



## Sleep disturbance as transdiagnostic: Consideration of neurobiological mechanisms

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### ABSTRACT

Sleep disturbance is increasingly recognized as an important, but understudied, mechanism in the complex and multi-factorial causation of the symptoms and functional disability associated with psychiatric disorders. This review proposes that it is biologically plausible for sleep disturbance to be mechanistically transdiagnostic. More specifically, we propose that sleep disturbance is aetiologically linked to various forms of psychopathology through: its reciprocal relationship with emotion regulation and its shared/interacting neurobiological substrates in (a) genetics – genes known to be important in the generation and regulation of circadian rhythms have been linked to a range of disorders and (b) dopaminergic and serotonergic function – we review evidence for the interplay between these systems and sleep/circadian biology. The clinical implications include potentially powerful and inexpensive interventions including interventions targeting light exposure, dark exposure, the regulation of social rhythms and the reduction of anxiety. We also consider the possibility of developing a 'transdiagnostic' treatment; one treatment that would reduce sleep disturbance across psychiatric disorders.

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### 1. High comorbidity between sleep and psychiatric disorders

Sleep disturbance is highly comorbid with many, if not most, psychiatric disorders (Benca, Obermeyer, Thisted, & Gillin, 1992; NIH, 2005). Moreover, sleep disturbance is increasingly recognized as an

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important, but understudied, mechanism in the complex and multi-factorial causation of the symptoms and functional disability associated with psychiatric disorders (A. G. Harvey, 2008a). As such, sleep disturbance may qualify for status as a transdiagnostic process.

Sleep disturbance in psychiatric disorders can present as objectively measured alterations in sleep architecture, as well as insomnia, hypersomnia, delayed sleep phase, reduced sleep need, nightmares and nocturnal panic attacks. In the classic meta-analysis by Benca, Obermeyer, Thisted and Gillin (1992), polysomnographic data from 177 studies provided strong evidence for a link between objective sleep disturbance and the presence of psychiatric disorder. For example, compared to controls, patients with affective disorders, anxiety disorders, dementia, schizophrenia and primary insomnia showed decreased total sleep times, reduced sleep efficiency (percentage of bedtime asleep) and increased sleep latency (time to fall asleep). Total sleep time was also reduced in alcoholism, and sleep efficiency was reduced in eating disorder patients. Across several disorders a decrement in non-Rapid Eye Movement (NREM) sleep was observed as well as a longer latency to the first REM episode. Also, increased percent of REM sleep was observed in the affective disorders. On most measures, patients with affective disorders diverged markedly from controls. Importantly for the present argument, however, patients diagnosed with an affective disorder did not differ significantly from members of other disorder classes on any measure, suggesting that sleep disturbance is not unique to the affective spectrum.

The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) lists sleep disturbance as a symptom of many psychiatric disorders. There are many other psychiatric disorders for which sleep disturbance is not a listed symptom but is recognized as part of the clinical presentation. For example, patients diagnosed with panic disorder often report sleep-onset insomnia and avoidance behavior relating to going to sleep due to the fear of having a panic attack during the night (Michelle G. Craske & Rowe, 1997; Lepola, Koponen, & Leinonen, 1994). Further, social phobia has been associated with significantly poorer sleep quality, longer sleep onset latency, more frequent sleep disturbance, and more severe daytime dysfunction compared to sex and age matched controls (Stein, Kroft, & Walker, 1993). Finally, patients with a diagnosis of schizophrenia have shown increased sleep disturbance and insomnia prior to relapsing into a psychotic episode (Chemerinski, et al., 2002).

## 2. Advantages of identifying transdiagnostic processes

As discussed elsewhere (Harvey, Watkins, Mansell, & Shafran, 2004), processes may be *descriptively transdiagnostic* by virtue of simple co-occurrence across a range of psychiatric disorders. More interesting, of course, are processes that are *mechanistically transdiagnostic*, i.e. co-occurrence demonstrably arises from some form of causal interrelationship between the process and psychiatric disorders.

Confirmation that a process is mechanistically transdiagnostic has clinical implications. First, it provides a new perspective on issues of diagnostic overlap across psychiatric disorders. Results of the National Comorbidity Survey make a strong case for the relative rarity of 'pure' cases: Indeed, the vast majority of the lifetime disorders are comorbid disorders (Krueger & Markon, 2006). A transdiagnostic perspective raises the possibility that disorders co-occur because they share common mechanisms (sleep disturbance being one candidate). Second, if some psychiatric disorders are similar with respect to the processes that maintain them, advances made in the context of one disorder will be more rapidly tested for their application to other disorders. This already happens to some extent. However, transfer is often alarmingly slow. For example, see Table 1 for a demonstration of the time lag (for two decades!) for the transfer of knowledge of cognitive behaviour therapy for insomnia to other psychiatric

disorders. The advantage of the transdiagnostic perspective is that it could lead to more rapid transfer of advances to a broader range of disorders. Third, a transdiagnostic approach might lead to the specification of a single treatment module or principal that is effective across a wide range of disorders (McHugh, Murray, & Barlow, in press). For example, a fascinating possibility with significant public health implications would be the potential for developing and testing a transdiagnostic sleep intervention (A.G. Harvey, 2008a; 2009b).

## 3. Aim

The aim of this paper is to continue the examination of sleep disturbance as a transdiagnostic process. Specifically, we will consider if it is biologically plausible for sleep disturbance to be mechanistically transdiagnostic<sup>1</sup>. As summarised above, phenomenological overlap between sleep disturbance and various psychiatric disorders is well recognised, but *neurobiological characterisation* of this association would further support a mechanistic role for sleep disturbance, and encourage modular interventions targeting the sleep disturbance component of psychiatric disorders. The argument developed herein can be represented schematically as in Fig. 1 below.

Before delving into the details and evidence, a number of features of Fig. 1 should be noted. First, the endpoint of the model is psychiatric disorder generally (box 4). There is evidence that the transdiagnostic significance of sleep disturbance extends to other pathologies including schizophrenia (see Kantrowitz, Citrome, & Javitt, 2009; Takao, Tachikawa, Kawanishi, Mizukami, & Asada, 2007), childhood onset disorders (see Matsuura, Tateno, & Aou, 2008; Nicholas, et al., 2007) and personality disorders (see Guile, et al., 2009; Hornung, et al., 2008). However, the existing literature provides strongest support for the mood and anxiety disorders. Second, we limit our neurobiological attention to molecular genetics (box 1) and the two most researched neurotransmitters (dopamine [DA] and serotonin [5-HT], box 2). Other biological processes that are shared by sleep disturbance and psychiatric disorder include functions of the amygdala, HPA axis and noradrenergic systems (Stunkard, Allison, & Lundgren, 2008). A detailed review of these processes is beyond the scope of this paper. Third, we have construed sleep disturbance and emotion regulation as linked phenomena (box 3) in the pathway to psychiatric disorder (box 4), but the causal dynamics between these three processes is likely multifaceted. Fourth, important feedback loops have not been included in the model: neurobiological states, for example, are affected by the behavioural consequences of circadian output and emotion regulation strategies (see below and Murray, in press). Finally, the single pathway in Fig. 1 adequately captures the topic of this review, but is patently not a comprehensive model of the aetiology of psychiatric disorder.

The core of this paper is a review of evidence that the neurobiology of the sleep/circadian systems interact with pathways known to be important in psychiatric disorders (box 2 of Fig. 1). Prior to considering this literature in Section 5, the nature and regulation of human sleep is briefly outlined (Section 4). Our characterisation highlights the fact that circadian and sleep systems are adapted to be open to environmental information (not shown in Fig. 1), with implications for transdiagnostic non-pharmacological interventions, the topic of the paper's final section (Section 6).

## 4. Human sleep: the sleep versus circadian distinction

Human sleep can be divided into rapid eye movement ('REM') sleep and non-rapid eye movement ('NREM') sleep, which is in turn divided into four stages (imaginatively called *Stages 1, 2, 3 and 4*).

<sup>1</sup> We do not imply that biological plausibility is more significant than cognitive or behavioural plausibility, but these are issues for future papers.

**Table 1**

Transfer of advances is slow!

CBT for Insomnia (e.g., Bootzin, 1972; Spielman, Saksik, & Thorpy, 1987)	CBT for Insomnia that is comorbid with: Alcohol dependence (Arnedt et al., 2007) Depression (Manber et al., 2008) Chronic pain (Currie et al., 2000) Substance use disorder (Currie et al., 2004) Fibromyalgia (Edinger et al., 2005) Medical and psychiatric comorbidity (Lichstein et al., 2000; Perlis et al., 2001)
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Sleep in adults follows an organized pattern starting with Stage 1 NREM sleep, deepening to Stage 4 NREM sleep, and then moving into REM, with each NREM-REM cycle taking between 70 and 120 min (Hirshkowitz, Moore, O'Connor, Bellamy, & Cunningham, 1997; Shneerson, 2000).

The sleep/wake cycle is regulated by an interaction between two processes. The first is *circadian* (also known as Process C), arising from the endogenous pacemaker in the hypothalamic suprachiasmatic nuclei (SCN) (Reppert & Weaver, 2002). The SCN receives photic information gathered by photoreceptor cells in the retina. The retina does not only contain the classical photoreceptors (rods and cones) but also photoresponsive retinal ganglion cells containing the pigment melanopsin, which follow a pathway called the retinohypothalamic tract, terminating in the SCN (Moore, 2007). Light received at the retina is then transformed into a neural signal and sent to the brain (Reme, Wirz-Justice, & Terman, 1991). Light is also associated with the increased release or suppression of cortisol, melatonin and thyroid stimulating hormone (Leproult, Colecchia, L'Hermitte-Baleriaux, & Van Cauter, 2001). The output of the SCN cannot be directly measured in humans, but it can be discerned in the 24-hour rhythms of processes it regulates (including core body temperature, secretion of melatonin and cortisol) (Redfern, Waterhouse, & Minors, 1991). At the molecular level, intrinsically rhythmic cells of the SCN generate self-sustained rhythmicity via an auto-regulatory transcription-translation feedback loop regulating expression of the *Period* (*Per1*, *Per2*, *Per3*), cryptochrome (*Cry1*, *Cry2*), TIM, DEC1 and DEC2 genes (Takahashi, Hong, Ko, & McDearmon, 2008). One important downstream projection of the SCN is the pineal gland, which secretes melatonin. Secretion of melatonin peaks at night and is practically non-existent during the day. Melatonin is a crucial factor in the initiation of sleep.

The endogenous period generated in the SCN is close to, but generally not equal to 24 h. The process by which the pacemaker is both set to a 24 h period and kept in appropriate phase with seasonally shifting astronomical daylength is called entrainment. An important

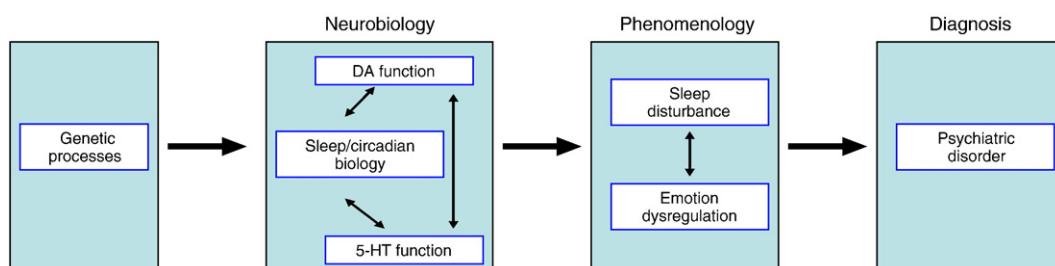
adaptation of the circadian system, therefore, is its fundamentally open nature (Mrosovsky, 1999). Entrainment occurs via *zeitgebers* which are environmental events that can affect the phase and period of the clock. The primary *zeitgeber* in most species is the daily alteration of light and dark caused by the planet's rotation (Roennebert & Foster, 1997). This is because light reception on the retina is transformed into a neural signal and sent to the brain (Reme, et al., 1991). The SCN is also responsive to *non-photic* cues such as arousal/locomotor activity, social cues, feeding, sleep deprivation and temperature (Mistlberger, Antle, Glass, & Miller, 2000). For example, higher daily regularity in social rhythms (the timing of social interactions, mealtimes, etc.) has been found to be associated with a stronger endogenous temperature rhythm, suggesting stronger overall circadian functioning (Monk, Petrie, Hayes, & Kupfer, 1994). Exogenous factors have a powerful impact on both the circadian and sleep systems. Indeed, stronger social rhythms are associated with better subjective sleep quality (Monk, et al., 1994). As these exogenous factors are relatively easy to modify, they have become the target of powerful and affordable interventions, an issue to which we will return.

The second process regulating sleep-wake is *homeostatic* (also known as Process S). Process S regulates the duration and structure of sleep on the basis of the history of sleep and wakefulness: sleep pressure increases during wake and dissipates during sleep. Circadian and homeostatic processes act in concert to maintain wakefulness during the day and to promote a consolidated sleep period at night (Borbely, 1982; Dijk & Franken, 2005).

Under natural conditions, Process C and Process S operate in synchrony, and their independent actions can only be discerned with laboratory-based manipulations. In the gold-standard forced desynchrony (FD) protocol (Czeisler, et al., 1999), participants live on an imposed non-24 hour (typically 28 h) sleep schedule. Under these conditions, the circadian oscillator continues to cycle at approximately 24 h and desynchronises from the sleep/wake cycle which adopts the enforced 28-hour period, thereby enabling the separate estimate of circadian and sleep-homeostatic components (Czeisler, et al., 1999). The FD protocol is emotionally and physically challenging, raising ethical and clinical concerns for participants with a psychiatric diagnosis. Consequently, very few diagnosed patients have undergone FD protocols, limiting our understanding of circadian\*sleep interactions in psychiatric disorder. Because of the difficulty separating circadian and sleep-related drivers, the less specific term "biological rhythms" will be used below when the data does not support a clear distinction.

## 5. Sleep disturbance and psychiatric disorder: evidence for shared/interacting neurobiology

The notable co-occurrence of sleep disturbance and psychiatric disorders has been discussed elsewhere (Benca, et al., 1992; A.G. Harvey, 2008a,b). Here, we take the argument for transdiagnostic significance a step further. We propose that sleep disturbance is aetiologically linked to various forms of psychopathology through: i) its reciprocal relationship with emotion regulation (box 3 of Fig. 1),



**Fig. 1.** The biological plausibility of sleep disturbance as a transdiagnostic process in the multifactorial cause and/or maintenance of psychiatric disorder.

ii) shared/interacting neurobiological substrates in genetics (box 1) and iii) dopaminergic and serotonergic function (box 2).

### 5.1. Association between sleep disturbance and emotion dysregulation

Behavioural data support the common lay observation that sleep disturbance strongly increases negative mood (e.g., Dinges, et al., 1997; Drake, et al., 2001; El-Sheikh, Buckhalt, Cummings, & Keller, 2007; Franzen, Siegle, & Buysse, 2008; Hamilton, Catley, & Karlson, 2007; Novati, et al., 2008). Sleep loss has been shown to not only increase negative emotional response to goal-thwarting events, but also decrease positive emotional responses to goal-enhancing events (Zohar, Tzischinsky, Epstein, & Lavie, 2005). High levels of emotional arousal can also disturb sleep, raising the possibility of vicious cycles between sleep disturbance and emotion dysregulation (Dahl & Lewin, 2002). At the neural systems level, sleep deprivation has been linked to decreased medial-prefrontal cortical activity and increased amygdala activation, a distribution of activation consistent with impaired top-down regulation of emotional responses (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Conversely, emotion circuits affect homeostatic and circadian drives for sleep (Saper, Cano, & Scammell, 2005; Yoshida, McCormack, Espana, Crocker, & Scammell, 2006)<sup>2</sup>.

The bidirectional relationship between sleep disturbance and emotion regulation is consistent with the former as a transdiagnostic process. An area for future research is the question of which part of the dynamic affords greatest therapeutic leverage.

### 5.2. Association between circadian genes and psychiatric disorder

Genes known to be important in the generation and regulation of circadian rhythms have been linked to a range of disorders (Lamont, Legault-Coutu, Cermakian, & Boivin, 2007). The most-replicated findings pertain to mood disorders. Bipolar disorder has been associated with *Timeless*, *Clock* (311 T to C) and *BMAL1* (Murray & Harvey, 2010), polymorphisms in the *CLOCK* protein (homozygous for the C alleles) are related to sleep abnormalities in major depressive disorder (Serretti, et al., 2003) and *PERIOD2*, *NPAS2*, and *BMAL1* are associated with seasonal affective disorder (Partonen, et al., 2007).

Associations between circadian genes and non-mood disorders have also been reported. For example, *Per1* and *BDNF* have been associated with ADHD (Lasky-Su, et al., 2008), *PER3* and *TIMELESS* have been found to be associated with schizophrenia/schizoaffective disorder (Mansour, et al., 2006) and a haplotype of the *hPer2* gene was associated with high versus low alcohol intake in a sample of 215 alcohol-dependent patients (Schumann, 2007; Spanagel, et al., 2005).

Importantly, consistent with the proposal that psychiatric disorders are likely to be associated with multiple genes of small effect (Mansour, Monk, & Nimgaonkar, 2005), most of the associations reported above are modest and failures to replicate are common (Monteleone, et al., 2008; Tortorella, Monteleone, Martiadis, Perris, & Maj, 2007).

Compared with our understanding of circadian genes in psychiatric disorders, much less is known about the genes involved in sleep and their potential involvement in psychopathology (Bamme, Mansour, Monk, Buysee, & Nimgaonkar, 2010). Specific criteria for the constituents of a 'sleep gene' are currently under discussion (Andretic, Franken, & Tafti, 2008), and the possible association of sleep genes with psychiatric disorders is a priority for future research.

### 5.3. Serotonin and dopamine systems in psychiatric disorders

Alterations in the brain monoamines serotonin (5-HT) and dopamine (DA) have been implicated in the aetiology and pharmacotherapy of a range of psychiatric and medical disorders. Both monoamines are associated with cognitive, emotional and bodily functioning; serotonin plays a role in attention, cognition, and information processing (Richtand & McNamara, 2008; Richtand, et al., 2008), while dopamine is important for motivation, psychomotor movement, reward processing and the ability to experience pleasure (Bressan & Crippa, 2005; Dunlop & Nemerooff, 2007).

Disturbed serotonergic function is a recognised pathway to mood disorders (Carver, Johnson, & Joormann, 2008), anxiety disorders, eating disorders (Kaye, 2008; Vaswani, Linda, & Ramesh, 2003), schizophrenia, addiction and non-psychiatric conditions including epilepsy, migraines and pain (Hedlund, 2009). At the genetic level, polymorphisms of serotonin transporter genes have been linked to both bipolar disorder and unipolar depression (Lotrich & Pollock, 2004; Luddington, Mandadapu, Husk, & El-Mallakh, 2009). The literature also recognises serotonergic function in a diathesis-stress framework: for example, an interaction between environmental stress and polymorphisms of the transporter genes has been linked to susceptibility to depressed mood (Khan, Jacobson, Gardner, Prescott, & Kendler, 2005).

Disturbed dopaminergic function is a replicated correlate of psychotic disorders, most notably schizophrenia where high levels of dopamine release are associated with hallucinations (Lyon, et al., 2009). Dopamine circuitry is also strongly involved in addiction (Carlezon & Thomas, 2009), mood disorders (Berk, et al., 2007; Malhi & Berk, 2007), eating disorders (Bergen, et al., 2005), pathological gambling and hypersexuality (Goodman, 2008). Changes to the mesolimbic dopaminergic system may be a factor in the faulty reward processing of anhedonic depressed patients (Martin-Soelch, 2009). As with serotonin, a diathesis-stress model of dopamine's involvement in psychopathology has received support (Moghaddam, 2002; E. Walker, Mittal, & Tessner, 2008).

The DA and 5-HT systems do not operate independently, and their interaction is probably important in psychopathology (Esposito, Di Matteo, & Di Giovanni, 2008). For example, animal models suggest that 5-HT2 receptor antagonism modulates DA neuron firing activity due to antipsychotic medication (Olijslagers, Werkman, McCreary, Kruse, & Wadman, 2006). Similarly, 5-HT2C receptor agonists decrease, while 5-HT2C receptor antagonists enhance mesocorticolimbic DA function (Esposito, 2006).

In summary, there is ample evidence that the separate and interacting effects of DA and 5-HT are etiologically important in a range of psychiatric disorders. Next, we review literature showing the interplay between these systems and sleep/circadian biology.

### 5.4. Links between the sleep/circadian systems and the serotonin system

The SCN contains one of the densest serotonergic plexes in the brain (L. P. Morin, 1999). Electrical stimulation of the serotonergic medial (MRN) and dorsal raphe nuclei (DRN) increases 5-HT content in the SCN, confirming raphe nuclei involvement in the serotonergic activity of the SCN. Gross disruption of serotonergic function (lesioning the raphe nuclei or chemically disrupting 5-HT neurons) does not obliterate circadian rhythms but produces a diminution of overall amplitude, as well as a tendency towards phase advance and increased period (Prosser, 2000). Functionally, therefore, 5-HT seems to enhance the overall stability of circadian rhythmicity via its efferent from the MRN (Hannibal & Fahrenkrug, 2006). Serotonin is also specifically involved in the regulation of the SCN by non-phototic zeitgebers (Hannibal & Fahrenkrug, 2006; Jiang, Teshima, Yang, Yoshioka, & Allen, 2000), and the stabilising effect of 5-HT may arise

<sup>2</sup> We prioritise *emotion regulation* as a process that interacts with sleep disturbance in the predisposition to psychiatric disorder solely because of the weight of data in this area. However, we recognize that the domains of *arousal* and *neurocognitive function* are also abnormal in many psychiatric disorders and modulated by sleep/circadian systems. Attention to these features of disorder would have demanded attention to additional neurotransmitters, particularly noradrenaline.

from its part in the reciprocal interplay between photic and non-photic zeitgebers (Hannibal & Fahrenkrug, 2006).

There is also evidence that circadian function modulates the serotonin system (Miller, Morin, Schwartz, & Moore, 1996; Mistlberger, et al., 2000). The marked diurnal rhythm in serotonergic activity in the brain, including the SCN (Glass, Grossman, Farnbauch, & DiNardo, 2003) and the raphe nuclei (Cagampang, Yamazaki, Otori, & Inouye, 1993) has an endogenous circadian component, as does the rhythm of 5-HT receptor activity (see Nagayama, 1999 for a review). Furthermore, 5-HT activity is influenced by light exposure and season (Lambert, Reid, Kaye, Jennings, & Esler, 2002).

Based on a series of investigations in *Drosophila*, Yuan and colleagues (2005) identified a molecular connection between serotonin signaling and the central clock component TIM (viz., the serotonin receptor d5-HT1B inhibits molecular and behavioural responses of the clock to light) and showed that serotonin signaling is in turn modulated by light and circadian components (viz., d5-HT1B levels are altered in fly circadian mutants). The authors conclude that "Mutual regulation of the circadian and serotonin systems may be necessary to maintain the normal physiological functions of both systems" (p. 125).

The circadian\*serotonergic interaction in fact appears in some existing models of psychiatric disorder. For example, a bidirectional relationship between circadian and serotonergic function is a prominent feature of Mistlberger et al's conceptual model of depression (Mistlberger, et al., 2000). Specifically, it is hypothesised that serotonin mediates phase-shifting effects of behavioural stimuli on circadian rhythms. It has also been proposed that the serotonergic projection from the MRN to the SCN is the anatomical interface between circadian function and mood disorder (Reghunandanan & Reghunandanan, 2006; J. Sprouse, 2004; see also J. Sprouse, Braselton, & Reynolds, 2006).

The relationship between serotonin and sleep per se is complex, and advances in technology have led to overturning of earlier conclusions (see Ursin, 2002). Serotonergic neurons in the MRN and DRN are one component of the ascending arousal system (Fuller, Gooley, & Saper, 2006). The firing of these neurones correlates with wakefulness, and they are virtually inactive during REM sleep (Adrien, 2002). Moreover, sleep deprivation induces neurochemical changes similar to depression, including decreased sensitivity of the 5-HT1A receptor system (Novati, et al., 2008; Roman, Walstra, Luiten, & Meerlo, 2005).

A range of evidence therefore suggests that the sleep/circadian systems are intimately involved in serotonergic function and vice versa. One final vivid example of the link: the circadian hormone melatonin is a derivative of serotonin, and the SCN modulates serotonin's metabolising into melatonin (Snyder, Borjigin, & Sassone-Corsi, 2006).

##### 5.5. Links between the sleep/circadian systems and the dopamine system

Extensive research into the psychiatric implications of a circadian\*dopaminergic interaction has emphasised dopamine's role in reward activation. The brain's reward pathways can be parsed into appetitive/dopaminergic and consummatory components, with the former being most clearly associated with positive affects and reward activation (Ashby, Isen, & Turken, 1999; Bressan & Crippa, 2005).

The involvement of the circadian system in the reward activation of animals is well understood (e.g., Abarca, Albrecht, & Spanagel, 2002; Andretic, Chaney, & Hirsh, 1999; Cain, Ko, Chalmers, & Ralph, 2004; Dudley, et al., 2003; Garcia, et al., 2000; McClung, et al., 2005; Ralph, et al., 2002; Reick, Garcia, Dudley, & McKnight, 2001; Sleipness, Sorg, & Jansen, 2005, 2007). We have recently shown that in humans, positive moods and other measures of reward activation are moderated by the circadian system (Murray, et al., 2009), and hypothesised that disturbance in an interacting circadian\*reward circuit is causally important in mood disorders. Consistent with this hypothesis, Roybal et al. (2007) have shown that Clock mutant mice

display increased dopaminergic activity in the ventral tegmental area (VTA), as well as behaviours homologous to mania (hyperactivity, decreased sleep, increase in the reward value of cocaine, etc.). Significantly, these behaviours are normalised by administration of lithium, and by expression of a functional CLOCK protein specifically in the VTA.

The dopaminergic system is also prominent in the neurobiology of sleep per se. Dopamine has been called a key substance in the regulation of sleep-wake (Lima, et al., 2008), and dopaminergic neurons of the ventral tegmental area and substantia nigra pars compacta are implicated in this process (Monti & Monti, 2007). The dopaminergic D2 receptor, in particular, seems to play a specific role in REM sleep (Dahan, et al., 2007; Lima, et al., 2008). Accordingly, sedation is an unwanted side-effect of antipsychotic medications, which operate by blocking dopaminergic receptors (Ongini, Bonizzoni, Ferri, Milani, & Trampus, 1993), and the wake-promoting effects of modafinil, amphetamine and caffeine have been shown to depend on the dopamine transporter gene (Wisor, et al., 2001).

Finally, as noted above, DA and 5-HT systems are interacting players in the pathway to psychiatric disorder. It is interesting that this DA\*5-HT interaction can be traced into circadian function. For example, dopaminergic and serotonergic pathways play functional roles in the activity of the endogenous circadian pacemaker. Phtic input is conveyed from the eye to the SCN via the retinohypothalamic tract (RHT) and indirectly by the geniculohypothalamic tract (GHT) from the intergeniculate leaflet (Moore, 1996). Both dopamine (Yan, Bobula, Svenningsson, Greengard, & Silver, 2006) and serotonin (Moyer & Kennaway, 2000) participate in these entrainment pathways.

One important domain for future research is to focus on the architecture of sleep across disorders. Since the classic meta-analysis by Benca et al. (1992), the sleep architecture findings have become more complicated with findings emerging specific to gender (Armitage, 2007), to the second versus the first half of the night (Cartwright, Young, Mercer, & Bears, 1998) and influence by medications (Eidelman, Talbot, Gruber, Hairston, & Harvey, 2010). Developments in knowledge about the role of specific stages of sleep in non-patient groups (M. P. Walker & Stickgold, 2006), along with more sophisticated scoring methods (Armitage, 1995), will breathe new life into this aspect of transdiagnostic sleep research.

##### 5.6. Summary and provisional conclusion

The serotonergic and dopaminergic systems are strongly implicated in a range of diagnoses through their impact on fundamental cognitive, emotional, motivational and motor processes. The preceding review provides a range of converging evidence that the sleep/circadian systems are intricately connected with these two prominent aetiological factors.

It seems reasonable to provisionally conclude that the transdiagnostic significance of sleep disturbance is not limited to its phenotypic association, but extends to its participation in the mechanisms underpinning psychopathology. Specifically, one of the ways that sleep disturbance is causally involved in psychiatric disorder is a shared substrate – sleep disturbance and psychiatric disorder are neurobiologically intertwined.

##### 6. Clinical implications of sleep disturbance as a transdiagnostic process

A number of clinical hypotheses arise from the provisional conclusion that sleep disturbance is mechanistically transdiagnostic. First, if sleep disturbance and the symptoms/processes of psychiatric disorders are jointly maintained, then interventions for sleep/circadian functioning may also reduce the symptoms associated with the comorbid psychiatric disorder. Second, as flagged earlier, if sleep

disturbance is truly transdiagnostic in this mechanistic sense, practitioners could be trained in the application of a sleep intervention with broad application across disorders and profound public health implications (A.G. Harvey, 2008a). Third, although not reviewed here, there is a well-known association between poor sleep and impaired quality of life (Roth & Ancoli-Israel, 1999). It seems likely that improving sleep/circadian functioning will have impacts beyond symptom reduction across a range of psychiatric disorders (for implications for physical health, quality of life and the development of other psychiatric disorders see (Harvey, 2009a).

Finally, the preceding arguments hold particular relevance for interventions offered by clinical psychologists. As noted above, the sleep/circadian systems are adapted to be responsive to unconditioned environmental stimuli, particularly light, eating and social activity. Therefore, unlike serotonergic and dopaminergic function, the neurobiology of sleep/circadian function can be modulated non-pharmacologically. Behavioural and light manipulations for sleep and circadian function therefore constitute transdiagnostic interventions for the clinical psychologist's armamentarium.

Two types of therapeutic intervention will be briefly described — modulation of biological rhythms by timed light exposure and modulation of biological rhythms by stabilisation of social/behavioural rhythms. The majority of work into these strategies has been in the context of mood disorders (see Wirz-Justice, et al., 2005; Wirz-Justice, Benedetti, & Terman, 2009; Wirz-Justice, et al., 2004), but the review above gives confidence that they have broader potential application. Like other behavioural interventions, light and social rhythm manipulations are best presented within a collaborative therapeutic framework (Berk, Berk, & Castle, 2004; Corsini & Wedding, 2005). More specific detail about chronotherapeutic interventions can be found in several excellent clinical texts (e.g., E. Frank, 2005; Wirz-Justice, et al., 2009).

### 6.1. Therapeutic modulation of light exposure

Bright light exposure is the first line treatment for depressions with a seasonal pattern, and has also proven effective (to a lesser extent) in purely nonseasonal depression (Even, Schröder, Friedman, & Rouillon, 2008; Golden, et al., 2005; Tuunainen, Kripke, & Endo, 2006). Limited trials of light therapy have also been conducted in schizoaffective disorder (Oren, Cubells, & Litsch, 2001), ante-partum depression (Oren, et al., 2002) and chronic fatigue syndrome (M. Terman, Levine, Terman, & Doherty, 1998).

Light treatment involves the patient sitting in front of a light therapy unit at a distance yielding a benchmark intensity of light, usually ranging from 2500 to 10,000 lx (J. S. Terman, et al., 1990). The distance will vary somewhat with different light sources but roughly 16–24 in. is optimal. The placement should be such that the area around the eyes is illuminated. It is not necessary for the patient to look directly at the unit, and most patients read or eat while undergoing light exposure. As with all behavioural interventions, clinicians must pre-empt problems adhering to light treatment (Michalak, Murray, Wilkinson, Dowrick, & Lam, 2007).

Light restriction may also be effective for the hyperarousal component of some psychiatric disorders. For example, Barbini, Benedetti, Colombo, Dotoli, Bernasconi, Cigala-Fulgosi et al. (2005) randomly allocated bipolar patients in a manic episode to 14 h of darkness over three 3 consecutive days, or treatment as usual. Those who received dark therapy exhibited a startling and rapid decrease in manic symptoms relative to the treatment as usual group.

An important caveat on manipulation of light is that some individuals may be hypersensitive to light's mood and arousal effects. For example, Sit and colleagues (2007) attempted to treat bipolar depression by exploring 3 durations at 2 times of day using 7000 lx white light. Comparing exposures of 15, 30, or 45 min/d across 2-wk epochs and measuring overall levels of depression, 1 of 4 women

treated in the morning entered a sustained period of remission whereas 3 developed mixed mood states (including irritability, elevated energy and racing thoughts). The optimal titration and timing of light in light sensitive individuals is a matter of ongoing interest (Anderson, Glod, Dai, Cao, & Lockley, 2009).

Recent discoveries as to the neurobiological effects of light are likely to have a major impact on light treatment research and practice. Novel photoreceptors have been identified in the mammalian eye that are most sensitive to short-wavelength blue light (G. Vandewalle et al., 2007a,b; Gilles Vandewalle et al., 2007a,b). In humans, it appears that blue light is the most effective wavelength for suppressing pineal melatonin production during the night. As compared to an equal photon density of green (555 nm), blue light (460 nm) is twice as effective at phase-shifting the timing of the circadian clock and preferentially improves alertness, as measured by subjective ratings, changes in activation state in the brain, and auditory performance (Lockley, Brainard, & Czeisler, 2003). A small number of studies have investigated the functional and clinical implications of the importance of wavelength in quantifying the 'dose' of light (Anderson, et al., 2009; Phelps, 2008; G. Vandewalle et al., 2007a,b), but the implications of these findings are far-reaching (Brainard & Hanifin, 2005).

The recent discovery that light's neurobiological effects are blue-shifted raises the possibility for more sophisticated research into type of light exposure and dosage. We also emphasize that behavioral interventions focused on the management of natural sources of light are an even less expensive way of taking advantage of this powerful input to the circadian system. Behavioral activation and behavioral scheduling protocols can include an emphasis on exposure to sunlight, especially for patients who have trouble waking in the morning (e.g., depressed adolescents with a delayed phase or hypersomnic patients). Similarly, completing a functional analysis of exposure to light in the evening can help patients downregulate sufficiently and allow the biology governing sleep onset to take over. For example, turning off television, computers and turning down lights an hour before bedtime can be a simple but powerful intervention for some patients. We note the intriguing case report of two severely manic patients who were asked to enter a darkened room for a daytime nap. Van Sweden (1986) reported that both 'showed Stage 2 NREM sleep, the usually objective marker of "true" sleep, within seconds following eye closure' (p. 312). This study raises the provocative idea that the reduced sleep need evident patients with bipolar disorder during hypomania and mania may be a problem of insufficient opportunity to sleep rather than a disorder of lowered sleep need per se. This is a possibility that chimes well with Johnson's (2005) research documenting the propensity toward excessive goal seeking among bipolar patients. Preoccupation with goal pursuit may contribute to the perception of a decreased need for sleep in manic patients.

### 6.2. Social rhythm therapy

As noted above, the circadian system is primarily entrained by light, but is also sensitive to activity and social cues. Ehlers, Frank and others (Ehlers, Frank, & Kupfer, 1988; E. Frank, 2007; Healy & Waterhouse, 1995) have argued that rhythmic features of the social environment (such as the timing of sleep, eating and exercise) are significant components of human circadian entrainment. Consequently, the social zeitgeber hypothesis of depression proposes that major life events (such as loss of a significant relationship) not only have psychological meaning but also weaken zeitgeber information through destabilization of daily activities and light exposure (see Grandin, Alloy, & Abramson, 2006 for an overview). Consistent with the social zeitgeber hypothesis, two studies have found that onset of manic episodes is associated with life events that involve disruption of social rhythms (Malkoff-Schwartz, et al., 1998; Malkoff-Schwartz, et al., 2000).

The clinical application of the social zeitgeber hypothesis is Social Rhythm Therapy, a largely behavioural psychotherapy designed to

**Table 2**

Sleep restriction (Spielman et al., 1987) and stimulus control (Bootzin & Epstein, 2000) instructions.

Method	Instructions
Sleep restriction	Keep a sleep diary for 7–14 days Calculate total sleep time (TST) and time in bed (TIB) for each night Compute sleep efficiency (SE) = TST/TIB × 100 Next week: cut bedtime to actual amount patient reports sleeping, but not <5 h/night Prohibit sleep outside of these hours (if too sleepy then allow 30 minute nap before 3 pm) Based on average of 5 nights, when SE is >85%, increase bedtime by 15 min With the elderly, SE increase bedtime when SE reaches 80%.
Stimulus control	Go to bed only when sleepy Use the bed only for sleeping – do not read, watch TV, or eat in bed If unable to sleep (in 20 min), move to another room. Stay up until really sleepy. The goal is to associate the bed with falling asleep quickly Repeat tactic immediately above as often as necessary Awaken at the same time every morning regardless of total sleep time Do not nap

maintain stability in social rhythms. In the treatment of bipolar disorder, Social Rhythm Therapy is typically integrated with principles from interpersonal psychotherapy in a treatment known as Interpersonal and Social Rhythm Therapy (IPSRT, E. Frank, et al., 1994). IPSRT has proven effective for bipolar disorder in two large studies (Ellen Frank, et al., 2005; Miklowitz, et al., 2007). Indeed, stabilising of social rhythms is a core component of all psychosocial treatments for bipolar disorder (Miklowitz, Goodwin, Bauer, &

Geddes, 2008), and is a prominent wellness tool amongst high functioning patients (Suto, Murray, Hale, Amari, & Michalak, 2010).

To our knowledge, IPSRT is yet to be tested outside bipolar disorder, but the literature reviewed in Section 4 above suggests that behavioural support for biological rhythm regularity potentially has beneficial effects on various symptoms associated with a range of disorders.

### 6.3. Sleep focused versus anxiety focused interventions

As suggested above, there is strong evidence for a reciprocal relationship between sleep disturbance and problems with emotion regulation. An intriguing clinical question is whether psychological interventions should focus on improving sleep/circadian function or whether the focus of intervention should be on improving emotion regulation, particularly elevated levels of anxiety. One of the leading treatments (in terms of the compelling evidence base), cognitive behaviour therapy for insomnia (C. M. Morin, et al., 2006), focuses mainly on improving sleep and circadian functioning. As described in Table 2, the stimulus control and sleep restriction interventions, for which the most evidence has accrued, emphasize regularity in the sleep-wake schedule.

The alternate or additional possibility, that intervention should focus on reducing anxiety, is an implication of Saper et al.'s (Cano, Mochizuki, & Saper, 2008; Saper, Chou, & Scammell, 2001) model of sleep which states that sleep is controlled by a 'flip-flop switch' between the ventrolateral preoptic nucleus (VLPO; neurons in the VLPO are activated during sleep) and the arousal system. Saper and colleagues propose that sleep disturbance occurs when the VLPO is fully activated but not able to

**Table 3**

Core and optional modules of a transdiagnostic sleep intervention (Harvey, 2009b).

Case formulation	Case formulation involves a detailed functional analysis of a typical recent night and a recent day: 1. Ask the patient to select a very specific (but typical) night in which they experienced sleep disturbance. 2. Ask questions to determine the antecedents or events that might have influenced the insomnia experienced that night (e.g., conflict with spouse). 3. Obtain a very detailed description of exactly what happened and the consequences of it. 4. Work through the events, and corresponding thoughts, feelings and behaviors across one night, measure their contribution to the insomnia and create a rationale for intervention. 5. Repeat this for a typical day that was adversely affected by poor sleep.
Sleep education (core module)	Provide education about the endogenous (e.g., the circadian clock) and exogenous (e.g., light, social rhythms) processes that govern sleep.
Motivational interviewing (core module)	Assist the patient to honestly review the pros and cons of change.
Regularizing the circadian phase (core module)	The goal is to gradually move toward a regular sleep schedule 7 days a week (with no more than a 2 hour difference between weekdays and weekends). Approaches: 1. Week-by-week process of either moving bedtime forward (for delayed phase) or backward (for advanced phase) by 20–30 min per week. 2. Devise a 'wind-down' period of 30–60 min prior to sleep in which relaxing, sleep enhancing activities are engaged in. 3. Devise a 'wake-up protocol' (e.g., not hitting snooze on the alarm; head for the shower). 4. Emphasize the importance of minimal fluctuation in the sleep–wake schedule across the nights of the week. 5. Wake up at the same time every day.
Daytime functioning (core module)	Interventions that assist the patient to generate energy (Ree & Harvey, 2004).
Treating insomnia (optional module)	Stimulus control and sleep restriction (see Table 2).
Treating hypersomnia (optional module)	Collaborate to set sleep goals (reduce to approximately 8 h per night) and set life goals (so there is something to get up for). Assist the patient to identify one small step toward these goals for the coming week. Engage in a detailed discussion of how to achieve these goals and identify possible obstacles.
Nightmares (optional module)	Imagery rehearsal therapy is a two-tier process wherein: 1. The patient is introduced to the notion that nightmares are an acquired behavior, sustained by habit. 2. The patient learns to consciously manipulate the imagery of the nightmare, and rehearses the manipulated version of the dream (10–15 min a day) (Krakow & Zadra, 2006).
Nocturnal panic (optional module)	Provide accurate information about panic attacks, with an emphasis on the harmless nature of physiological fluctuations during sleep. Exposure therapy to induce physical sensations associated with panic (e.g., heart increase, hyperventilation, dizziness) in order to help the patient weaken associations between internal physiological cues and the typical panic response (Craske & Tsao, 2005).
Reduced sleep need (optional module)	Characteristic of mania and hypomania within the bipolar spectrum disorders. A preliminary trial of 'dark therapy' has been published by Barbini et al. (Harvey, 2009b). Bipolar patients in a manic episode were given 14 h of enforced darkness for 3 consecutive days or treatment as usual. Those who received dark therapy exhibited a decrease in manic symptoms relative to the treatment as usual group. This finding raises the possibility that a behavioural intervention that controls light and dark may be helpful for reduced sleep need.

flip off the arousal system because it's being 'excited intensely' by the limbic system (Cano, et al., 2008). A hypothesis arising from this model is that intervention should target reducing limbic activation. The latter may well be possible with the cognitive therapy (Harvey, Sharpley, Ree, Stinson, & Clark, 2007) and mindfulness interventions (Heidenreich, Tuin, Pflug, Michal, & Michalak, 2006; Ong, Shapiro, & Manber, 2008) that have been developed in recent years for sleep problems. These interventions focus on developing new skills for more effectively managing worry, rumination and intrusive thoughts as well as other cognitive processes so as to reduce the associated limbic system activation and sleep-interfering arousal.

#### 6.4. Transdiagnostic versus disorder specific sleep treatments

Will it be possible to develop a 'transdiagnostic' treatment, one treatment that will reduce sleep disturbance across patients with psychiatric disorders? If it were possible, a transdiagnostic treatment would have the great advantage of easy dissemination. This is important as developing and disseminating transdiagnostic treatment protocols (as opposed to disorder specific treatment protocols) would reduce the heavy burden on clinicians, who must already learn multiple treatment protocols that often share many common theoretical underpinnings and interventions.

However, we also emphasize that the type of sleep disturbance across psychiatric disorders is complex which reduces the likelihood that there will be a 'one size fits all approach'. There are various types of sleep disturbance, all different, that can present as comorbid with psychiatric disorders. These include insomnia, hypersomnia, delayed sleep phase, reduced sleep need, nightmares and nocturnal panic attacks. As such, perhaps it will be necessary to develop sleep specific treatments for the various psychiatric disorders.

One possible resolution may be to devise a sleep-focused treatment that includes 'core' modules that would be delivered to all patients, regardless of diagnosis, and 'optional' modules to cover the disorder-specific aspects of the sleep disturbance. One such approach is briefly summarized in Table 3 (Harvey, 2009b).

## 7. Conclusions

We have reviewed evidence suggesting that it is biologically plausible for sleep disturbance to be an important transdiagnostic process. We have shown that sleep disturbance is aetiologically linked to various forms of psychopathology through (a) its reciprocal relationship with emotion regulation, (b) genes known to be important in the generation and regulation of circadian rhythms that have been linked to a range of disorders and (c) the interplay between systems known to be important across a range of psychiatric disorders, namely the dopamine and serotonin systems, as well as sleep/circadian biology. We are excited about the simple but powerful interventions that arise from this review. Interventions targeting light exposure, dark exposure, the regulation of social rhythms and/or the reduction of anxiety may be helpful in improving sleep across a range of disorders. Although we recognize the complexity of the sleep disturbance that can be characteristic of psychiatric disorders, research into a 'transdiagnostic' sleep treatment is now warranted.

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