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Interindividual differences in circadian rhythmicity and sleep homeostasis in older people: effect of a *PER3* polymorphism

Antoine U. Viola[a,1,*], Sarah L. Chellappa[a,b,1], Simon N. Archer[c], Fiona Pugin[a], Thomas Götz[a], Derk-Jan Dijk[c], Christian Cajochen[a]

[a] *Centre for Chronobiology, University of Basel, Basel, Switzerland*
[b] *The CAPES Foundation/Ministry of Education of Brazil, Brasilia, Brazil*
[c] *Surrey Sleep Research Centre, University of Surrey, Guildford, UK*

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Abstract

Aging is associated with marked changes in the timing, consolidation and structure of sleep. Older people wake up frequently, get up earlier and have less slow wave sleep than young people, although the extent of these age-related changes differs considerably between individuals. Interindividual differences in homeostatic sleep regulation in young volunteers are associated with the variable-number, tandem-repeat (VNTR) polymorphism (rs57875989) in the coding region of the circadian clock gene *PERIOD3* (*PER3*). However, predictors of these interindividual differences have yet to be identified in older people. Sleep electroencephalographic (EEG) characteristics and circadian rhythms were assessed in 26 healthy older volunteers (55–75 years) selected on the basis of homozygosity for either the long or short allele of the *PER3* polymorphism. Homozygosity for the longer allele ($PER3^{5/5}$) associated with a phase-advance in the circadian melatonin profile and an earlier occurrence of the melatonin peak within the sleep episode. Furthermore, older $PER3^{5/5}$ participants accumulated more nocturnal wakefulness, had increased EEG frontal delta activity (0.75–1.50 Hz), and decreased EEG frontal sigma activity (11–13 Hz) during non-rapid eye movement (REM) sleep compared with $PER3^{4/4}$ participants. Our results indicate that the polymorphism in the clock gene *PER3* may contribute to interindividual differences in sleep and circadian physiology in older people.
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Keywords: Sleep-wake cycle; Circadian rhythms; Constant routine; Melatonin; EEG power density; Clock gene polymorphism; Age

1. Introduction

Aging is associated with numerous changes in sleep, such as increased number and duration of awakenings, and reduced time spent in slow wave sleep (SWS), as well as earlier wake-up time (Cajochen et al., 2006; Dijk et al., 1999). The decline in sleep consolidation, together with the advance of sleep timing, may reflect age-related changes in the homeostatic and/or circadian aspects of sleep regulation (Cajochen et al., 2006; Dijk et al., 1999). From the sleep homeostatic perspective, older people display a shallower dissipation of sleep pressure, as indexed by reduced SWS and slow wave activity (SWA) (electroencephalographic [EEG] power density between 0.75 and 4.5 Hz, also referred to as delta activity) dynamics across the night (Dijk and Beersma, 1989; Landolt et al., 1996). From a circadian standpoint, aging can be associated with a reduced circadian amplitude of the core body temperature (CBT) rhythm, and a phase advance of the CBT and melatonin rhythm (Dijk et al., 1999). However, changes in circadian parameters with aging are less consistent than age-related changes of sleep parameters, and SWS in particular. Thus, some (Czeisler et al., 1992; Münch et al., 2005; Van Coevorden et al., 1991; Weitzman et al., 1982), but not all, studies report a decline in the amplitude of CBT, melatonin, and cortisol

* Corresponding author at: Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Wilhelm Kleinstrasse 27, CH-4012 Basel, Switzerland. Tel.: +41613255318; fax: +41613255556.
E-mail address: antoine.viola@upkbs.ch (A.U. Viola).
[1] Both authors contributed equally to this work.

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(Monk, 2005; Niggemyer et al., 2004; Zeitzer et al., 1999). The disparity of these findings points to rather large interindividual differences in sleep and circadian rhythmicity with age and leaves the question open as to what is driving these individual differences (Van Cauter et al., 2000). Progress in understanding the genetic and molecular basis of sleep and circadian rhythmicity has led to the identification of genes contributing to interindividual differences in sleep architecture, timing, and duration in humans and mice (Franken and Dijk, 2009; Landolt, 2008; Rétey et al., 2005).

The primate-specific (Jenkins et al., 2005), variable-number tandem-repeat (VNTR) polymorphism within the coding region of the clock gene *PERIOD3* (*PER3*) contains a 54-nucleotide unit that is repeated 4 ($PER3^{4}$ allele) or 5 ($PER3^{5}$ allele) times in humans (Ebisawa et al., 2001). In young people, the *PER3* VNTR predicts diurnal preference such that those homozygous for the long repeat ($PER3^{5/5}$) prefer earlier wake-up and sleep time (Archer et al., 2003; Lázár et al., in press). Furthermore, in young people, the *PER3* VNTR polymorphism also predicts interindividual differences in sleep structure and EEG power density in non-rapid eye movement (REM) sleep, REM sleep and wakefulness (Viola et al., 2007). $PER3^{5/5}$ individuals spent more time in SWS, have higher SWA in non-REM sleep, and a steeper dissipation of SWA during sleep episode as compared with those homozygous for the shorter, 4-repeat allele ($PER3^{4/4}$) (Viola et al., 2007). However, in young people, we did not observe significant differences between the genotypes with respect to the phase and amplitude of circadian markers, such as the hormones cortisol and melatonin and the clock genes *PER3*, *BMAL1*, and *PER2* (Archer et al., 2008; Dijk and Archer, 2010; Viola et al., 2007).

Since the *PER3* VNTR polymorphism affects sleep regulation in young individuals, we tested the hypothesis whether this polymorphism also predicts interindividual differences in sleep of older people. Specifically, we predicted that older participants homozygous for the longer repeat ($PER3^{5/5}$) exhibit more slow wave sleep and higher EEG power density in the delta frequency range than older participants homozygous for the shorter repeat ($PER3^{4/4}$).

2. Methods

2.1. Study protocol

Recruitment of volunteers was conducted through advertisements in newspapers, e-mails, radio, and posted advertisements in the Basel and Alsace areas. The screening procedure began with an interview by telephone or in person, involving a detailed explanation of the study. A total of 168 older men and women (age range: 55–75 years) were recruited, from whom DNA samples and questionnaire data were collected. All participants gave written informed consent. The study protocol, screening questionnaires, and consent forms were approved by the local ethics committee (EKBB, Basel, Switzerland) and conformed to the Declaration of Helsinki. All potential study participants were questioned about their sleep quality, life habits, and health state. They completed a consent form, the General Medical Questionnaire, the Short Form-36 (SF-36) Quality of Life Questionnaire, the Horne-Östberg Questionnaire, the Munich Chronotype Questionnaire, the Pittsburgh Sleep Questionnaire, the Epworth Sleepiness Scale, the Beck Depression Inventory, and the Insomnia Severity Index Questionnaire. Exclusion criteria were medical and sleep disorders, smoking, medication or drug consumption, shift work within the last 3 months, and transmeridian flights during 2 months before the study.

For the genotyping, all potential participants provided buccal swab samples, from which genomic DNA was extracted via the QuickExtract system (Epicentre Biotechnologies, Madison, WI, USA). Genotyping was performed with polymerase chain reaction (PCR) as previously described (Archer et al., 2003) with some modification (Vandewalle et al., 2009).

Volunteers with good general health were included in the field study. Forty participants wore actigraphs (wrist-worn Actiwatch L, Cambridge Neurotechnology, Cambridge, UK) to quantify their rest-activity profile and completed daily sleep diaries for approximately 3 weeks prior to the laboratory study. Complete data were obtained from 37 subjects, out of which 21 were $PER3^{5/5}$ (8 men, 13 women, mean ± standard error of the mean [SEM] = 63.02 ± 1.18, in years) and 16 were $PER3^{4/4}$ participants (8 men, 8 women, mean ± SEM = 63.38 ± 1.28, in years). The first 2 weeks were analyzed to characterize the habitual sleep-wake cycle for each study participant, who was then instructed to sleep and wake-up according to his/her habitual schedule for 1 week prior to the laboratory study. Compliance was verified by analysis of the sleep diaries and actigraphy data prior to the laboratory study. Participants who successfully completed the 3-week actigraphy underwent a medical examination, blood screening, and a polysomnography recorded adaptation night to exclude sleep disorders. Exclusion criteria were > 10 periodic leg movements per hour and an apnea-hypopnea index > 10. Thirteen $PER3^{4/4}$ individuals and 13 $PER3^{5/5}$ individuals were matched by age, body mass index, gender, and ethnicity and included in the laboratory part of the study. Table 1 describes the main demographic characteristics of these participants, together with data derived from questionnaires and the sleep-wake timings derived from sleep diaries.

2.2. Laboratory study

The laboratory part consisted of a baseline sleep episode, followed by approximately 40 hours of extended wakefulness under constant routine (CR) conditions, and a subsequent recovery sleep episode. The CR protocol (Duffy and Dijk, 2002a) was employed to assess the circadian phase and amplitude as well as homeostatic aspects of sleep regulation, which involved 40 hours of extended wakefulness

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