman, & Neubauer, 2016).

If melatonin is the signal of darkness to the body, then darkness itself may also be neurobiologically active. A few studies of the effect of "long nights" (14 hr darkness) on rapid cycling or mania (Dallaspezia & Benedetti, 2015) support the suggestion that bipolar patients are extremely sensitive to the environmental light–dark cycle which can trigger or augment symptoms of depression or mania. Following the discovery of blue wavelengths as mediating photic information to the circadian pacemaker and mood centres, it was postulated that blocking these wavelengths might also be therapeutic in particular situations. Thus, blue-blocking, amber-coloured sunglasses have been used to treat mania or to stop rapid cycling analogous to (and more simple than) the long-night treatment (Henriksen et al., 2016). Although not yet widely studied, programs have already been developed to modulate the blue-ish background screens of computers, i-phone devices, or change baby lamps and hospital rooms to amber or warm white spectra at night.

3.1 | Combined chronotherapeutics

We have presented these various treatments as single options. However, more and more trials have used chronotherapeutic combinations in order to prevent relapse after recovery sleep following sleep deprivation, together with lithium in bipolar patients (Baxter, 1985; Baxter et al., 1986) or antidepressants in unipolar depression (Martiny et al., 2012). Continuing ongoing lithium during chronotherapeutics leads to sustained remission over months, and stable euthymia is then obtained in the majority of patients without the need for other psychotropic drugs (Benedetti, Barbini, Fulgosi, et al. 2005; Benedetti, Colombo, Barbini, Campori, & Smeraldi, 1999; Colombo et al., 2000). Lithium not only sustains response to SD, but it enhances it as well, probably by overcoming the effect of unfavourable genetic predispositions which affect neurotransmission (Benedetti, Barbini, Bernasconi, Fulgosi, Campori, et al., 2008; Benedetti et al., 2012).

Synergy is documented for SD with effective antidepressant drugs, independent of their mechanism of action (Wirz-Justice, Benedetti, & Terman, 2013), and with other chronotherapeutic techniques, such as LT and sleep phase advance. For this latter combination, a phase advance of the sleep–wake cycle and of the rest–activity rhythms is a correlate of antidepressant response to SD (Benedetti, Dallaspezia, Fulgosi, et al., 2007). The efficacy of the triple combination of SD, LT and sleep phase advance has been tested in multiple clinical settings and ethnic groups, with consistently replicated antidepressant effects and similar effect sizes (Benedetti, Barbini, et al., 2001; Berger et al., 1997; Echizenya, Suda, Takeshima, Inomata, & Shimizu, 2013; Gottlieb & Terman, 2012; Hurd, Herrera, Brant, Coombs, & Arzubi, 2019; Sahlem et al., 2014; Voderholzer et al., 2003; Wu et al., 2009).

Repetition of SD at short time intervals (every 2–3 days) leads to progressively better acute antidepressant effects (Benedetti & Colombo, 2011; Suzuki et al., 2018), and SD once a week has also been proposed as a prophylactic treatment to sustain response and prevent relapse (Papadimitriou, Christodoulou, Katsouyanni, & Stefanis, 1993). In everyday clinical settings, the combination of repeated SD, LT and lithium is able to produce sustained antidepressant effects, most strikingly in about one-half of bipolar patients who did not respond to several antidepressant drug trials, and who had developed hopelessness and suicidality as a consequence of their long-lasting, untreatable depression (Benedetti, Barbini, Fulgosi, et al. 2005; Benedetti, Riccaboni, et al., 2014). This high rate of efficacy in non-responders to antidepressants is likely to be due to the multiple mechanisms of action of chronotherapeutics, as summarised above and further addressed in the last part of this review.

4 | WHAT ARE THE PERSPECTIVES?

Chronotherapeutics has been proposed as an experimental model to study the biological basis of depressive psychopathology and antidepressant response (Benedetti & Smeraldi, 2009; Gillin, Buchsbaum, Wu, Clark, & Bunney, 2001). Current knowledge points to multiple neurobiological effects as responsible for the clinical mood amelioration, suggesting a multi-target mechanism of action. New data allow us to reverse-translate these new insights in neuroscience from mood disorders to human physiology.

4.1 | Neurotransmitter switching, stress and cortico-limbic reactivity

Neurotransmitter expression has been considered a constant and immutable aspect of neuronal identity, but recent studies have shown that neurons can re-specify their neurotransmitters (Spitzer, 2012). Exposure to light and darkness can trigger this neurotransmitter switching. In nocturnal rodents, hypothalamic neurons shift the release of neurotransmitters from dopamine to somatostatin during long days, and back to dopamine during short days (Dulcis, Jamshidi, Leutgeb, & Spitzer, 2013), while neurons in the paraventricular nuclei exhibit a similar switching between dopamine and glutamate (Meng, Li, Deisseroth, Leutgeb, & Spitzer, 2018). In turn, the increased dopamine signalling leads to decreased activation of the HPA axis, and to a decrease in stress-related behaviours (Dulcis et al., 2013; Meng et al., 2018). In humans and in other diurnal animals, short days are associated with depressive-like behaviours, higher behavioural and hormonal responses to stress, and higher HPA axis activity (Ashkenazy, Einat, & Kronfeld-Schor, 2009; Ikeno, Deats, Soler, Lonstein, & Yan, 2016; Qin et al., 2015), the latter being a consistently observed phenotype in human depression (Pariante & Lightman, 2008).

It can be surmised that neurotransmitter switching could provide a core biological underpinning for circadian preference in diurnal and nocturnal animals and for the antidepressant effects of chronotherapeutics. Neuroimaging studies provide indirect evidence for the above. In healthy humans, exposure to light reduces threat-related amygdala and prefrontal reactivity and dose dependently increases amygdala-prefrontal and intraprefrontal functional coupling (Fisher et al., 2014); it induces a dose-dependent increase in striatal response to risk, paralleling a dose-dependent increase in risk-taking (Macoveanu et al., 2016); it reduces both conditioned response to fear, and extinction-related prefrontal activity, facilitating fear extinction and sustaining tolerance to fear re-conditioning (Yoshiike, Honma, Yamada, Kim, & Kuriyama, 2018). These non-image forming, direct effects of exposure to light include the modulation of cognitive brain function, with wavelength, duration and intensity of light exposure influencing both performance and brain responses to non-visual cognitive tasks (Vandewalle, Maquet, & Dijk, 2009).

In depressed patients, changes in the metabolism of limbic structures, and in the cortico-limbic responses to emotional stimuli and to tasks evoking the cognitive generation of affect, are the most consistently replicated correlates of antidepressant chronotherapeutics. Successful SD consistently normalised the significantly elevated metabolism observed in medial prefrontal—anterior cingulate cortex (Wu, Buchsbaum, & Bunney, 2001), while the combination of SD and LT enhanced neural responses to emotional stimuli in prefrontal cortex (Benedetti, Bernasconi et al., 2007) and normalised effective connectivity between cortico-limbic structures (Vai et al., 2015), whose inefficient functional coupling associates with depression, dysregulated response to environmental stimuli, and suicide (Radaelli et al., 2015).

These effects have been related to rapid changes in the release of 5-HT and of DA (Benedetti & Smeraldi, 2009; Ebert & Berger, 1998), which can be taken up and released by the same neurons (Zhou et al., 2005), also by volume transmission outside the synapses (Fuxe et al., 2007). They continuously covariate in the human CSF (Geracioti et al., 1998) following a clear circadian and seasonal pattern (Lambert, Reid, Kaye, Jennings, & Esler, 2002). These neurons could switch between neurotransmitters as a function of exposure to light and darkness, and/or of the sleep–wake cycle. Such an as yet unexplored mechanism might underlie these rapid changes.

Moreover, the recent discovery (Fernandez et al., 2018) that separate pathways convey light stimulation of distinct ipRGC subpopulations to distinct circuits for hippocampal learning and for mood-emotional regulation (the latter involving a direct functional connectivity between retina and the perihabenular nucleus, projecting to the ventral medial prefrontal cortex, thus skipping the SCN) opens a brand new approach to investigate the three main effects of light: as zeitgeber, as cognitive enhancer and as mood regulator. In this respect, it should also be noted that other brain structures beyond the SCN contain central timing mechanisms, including the lateral habenula, and project to core structures controlling monoaminergic transmission such as the ventral tegmental area and the raphé (Mendoza, 2017), thus suggesting a complex interplay, yet to be explored, between clock- and non-clock effects of light in the brain.

4.2 | Clock genes

At the cellular level, the circadian modulation of RNA expression and chromatin remodelling occurs on a genomewide scale. Genomewide circadian rhythms have been detected, regulating the recruitment of RNA polymerase II and histone modifications, with the majority of genes bound by circadian transcriptional regulators, coactivators and RNAPII being expressed, suggesting that gene expression in itself is correlated with circadian transcription factor binding (Koike et al., 2012). This transcriptional core clock machinery also controls the expression of cell-cycle regulators, while, in turn, cell-cycle proteins affect circadian rhythms of clock genes. At the cellular level, a common set of enzymes regulates the post-translational cell cycle and the circadian clock, thus suggesting that the two oscillating systems interact in shaping development and fate of all somatic cells (Gaucher, Montellier, & Sassone-Corsi, 2018). Considering the whole organism, these molecular rhythms translate into behaviour: in healthy humans, the circadian variation of activities matches the clock properties of peripheral cells, and the effects of the humoural regulators of the cells' circadian period are paralleled by effects on rhythmicity of behaviour. For example, individual chronotype can be predicted by the period of the circadian oscillations in gene expression detected in skin fibroblasts (Brown et al., 2008; Pagani et al., 2011). In turn, exposure to light can entrain these rhythms by epigenetic mechanisms, involving global changes in DNA methylation in the SCN which parallel the entrainment of circadian behaviour (Azzi et al., 2014).

Multiple gene variants in the clock machinery have been associated with depression (Garbazza & Benedetti, 2018). Several factors affecting the biological clock, such as gene polymorphisms of the core clock machinery or the seasonal change of daylight duration, exert a marked influence on the behaviour of patients affected by mood disorders. Experimental findings suggest that the relationship between clock and behaviour can be markedly more apparent in patients with mood disorders than in the general population (Benedetti & Terman, 2013). Examples from molecular genetics include the effects of variants of CLOCK and hPER3, which can delay or advance the preferred time for daily activities and influence homeostatic response to sleep loss in a healthy population (Goel, Banks, Mignot, & Dinges, 2009; Maire et al., 2014; McClung, 2013), but can also influence onset of illness, recurrence of mood episodes, symptom profile, and illness course and outcome in patients with mood disorders (Benedetti, Dallaspezia, Cigala Fulgosi, et al. 2007; Benedetti, Radaelli, et al., 2008; Benedetti et al., 2015; Benedetti, Serretti, et al., 2003; Dallaspezia et al., 2016, 2011; Serretti et al., 2003; Serretti, Cusin, et al., 2005). Examples from human neuroimaging include seasonal variation of the brain 5-HT transporter, which is normally higher in winter and lower in summer (Praschak-Rieder, Willeit, Wilson, Houle, & Meyer, 2008), but which, in patients with SAD, has higher seasonal amplitude (Tyrer et al., 2016a), is directly related with the severity of the depressive syndrome (Mc Mahon et al., 2016), and is a target for treatment (Harrison et al., 2015; Tyrer et al., 2016b).

This specific sensitivity can also be exploited for therapeutic purposes (Wirz-Justice et al., 2013).

Current models of the circadian system suggest that the hierarchical control exerted on circadian rhythms of behaviour and physiological functions by the core molecular machinery of the SCN (Takahashi, Hong, Ko, & McDearmon, 2008) also impacts many mechanisms which contribute to the observed behaviour and physiology. A dependence of behaviour on clock gene mutations similar to that observed in mood disordered patients occurs in rodents in the absence of other regulators of circadian rhythmicity, such as melatonin, and is abolished when these regulators are restored (Shimomura et al., 2010). Research approaches targeting cortical correlates of circadian and homeostatic processes are likely to provide new insights on this issue (Muto et al., 2016; Vandewalle et al., 2011).

A caveat must, however, be considered. Studies on the role of clock gene variants in mood disorders are in their infancy.

Though promising, they are mostly unreplicated and have been obtained in small samples. There are very few polymorphisms, such as the CLOCK -3111 T/C, which have been both studied in humans and modelled in animals to elucidate their neurobiological effects (Ozburn et al., 2016). A continuously evolving behavioural modelling of clock gene mutations in animals allows to deepen insights on the role of the molecular clock machinery in mammalian brain functioning (Parekh et al., 2018; Timothy et al., 2018), but this kind of evidence has not yet been matched with results of large genomewide association studies (GWAS) in mood disorders (McCarthy, 2018). Replication of single gene effects in humans, and modelling in animals, is needed before the clinical relevance of these gene variants can be assessed and possibly translated into clinical psychiatric practice, also anticipating the need for reverse-translational and reverse-phenotyping approaches to identify the role of single gene variants across current psychiatric illness categories (Demkow & Wolanczyk, 2017).

4.3 | Cortical neuroplasticity

According to the synaptic homeostasis hypothesis, plasticity processes during wakefulness lead to a net increase of synaptic strength in cortical circuits proportional to their engagement during learning and experience, whereas synaptic potentiation is followed by a homogeneous reduction in the strength of cortical synapses during sleep (Vyazovskiy & Faraguna, 2015). This sleep-dependent process is crucial to restore attentional capacity for new learning and goal-directed behaviour during the following wake period (Vyazovskiy, Walton, Peirson, & Bannerman, 2017).

There is a wide consensus that sleep loss is detrimental to many brain functions and impairs neuroplasticity (Areal, Warby, & Mongrain, 2017). In animal models, sleep loss has been consistently associated with impaired neurogenesis and neuroplasticity, particularly evident in the hippocampus, which parallels the deficits in attention, learning, memory, emotional reactivity, executive function and decision making which have been described in humans as well (Kreutzmann, Havekes, Abel, & Meerlo, 2015; McCoy & Strecker, 2011). The role of adult hippocampal neurogenesis in humans is debated (Kempermann et al., 2018), but, across species, sleep restriction and disruption affect the expression of genes related to neuronal plasticity, brain function, cognition, inflammation, cellular stress, impairment of protein translation, metabolic imbalance and thermal deregulation (da Costa Souza & Ribeiro, 2015). Clearly, these detrimental effects cannot explain the rapid improvement of mood-congruent cognition and neuropsychological functioning which has been consistently described in patients after therapeutic SD (Baving et al., 1997; Benedetti, Barbini, Florita, et al., 2005). However, when modelling in animals the same repeated SD protocols used in chronotherapeutics, behavioural antidepressant-like effects and activation are observed (Benedetti, Fresi, Maccioni, & Smeraldi, 2008), paralleled by an increase of spine densities in granular neurons of the dentate gyrus, and by an increased expression of the canonical Wnt signalling gene Wnt7a, of the microglia/macrophages genes Iba-1 and chemokine receptors Cx3cR1 and CxcR4, and of Arc/Arg3.1, thus strongly suggesting that chronotherapeutics induces neuroplasticity (Muzio et al., 2016). Moreover, in mice, ketamine and SD elicit common transcriptional responses in the ACC implicating distinct elements of the circadian clock and processes involved in neuronal plasticity (Orozco-Solis et al., 2017).

Sleep–wake-related changes of cortical excitability match the pattern of homeostatic synaptic potentiation and downscaling (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008), thus making it possible to non-invasively investigate them in humans by means of combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) (Canali, 2014). TMS/EEG confirms the pattern of increased cortical excitability/synaptic potentiation during wake and after SD, with the expected decreased excitability/synaptic reduction during recovery sleep in healthy humans (Huber et al., 2013); it also documents an interaction of sleep-related homeostatic processes and clock-related circadian rhythms in regulating cortical synaptic strength (Chellappa et al., 2016; Ly et al., 2016). The increased synaptic strength is paralleled by decreased LTP-like plasticity, possibly due to saturation after SD, which is restored after sleep (Kuhn et al., 2016). This has been formalised in a novel synaptic plasticity model of therapeutic SD in major depression (Wolf et al., 2016). Notwithstanding the impairment in neuropsychological tests targeting cortical functions, possibly due to saturation and altered signal/noise ratio associated with acute imbalance of circadian synaptic homeostasis, these experiments consistently suggest that one night of SD increases cortical excitability and synaptic strength in healthy humans. Similarly, there is new evidence for neuroplasticity of such an extent as to be associated with an increase of prefrontal cortical brain volumes detected in structural MRI after SD in healthy humans (Elvsashagen et al., 2017).

Up to now, only one study has addressed this question clinically, by studying TMS/EEG in bipolar depressed patients before, during and after a course of repeated SD combined with LT (Canali et al., 2014). Results showed that cortical excitability did not show sleep-related changes at baseline, but then progressively increased during the antidepressant treatment and as a function of time awake, thus normalising the time course of its daily homeostatic variation. Higher values differentiated responders from non-responders at baseline and during and after treatment on all measures. These results suggest then that synaptic potentiation, and its homeostatic fluctuation, plays a specific role in the antidepressant effect of chronotherapeutics, also considering that other TMS/EEG

measures, targeting the activation of the beta/gamma band unrelated to synaptic homeostasis, remain abnormal and unaffected by successful chronotherapeutics (Canali et al., 2017).

Studies in the field are in its infancy, but provide coherent results. The observation that in patients plasticity-related EEG measures change in the same direction after chronotherapeutics, ketamine (Duncan et al., 2013) and ECT (Casarotto et al., 2013) suggests, however, that rapidly promoting cortical neuroplasticity could be a mechanism common to all rapid-acting antidepressants.

4.4 | Connectomics

Consistent evidence associates behaviour and emotions both to cortical activity in multiple regions and to the function and integrity of the fibres connecting them (Baird, Colvin, Vanhorn, Inati, & Gazzaniga, 2005; Gazzaniga, 1989). The circadian timing system and sleep homeostasis influence connectivity among brain areas. In healthy controls, the functional integration of resting state networks, including dorsal attention, default mode, sensorimotor and hippocampal networks, decreases from morning to afternoon, and even further following sleep deprivation (Blautzik et al., 2013; Hodkinson et al., 2014; Kaufmann et al., 2016; Samann et al., 2010). These changes of resting state connectivity are reversed by sleep (Kaufmann et al., 2016), and longer sleep duration associates with higher cortico-limbic connectivity (Killgore, Schwab, & Weiner, 2012). Moreover, chronotype associates with markers of white matter structure and grey matter function: extreme early and late chronotypes, compared to intermediate chronotypes, show attenuated dorsolateral prefrontal cortex (DLPFC) activation during an attention task (Reske, Rosenberg, Plapp, Kellermann, & Shah, 2015), and late chronotypes show reduced fractional anisotropy in ACC regions (Rosenberg, Maximov, Reske, Grinberg, & Shah, 2014).

Functional connectivity associates with white matter microstructure (van den Heuvel, Mandl, Luigjes, & Hulshoff Pol, 2008), and sleep influences white matter microstructure. Sleep promotes myelination and oligodendrocyte precursor cell proliferation (Benedetti et al., 2016), enhances transcription of genes involved in synthesis and maintenance of membranes and myelin (Cirelli, Gutierrez, & Tononi, 2004) and modulates neuronal membrane homeostasis (Baldessarini et al., 2013). Moreover, water diffusion along white matter tracts changes rapidly in the normal human brain, following circadian patterns which are region specific (Jiang et al., 2014), and could possibly reflect different organisation of the extracellular matrix in different brain areas (Marcoli et al., 2015). Animal models showed that increased convective fluxes of interstitial fluid during sleep increased the rate of clearance of metabolites from the brain, including β-amyloid (Xie et al., 2013), whereas poor sleep quality in older adults was associated with increased brain levels of this dangerous metabolite (Spira et al., 2013).

One in vivo study in depressed patients with bipolar disorder correlated the duration of nocturnal sleep with diffusion-tensor imaging measures of the organisation of myelin and axonal structures (Benedetti, Melloni, et al., 2017), associating sleep loss with signs of disruption in key tracts, contributing to the functional integrity of the brain which associates with mood disorders (Vai, Bollettini, & Benedetti, 2014). This suggests that circadian and sleep disruption may contribute to impaired connectomics in neuropsychiatric diseases.

Functional connectivity between brain cortical areas is widely disrupted in neuropsychiatric disorders and is proposed as a major biological underpinning of emotional dysregulation and impaired cognition (Vai et al., 2014). Synchronous function among neural networks is ensured by myelination of white matter tracts (Lu et al., 2013), and in the case of mood disorders and of schizophrenia, abnormalities of diffusion-tensor imaging measures of white matter integrity have been described in cortico-limbic networks, and associated with core psychopathological symptoms, including cognitive deficits and affective instability (Benedetti et al., 2011; Johnston et al., 2017; Poletti et al., 2015). These structural abnormalities are well evident in patients soon at the beginning of illness, reflect altered developmental trajectories of anterior grey and white matter during adolescence (Najt et al., 2016), and are negatively influenced both by common genetic variation underlying risk for mood disorders (Whalley et al., 2013) and by exposure to adverse childhood experiences (Benedetti, Bollettini, et al., 2014; Poletti et al., 2018). It is suggested that a reduced integrity of white matter tracts could underpin dysfunctions in networks implicated in the generation and control of affect and cognition in neuropsychiatric disorders, reflecting the interaction of genetic and environmental factors (Benedetti & Bollettini, 2014).

This makes brain connectomics a new target for chronotherapeutics of depression. Patients with bipolar depression show a reduced cortico-limbic effective connectivity during emotional processing (Radaelli et al., 2015), and successful antidepressant sleep deprivation increases it in responders to treatment, but not in non-responders (Vai et al., 2015). Interestingly, enhanced functional connectivity with higher sleep pressure is the opposite of what is observed in healthy controls (see above), similar to the opposite effects of sleep deprivation on mood in patients with depression (antidepressant, and triggering euphoria) and in healthy controls (depressogenic).

4.5 | Neuroinflammation

Animal models show that sleep loss associates with measures of neuroinflammation, such as increased secretion of pro-inflammatory cytokines (Fernandes, Araujo, Tufik, &

Andersen, 2017), increased blood–brain barrier permeability (Hurtado-Alvarado et al., 2018) and activation of microglia (Wisor, Schmidt, & Clegern, 2011). Animal models also suggest that perturbations of microglial function lead to abnormal maturation of several brain cellular processes, including altered synaptogenesis, synaptic pruning, axonal growth and myelination, which result in behavioural abnormalities that emerge during the juvenile period (Johnson & Kaffman, 2018) and that imbalance of inflammatory cytokines in both hippocampus and plasma could mediate the detrimental effect of sleep restriction on memory (Wadhwa et al., 2017).

On the other hand, the immune/inflammatory system is needed to maintain sleep homeostasis. Cytokines interact with 5-HT to differentially regulate sleep architecture both in normal conditions and during infection, promoting NREM sleep (Imeri & Opp, 2009), and are needed for synaptic scaling (Stellwagen & Malenka, 2006). Blocking microglial activation and alternatively activating (M2) macrophages reduces both spontaneous sleep and the homeostatic increase in EEG slow wave activity which is expected after SD (Wisor et al., 2011), and which is a core correlate of synaptic potentiation during wake (Rodriguez et al., 2016), and the homeostatic sleep rebound after SD (Massie, Boland, Kapas, & Szentirmai, 2018). We have also observed microglial activation as a correlate of the antidepressant-like effects of SD and of SD-induced increase of hippocampal spine density (Muzio et al., 2016). Moreover, the immune system plays a key role in resolving neuroinflammation, maintaining brain homeostasis and clearing metabolites from the brain including beta-amyloid (Baruch et al., 2015; Baruch & Schwartz, 2013), a process that is likely to occur during sleep (Xie et al., 2013).

In patients with mood disorders, a dynamic pattern of T cell defects, flares of inflammation, and compensatory increases of immune cells subset is observed during their lifetime (Drexhage et al., 2011; Snijders et al., 2016). The interpretation of these findings is still under debate, and several different mechanisms have been proposed, including an inborn dysregulation of the immune system, leading to auto-inflammatory reactivity, stress and exposure to infectious agents (Anderson & Maes, 2015; Bergink, Gibney, & Drexhage, 2014; Dantzer, 2012; Leonard & Maes, 2012; Raison, Capuron, & Miller, 2006). In adult clinical populations, an increased production of pro-inflammatory cytokines, in the absence of active somatic immune diseases, is usually observed in a subgroup of patients. These pro-inflammatory phenotypes have been associated with worse outcomes of mood disorders, including suicide (Steiner et al., 2013), and with MRI signs of white matter disruption (Benedetti et al., 2016), but, on the other hand, possibly compensatory increases of certain subpopulations associate with brain integrity (Poletti et al., 2017).

Concerning chronotherapeutics, a study in a small case series suggests dysregulation of the circadian pattern of release of cytokines, correlating with core depressive symptoms (Alesci et al., 2005). We observed that pro-inflammatory compounds reflecting an M-1 like pro-inflammatory state of monocytes/macrophages are associated with a poor response to combined antidepressant SD and LT in bipolar depression (Benedetti, Poletti, et al., 2017). On the other hand, patients with SAD showed significantly higher macrophage activity and lower lymphocyte proliferation in winter compared to healthy subjects, and effective LT normalised both immune functions and depressive symptoms (Song et al., 2015).

These data are clearly not yet sufficient to draw complete models, but all suggest that the immune system could play a major role in pathogenesis and treatment of depression and that sleep and the circadian timing system closely interact with it.

5 | WHAT ARE THE HINDRANCES TO USING CHRONOTHERAPEUTICS?

One of the main hindrances in acceptance of these chronotherapies is the difficulty of carrying out the conventionally required double-blind placebo-controlled randomised trials in large numbers of patients and thus entering the canon (as is the convention for new drugs). Firstly, there is little funding for such research, and secondly, it requires motivation and careful instruction for the nursing staff who are the ones looking after the patients throughout the night, as well as a ward where wake therapy or shifted sleep phase can be incorporated without disturbing other patients. And thirdly, clinical research interest has moved from just studying a night awake (those psychiatrists who use it are convinced of its efficacy) to testing adjunctive methods to maintain the rapid response—such as light, antidepressants or lithium, and sleep stabilisation. Thus, trials are often different mixes of one to three nights wake therapy, combined with a shortened phase advance protocol and/or regular morning light treatment, added to treatment as usual. This leads to few studies being "pure enough" for inclusion in meta-analyses, and it is meta-analyses which provide the accepted basis for task-force recommendations by the professional societies.

An important issue is also that of patents. Even though "light" was patented in the early days of human light research, this patent was questioned as not recognising "prior art" and has not been enforced. The widespread manufacture and sales of light therapy devices undergo no FDA or equivalent control apart from electric safety. Some have been registered as medical devices and thus state in their brochures "only for SAD" or "counter-indicated in bipolar patients" that has led the EU to stringent definitions of use—certainly the opposite of that intended by the lighting companies (thereby limiting sales) and a legal blockage for clinical research and applications outside the diagnosis of SAD. This must be changed.

The natural product melatonin cannot be patented, whereas the agonists can, and as a new drug, undergo classical trials for efficacy. Given the easy availability of melatonin in drugstores as a "vitamin supplement," there is no financial incentive to develop and test the optimal doses and formulation of an efficacious soporific, nor to study the putative combinations of evening melatonin with morning light as a "double zeitgeber" pulse treatment for mood and sleep disorders. This is a further important research and development field.

Good sunglasses with optimal blue-blocking characteristics are fortunately available and should be added to the inexpensive armamentarium of methods for stabilising sleep and circadian timing (e.g., regular use in the evening before sleep).

Chronobiological treatment strategies such as light and melatonin require knowing the patient's internal circadian time for optimal treatment. Timing of treatment may also be important for many sleep disorders. The timing of the dim light melatonin onset (DLMO) has been used as the gold standard circadian marker over the last decades (needing multiple evening saliva or serum samples). In clinical practice, a chronotype questionnaire such as the Morningness-Eveningness Questionnaire (MEQ) may suffice (at a first step) to approximate circadian phase, as under normal conditions there is a good correlation of DLMO with chronotype (Terman & Terman, 2010). However, given the large interindividual variation of circadian timing in healthy subjects, clinical populations may have more scatter, requiring DLMO measurement. Yet it is still not known how precise (i.e., within what range, e.g., ±2 hr) the timing must be to elicit the best clinical response. In patients with SAD, one study showed striking differences between early morning and late morning light therapy (Terman, Terman, Lo, & Cooper, 2001), whereas another found no significant relationship between chronotype (early and late sleepers) and light therapy response at a fixed timepoint (8 a.m.) (Knapen, Gordijn, & Meesters, 2016).

The politics of a field also play a role—the zeitgeist of psychiatry is mainly pharmacological; such non-drug modalities do not have the financial underpinnings of industry and are often relegated to the domain of "alternative treatments" (which, paradoxically, is a reason why many patients are positively attracted to them). In fact, light is the first treatment in psychiatry developed from a neurobiological model and not a chance finding.

6 | WHAT NEXT?

First, a somewhat simple but important chronobiological concept should be incorporated into everyday psychiatric practice—recognising the value of good entrainment of the circadian sleep–wake cycle as necessary for psychological and behavioural health (Bhattacharjee, 2007; Wirz-Justice, Bromundt, & Cajochen, 2009). Here, we can use light, and/or melatonin, regular exercise and mealtimes, sleep stabilisation (in other words, increase zeitgeber strength). Cognitive behavioural therapy (CBT) for insomnia has entered psychiatric practice as a useful tool to emphasise the importance of sleep hygiene (e.g., (Sheaves et al., 2018). Such a CBT programme focused on sleep or sleep education could be a straightforward adjunct to other therapies. Additionally, there is a role for light as adjunct therapy to foster stable sleep timing that has not been sufficiently exploited. And surely light could be combined with many other therapeutic approaches (why not psychotherapy?). In fact, ensuring regularity of daily schedules is a long-established behavioural strategy in psychiatry; here, we just infer its usefulness within the conceptual framework of synchronising agents for the circadian system.

Second, ambulatory technology (phone apps, movement and sleep trackers) will play an increasingly important role in inexpensive non-invasive documentation of circadian sleep–wake cycles and behaviour over long periods, useful for therapy feedback and patient education. A new generation of molecular markers may provide the required individual phase information with only a single blood sample (Braun et al., 2018; Wittenbrink et al., 2018).

Growing dissatisfaction with the present available psychopharmaca and the interest in non-drug alternatives has already led many clinics in Europe to start using light and wake therapy, following the methodological guidelines in the practical manual for chronotherapy (Wirz-Justice et al., 2013). A model of rapid implementation has been initiated by the president of the Czech Psychiatric Association, who invited us to develop a course in theoretical and practical chronotherapeutics for affective disorders, for both psychiatrists and psychiatric nurses, leading to a diploma. These individuals now spearhead the use of light and wake therapy in clinics across the Czech Republic. In parallel, discussions with the medical insurance authorities ensured that light therapy was remunerated.

In summary, clocks and sleep have been recognised in neuropsychiatry for decades, both as symptoms and as indicators of diagnosis, and have led to novel therapies. We need to build on this available knowledge with new large-N controlled clinical trials to ensure the transfer and acceptance of the already broadly studied light and wake therapy as first-line treatments of affective disorders.

CONFLICTS OF INTEREST

The authors have no conflicts of interest, nor specific funding for writing this review. No primary data have been reported.

AUTHOR CONTRIBUTIONS

Each author wrote sections which were then edited by the other author until agreement.

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