Neuroscience and Biobehavioral Reviews 36 (2012) 1897–1919

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Altered circadian profiles in attention-deficit/hyperactivity disorder: An integrative review and theoretical framework for future studies

Lindita Imeraj[a,*], Edmund Sonuga-Barke[b,c], Inge Antrop[a], Herbert Roeyers[c], Roeljan Wiersema[c], Sarah Bal[a], Dirk Deboutte[a,d,e]

[a] Ghent University Hospital, Department of Psychiatry and Medical Psychology, Child and Adolescent Psychiatry Research Unit, 0K12F, De Pintelaan 185, 9000 Ghent, Belgium
[b] Southampton University, School of Psychology, Shackleton Building (B44), Highfield Campus, Southampton SO17 1BJ, United Kingdom
[c] Ghent University, Department of Experimental-Clinical and Health Psychology, Henri Dunantlaan 2, 9000 Ghent, Belgium
[d] Antwerp University, Collaborate Antwerp Psychiatry Research, Universiteitsplein 1, 2610 Antwerp, Belgium
[e] University Centre Child and Adolescent Psychiatry, Lindendreef 1, 2020 Antwerp, Belgium

ARTICLE INFO

Article history:
Received 19 February 2011
Received in revised form 20 April 2012
Accepted 23 April 2012

Keywords:
ADHD
Arousal
Circadian
Suprachiasmatic nucleus
Eveningness
Behavior
Sleep
Melatonin
Cortisol
Heart rate
Locus coeruleus

ABSTRACT

Disruptions in the sleep–wake cycle and the circadian system have been found in a wide range of psychiatric disorders and are generally correlated with clinical severity and diminished quality of life. Emerging evidence suggests similar disturbances may be found in attention-deficit/hyperactivity disorder (ADHD). Here we review the available literature on across the day fluctuations in ADHD-related processes in terms of; (i) time of day effects on behavior and activity; (ii) *morningness–eveningness* chronotypology; (iii) sleep/wake rhythms; and (iv) rhythmicity in neuroendocrine and neurophysiological responsiveness. On this basis, we propose a neurobiological framework to guide future study, which sees circadian effects in ADHD, along with other aspects of ADHD arousal-related deficits (e.g., cognitive energetic deficits), as being the result of dysregulated locus coeruleus function. Based on this perspective specific recommendations for future research are presented.

Contents

Abbreviations: APA, American Psychiatric Association; ADHD, attention-deficit hyperactivity disorder; SCN, suprachiasmatic nucleus; CLOCK gene, circadian locomotor output cycles kaput gene; LC, locus coeruleus; MSLT, multiple sleep latency test; PSG, polysomnography; ODD, oppositional defiant disorder; CD, conduct disorder; CBCL, child behavior checklist; MEQ, morningness–eveningness questionnaire; SOI, sleep onset insomnia; DLMO, dim light melatonin onset; HPA axis, hypothalamic-pituitary-adrenal axis; CRF, corticotropin releasing factor; RAS, reticular activation system; DMH, dorsomedial hypothalamic nucleus; VLPO area, sleep-related ventrolateral preoptic area; NE, noradrenaline; PFC, prefrontal cortex; DRD-4 gene, dopamine receptor D_4 gene; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; EEG, electroencephalogram; ERP, event related potential.

* Corresponding author. Tel.: +32 9 332 48 74; fax: +32 9 332 27 58.
E-mail address: lindita.imeraj@ugent.be (L. Imeraj).

0149-7634/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2012.04.007

1. Introduction

There is mounting evidence to support the notion that circadian rhythms are altered in a wide range of psychiatric diseases, especially affective disorders (see for reviews: Boivin, 2000; Germain and Kupfer, 2008; McClung, 2007; Wirz-Justice, 2006). For example, impaired sleep and daytime fatigue are included in the diagnostic criteria for depressive disorders (American Psychiatric Association, APA, 2000) where diurnal variations in symptoms (e.g., mood and psychomotor activity) have frequently been reported. These fluctuations are reflected in physiological measures such that, compared to a control population, depressive patients show alterations in circadian rhythms of melatonin and (Pacchierotti et al., 2001) cortisol levels (Deuschle et al., 1997); body temperature (Daimon et al., 1992); and heart rate (Stampfer, 1998). Moreover, some interventions that change the timing of the biological clock in the brain (e.g., sleep deprivation, light therapy) have efficacy as treatments for these conditions (Wehr et al., 1979). For instance, Agomelatine, a new antidepressive agent with phase advancing characteristics has become available (Fornaro et al., 2010; San and Arranz, 2008) and appears to be effective in at least a subgroup of patients (Duke, 2008). Diurnal variations in symptoms and altered profiles of circadian markers are also found in seasonal depressive disorder (Lewy et al., 2006), bipolar disorder (Harvey, 2008), and schizophrenia (Rao et al., 1994).

In attention-deficit/hyperactivity disorder (ADHD) it is well-established that behavioral symptoms and performance fluctuate both spontaneously over time and in response to changing environmental contexts (Antrop et al., 2005a; Luman et al., 2005; Power, 1992; Sonuga-Barke et al., 1996; Toplak and Tannock, 2005; Wiersema et al., 2006b; Zentall and Zentall, 1976). In clinical practice, sleep–wake problems are frequently reported by individuals with ADHD or their parents, even though these problems are not currently included in the diagnostic criteria. As disruptions of circadian rhythms and sleep–wake cycles are generally expected to have a significant impact on symptom severity (Fallone et al., 2001), daytime functioning (Bearpark and Michie, 1987), and health outcomes (Gangwisch, 2009; Scheer et al., 2009), in recent years, researchers have become increasingly interested in the possibility that such effects are implicated in ADHD pathophysiology. Gathering knowledge on diurnal variations in ADHD is important as these results may improve educational guidelines (such as optimal timing of academic lessons) and diagnostic and therapeutic assessments. For example, knowledge of time of day effects could lead to the adjustment of dosing and timing of ADHD medication to optimally observe and treat problematic behavior at a particular time of day. Furthermore, if findings on disrupted circadian rhythms are confirmed in ADHD, they may point to the value of circadian-based therapies in ADHD such as melatonin treatment and light therapy. To the best of our knowledge, there is no review that assesses findings on circadian effects in ADHD.

To date, the underlying mechanisms of circadian rhythm alterations in psychiatric disorders in general, or in some of these conditions specifically, are still unknown. The suprachiasmatic nucleus (SCN) in the ventral hypothalamus (Weaver, 1998) is thought to drive these 24-h fluctuations in both physiological (e.g., body temperature, heart rate, hormone secretion) and psychological (cognitive performance, personality and behavior) functions (Carrier and Monk, 2000; Haus, 2007; Hofstra and de Weerd, 2008; Tankova et al., 1994; Young, 2006). This biological clock has an endogenous nature – rhythms persist even in the absence of external, environmental information. However, exogenous cues, also called zeitgebers (e.g., light, but also sleep deprivation and social cues), tune this clock to a specific rhythm. The SCN is responsible for the functional time synchronization of all peripheral oscillators found in cells, tissues, and organs. Communication to peripheral structures takes place through both neural and endocrine factors, and enhances synchronized functioning of different human systems, including the central nervous system, the autonomic nervous system, and the endocrine tissues (Haus, 2007). The sleep–wake cycle is also regulated by the SCN. However, this circadian process (process C) interacts with a homeostatic process (process S) to maintain wakefulness (which we further refer to as arousal; a physiological and psychological state of being awake, aware, and alert) during the day and to consolidate sleep at night. Whereas the process C is particularly important in the timing of sleep and arousal states, the process S regulates the duration and structure of sleep (Borbély, 1982). When considering the available evidence, disruptions in circadian rhythms and sleep–wake cycles have usually been related to changes in the timing of the biological clock (though alternative hypotheses have been provided; e.g., social zeitgeber theory, process S deficiency; Boivin, 2000; Grandin et al., 2006). Alterations in biological clock timing have been seen as a consequence of changes in neurotransmitter activity related to