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PHYSIOLOGICAL REVIEW

Phenotyping of PER3 variants reveals widespread effects on circadian preference, sleep regulation, and health

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SUMMARY

Period3 (*Per3*) is one of the most robustly rhythmic genes in humans and animals. It plays a significant role in temporal organisation in peripheral tissues. The effects of *PER3* variants on many phenotypes have been investigated in targeted and genome-wide studies. *PER3* variants, especially the human variable number tandem repeat (VNTR), associate with diurnal preference, mental disorders, non-visual responses to light, brain and cognitive responses to sleep loss/circadian misalignment. Introducing the VNTR into mice alters responses to sleep loss and expression of sleep homeostasis-related genes. Several studies were limited in size and some findings were not replicated. Nevertheless, the data indicate a significant contribution of PER3 to sleep and circadian phenotypes and diseases, which may be connected by common pathways. Thus, PER3-dependent altered light sensitivity could relate to high retinal PER3 expression and may contribute to altered brain response to light, diurnal preference and seasonal mood. Altered cognitive responses during sleep loss/circadian misalignment and changes to slow wave sleep may relate to changes in wake/activity-dependent patterns of hypothalamic gene expression involved in sleep homeostasis and neural network plasticity. Comprehensive characterisation of effects of clock gene variants may provide new insights into the role of circadian processes in health and disease.

Introduction

Disruption of sleep and circadian rhythms is prominent in mental and physical diseases. Inter-individual variation in sleep and circadian rhythmicity and risk for physical and mental diseases is in part explained by genetic variation. Here we review how variation in the *PERIOD3* (*PER3*) gene contributes to inter-individual differences in sleep and circadian rhythmicity phenotypes and disease risk. We pay attention to the wide range of phenotypic associations and attempt to understand how these associations may be connected through common pathways.

PER3 is a molecular component of the circadian clock

PER3 is a molecular component of the circadian clock and is a member of the protein-binding family that contain PAS (PER-ARNT-SIM) domains which enable protein dimerization. It binds with other PERIOD and CRYPTOCHROME (CRY) proteins in the negative limb of the transcriptional/translational feedback loop and inhibits the expression of core clock genes and clock-controlled genes by the heterodimer transcription factor CLOCK/BMAL1 which binds to promoter region E-box motifs (Fig. 1) [1]. Recently, electron microscopy has been used with mouse liver cell extracts to show that PER3 protein forms part of a mature cytoplasmic multi-globular complex with PER1, PER2, CRY1, CRY2, casein kinase 1 delta (CK1δ) and that this complex migrates to the nucleus to bind to and inhibit CLOCK/BMAL1 [2].

Evolutionary history of PER3

Three *Per* paralogues exist in most vertebrates and have likely evolved via two genome duplication events from a single ancestral gene [3]. After such evolutionary events, duplicated genes are commonly lost if they confer no diverse functional adaptation, or are retained if accumulating genetic variation provides a selective advantage. Because PER3 exists in humans, this implies that functions associated with it have been positively selected and maintained, unlike PER4 which has been lost from the genome [3].

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Abbreviations

ASPD	advanced sleep phase disorder
BDNF	brain derived neurotrophic factor
BMI	body mass index
CK1	casein kinase 1
CRSWD	circadian rhythm sleep–wake disorders
CRY	cryptochrome
CT	circadian time
dLAN	dim light at night
DSPD	delayed sleep phase disorder
EEG	electroencephalogram
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
GWAS	genome-wide association study
HCC	hepatocellular carcinoma
IGF-1	insulin-like growth factor 1
IL6	interleukin 6
KO	knock out
MD	mean diffusivity
NREM	non rapid eye movement
OVLT	organum vasculosum lamina terminalis
PER	period
PSD	partial sleep deprivation
PVT	psychomotor vigilance task
RD	radial diffusivity
REM	rapid eye movement
SAD	seasonal affective disorder
SCN	suprachiasmatic nucleus
SD	sleep deprivation
SNP	single nucleotide polymorphism
SWA	slow wave activity
SWE	slow wave energy
SWS	slow wave sleep
TSD	total sleep deprivation
VLPO	ventrolateral preoptic nucleus
VNTR	variable number tandem repeat
WM	white matter

PER1 or PER2 are essential for normal circadian function but PER3 alone cannot drive the central circadian clock in the suprachiasmatic nuclei (SCN) of the hypothalamus [4]. The absence of PER3 has only minor effects on behaviour driven by the SCN clock [5]. However, in peripheral tissues, circadian period and phase are disrupted in *Per3* knock out (KO) mice [6]. Thus, the evolutionary selective pressure to retain the duplicated *Per3* gene is unlikely to have derived from its role within the central, hypothalamic clock, but more likely came from novel functions in peripheral clocks and associated phenotypes. These phenotypes include diurnal preference, sleep homeostasis, circadian rhythm sleep–wake disorders (CRSWDs), cognitive performance, light sensitivity, mental disorders, and cancer. Thus, although PER3 has often been neglected as a circadian clock gene, there is a wealth of data that links it with physiological and health phenotypes. The question remains, what are the characteristics of PER3 and the underlying mechanisms that give rise to this?

PER3 is one of the most highly rhythmic genes in the CNS and periphery

In mice, robust expression levels of *Per3* have been found in the CNS including the ventromedial hypothalamic nucleus, gyrus dentatus, arcuate nucleus and medial amygdaloid nucleus, with moderate expression levels in the cingulate cortex, hippocampal pyramidal cells, cerebellar cortex and the nucleus tractus solitarius [7]. *Per3* is also strongly expressed in peripheral mouse tissues, including in heart, lung, liver, skeletal muscle, kidney and testis [7,8]. Robust, rhythmic expression of *Per3* occurs in the SCN and the organum vasculosum lamina terminalis (OVLT), with peak expression at circadian time (CT) 4 and 8, respectively (CT0 = subjective dawn) [7]. The peak of rhythmic expression of *Per3* in peripheral mouse tissues and certain CNS regions (liver, skeletal muscle, testis, arcuate nucleus, ventromedial hypothalamic nucleus, and retina) appears shifted relative to the SCN to between CT9 and 21 [7,8]. Of interest, *Per3* expression in the rat sleep-related ventrolateral preoptic nucleus (VLPO) is 12 h out of phase with its expression in the SCN [9].

The role of PER3 in the periphery

The role of PER3 in the SCN may be redundant but its contribution to peripheral clocks is more significant. In *Per3* KO mice, the period and phase of tissue explants from pituitary, liver, lung, adrenal, oesophagus, aorta, thymus, arcuate complex, and gonadal adipose were significantly shorter and/or advanced compared to wild type mice [6,10]. Period length was also shorter in fibroblast, adipocyte, and hepatocyte cell cultures where *Per3* had been silenced [11]. SCN explants from *Per3* KO mice showed only a small reduction in luciferase reporter period [11], which were similar to previous reports for *Per3* KO locomotor activity period [5]. However, when explanted SCN cells were dissociated they showed a substantially shorter luciferase reporter period in *Per3* KO compared to wild type (25.58 ± 0.12 h vs. 27.23 ± 0.24, mean ± SEM) [11]. All these findings underline a potential prominent role for PER3 in the periphery, but also in the SCN, where its importance only becomes apparent when the coupling between pacemaker neurons in the intact tissue is removed.

PER3 and light phenotypes

Unlike *Per1* and *Per2*, *Per3* expression in the SCN is not induced by light [7,8]. Nevertheless, high levels of rhythmic expression of *Per3* were found in the mouse retina and specifically in photoreceptors [8,12], as well as in rat pineal [13]. In human tissues the highest levels of *PER3* are recorded in retina, thyroid and pineal, while in the mouse the highest levels are found in the salivary and lacrimal glands, the pituitary and adrenal glands, and many compartments of the eye including the retina (BioGPS GeneAtlas, biogps.org). Thus, in addition to its wide expression throughout the body (Fig. 1), PER3 is also specifically present in tissues involved with light-dependent phenotypes. This may be related to some of the light-dependent phenotypes observed in *Per3* KO mice [14] and also in humans [15,16] (see below).

Rhythmic expression of PER3 in human and animal tissues

In humans, assessment of the time course of *PER3* across the 24-h day has been carried out by targeted quantitative polymerase chain reaction (PCR) in white adipose tissue [17] and blood cells (e.g., [18,19]), and by genome-wide microarray transcriptomic profiling in hair follicles [20], keratinocytes [21], post-mortem brain tissue [22–24], bone cell cultures [25], and whole blood in different sleep–wake conditions [26–28]. A novel machine learning-based approach has also been used to order samples with no time stamps to form a time series showing robust expression of

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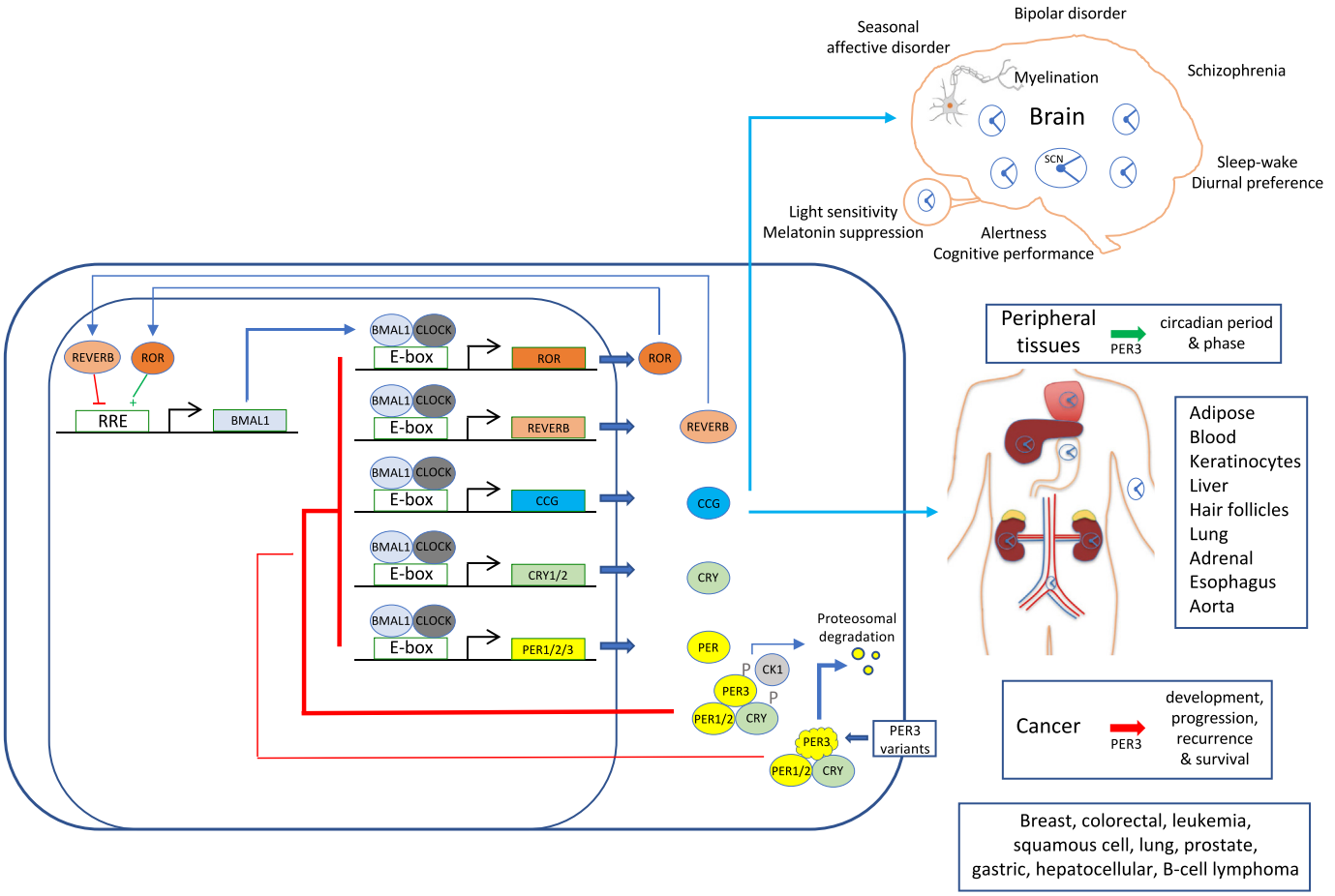

Fig. 1. The circadian molecular clock and the influence of PER3 on phenotypes and disease in peripheral tissues. The circadian clock consists of positive and negative integrated transcription and translation feedback loops. The transcription factors BMAL1 and CLOCK bind to E-box motifs in the promoters of clock controlled genes (CCGs) including the core clock genes *PER1/2/3*, *CRY1/2*, *REVERB* and *ROR*. ROR and REVERB proteins feedback and bind to ROR/REVERB response elements (RRE) in the promoter of BMAL1 and either enhance or suppress its expression, respectively. PER and CRY proteins form complexes together with CK1, which phosphorylates them determining stability and proteosomal turnover (thin blue arrow). PER3 stabilises PER1/2 in PER/CRY complexes, which feedback and suppress the promotion by BMAL1/CLOCK (thick red line). PER3 variants can affect the stability of PER3 causing greater degradation (thick blue arrow), reduced PER1/2 stability, and reduced suppression of BMAL1/CLOCK (thin red line). This provides a mechanism by which PER3 can influence circadian period and phase in peripheral tissues (including the brain) and also the expression of many CCGs. The influence of PER3 variants on the circadian clock and CCGs potentially underlies the wide range of phenotypes and disease conditions that have been associated with PER3 variants. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PER3 also in human liver biopsies [29]. An analysis of a subset of these human datasets, together with 16 mouse time series data from different tissues and conditions revealed that *PER3* is the third most robustly expressed clock gene (after *NR1D1* and *NR1D2*), being rhythmic in 94% of mouse tissue time series and 86% of the few human tissues investigated (Fig. 2) [30]. These studies all confirm *PER3* as ranking among the top rhythmically expressed genes in peripheral tissues. The peak of *PER3* expression in human non-brain tissues is reported to be around relative clock time 6–10 (~4–8 am; Fig. 2), while in the brain *PER3* expression is around relative clock time 4–6 (~4–6 hours after onset of pseudoday; Fig. 2), although given the sampling resolution it remains to be firmly established whether these differences are robust. In a study of prefrontal cortex post-mortem samples from young and old individuals, core clock gene expression was found to be phase-advanced and reduced in amplitude in older individuals except for *PER3*, which remained unchanged [24].

What drives the robust, rhythmic expression of PER3?

A recent detailed analysis of transcription factor units within the human *PER3* transcription regulatory region has revealed three E-box and two D-box motifs [31]. CLOCK/BMAL1 and DBP (D-box binding PAR BZIP transcription factor), independently bind to the E box and D box motifs, respectively, to drive expression of *PER3*. By removing different combinations of the motifs from the *PER3* regulatory region, Matsumura et al. showed that the motifs contributed differentially to the overall amplitude and phase of expression, and that their combined activation led to robust, high amplitude expression. This observation likely accounts for the consistent observation in the literature of robust *PER3* expression.

PER3 polymorphisms

The study of sequence variation within a gene and genotype/phenotype associations is a powerful way to identify functional characteristics of the encoded protein. The human *PER3* sequence together with a catalogue of its polymorphisms was published soon after it was first isolated in mice [32]. Compared with *PER1* and *PER2*, *PER3* is highly polymorphic [33] and subsequently many more coding and non-coding polymorphisms have been found that associate with diverse phenotypes and disease (see Table 1).

One *PER3* polymorphism (rs57875989) of particular interest is the coding-region (exon 18) variable number tandem repeat

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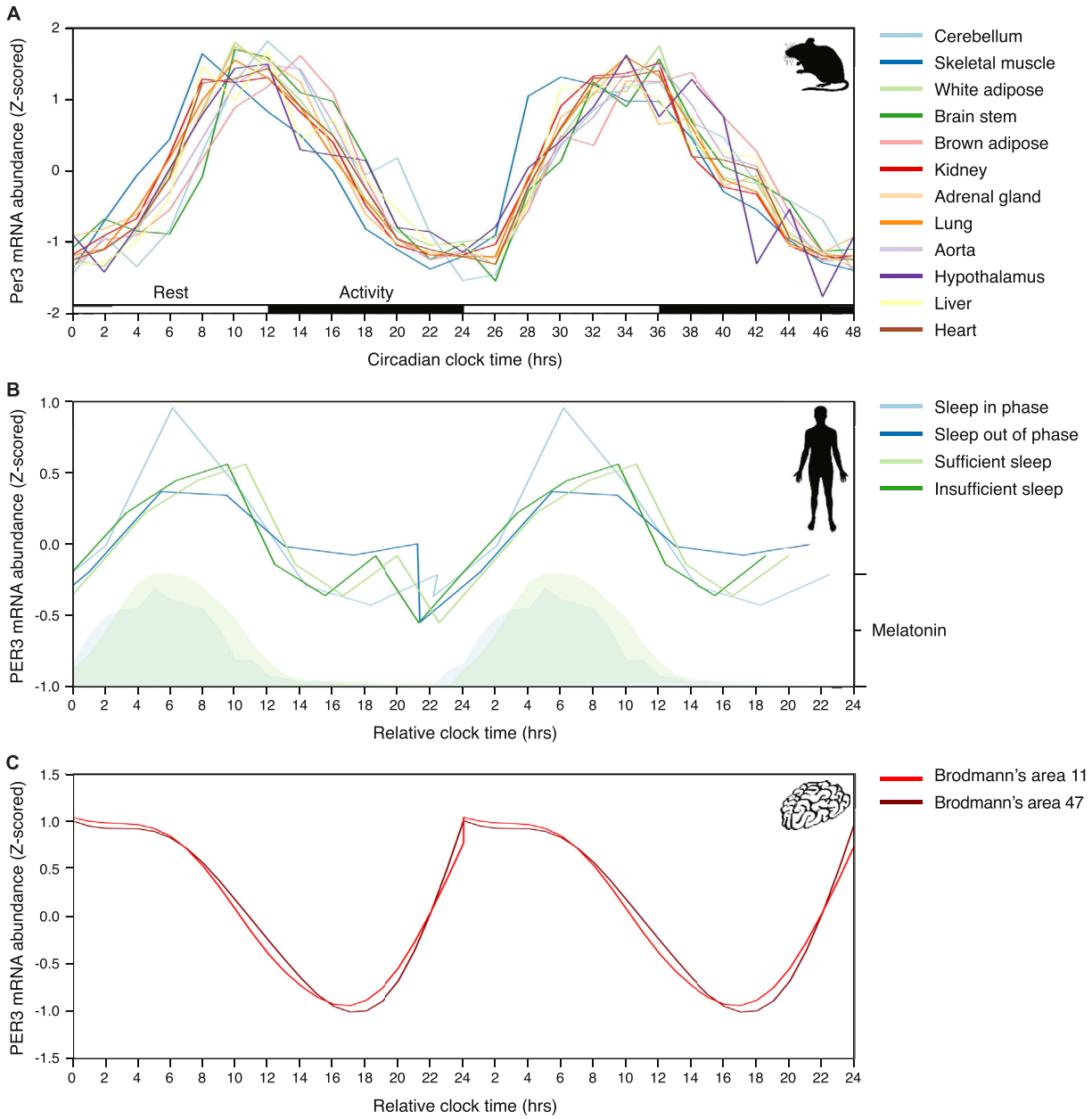

Fig. 2. PER3 gene expression in different mouse and human tissues. A) Mouse data from 12 different tissues measured in constant darkness (previous light/dark cycle indicated) across 48h were extracted from CircaDB (http://circadb.hogeneschlab.org/). The data were Z-scored prior to plotting. B) Human blood expression data were taken from Möller-Levet et al., 2013 and Archer et al., 2014, GEO accession numbers: GSE39445 and GSE48113. Z-scored average PER3 mRNA abundance values (across multiple probes and participants) were calculated for each sampling point in each of the four conditions assessed (sleeping in phase with melatonin [light blue], sleeping out of phase with melatonin [dark blue], during total sleep deprivation after one week of sufficient sleep [light green], and total sleep deprivation after one week of insufficient sleep [dark green]). Each sampling point was assigned the average relative clock time of that sample, as indexed by the dim light melatonin onset (DLMO = 0, approximately 10pm). In the protocol of Möller-Levet et al., 2013, three samples prior to DLMO were collected whereas in Archer et al., 2014, only one sample prior to DLMO was collected. To readily compare the data between protocols, the double-plotted data shown are the time series from one sampling point prior to DLMO to 24h. Average melatonin curves for the sleeping in phase (light blue) and sufficient sleep (light green) conditions are shown. C) Z-scored PER3 mRNA abundance values from human post-mortem data obtained from the processed GEO data set GSE71620 (Chen et al., 2016). A cubic smoothing spline was fitted to the data (5 knots, smooth.spline function in R) and the fitted data are double plotted. Data are shown from two brain areas; Brodmann's area 11 (dark grey) and area 47 (light grey). Relative clock time refers to hours after the onset of a pseudoday (= 0; see Chen et al., 2016).

(VNTR). The 18-amino-acid tandem motif is repeated 4 or 5 times in humans such that individuals are homozygous (*PER3*$^{4/4}$ [~45%] or *PER3*$^{5/5}$ [~10%]) or heterozygous (*PER3*$^{4/5}$ [~45%]) for the two alleles. PER3 is phosphorylated by CK1 and translocates to the nucleus to inhibit CLOCK/BMAL1 in the presence of PER1 [34]. The VNTR motif contains clusters of potential phosphorylation sites for CK1 [35]. Post-translational modification by CK1 affects the stability and nuclear translocation of PER [36]. Mutation in a single CK1 phosphorylation site in PER2 is associated with shortened circadian period and advanced sleep–wake timing in familial advanced sleep phase disorder (ASPD) [37,38]. Thus, the presence of 4 or 5 repeats in PER3 could change overall protein phosphorylation levels by ~20% [35] and could also significantly change protein tertiary structure, with implications for the way in which PER3 interacts with other core clock proteins in the multi-globular repressor complex [2].

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PER3 and diurnal preference

The PER3 VNTR

Because the PER3 VNTR could change protein phosphorylation levels in addition to tertiary protein structure and interactions with binding partners, this led to the hypothesis that the VNTR would cause functional changes in PER3 that would be associated with measurable individual phenotypic differences [35]. This hypothesis was validated through the association of the 5-repeat allele with morning diurnal preference and its lower than expected frequency within patients suffering from delayed sleep phase disorder (DSPD) [35]. The PER3 VNTR appears to be primate-specific [39] and it has been speculated that the expansion of the VNTR region enabled Simiiforme primates to adapt to a diurnal niche [40].

The association between PER3 and diurnal preference has since been replicated in several studies [41–44], including a large study population of 675 individuals [45]. The latter study did not select participants according to extreme chronotype and only investigated the effects of the PER3 VNTR, thereby avoiding the risk of false positive findings. While observed diurnal preference differences between the genotypes were modest in that study (e.g., mean [±SD] diurnal preference scores of 51.06 ± 7.89 vs. 53.31 ± 7.90 for $PER3^{4/4}$ and $PER3^{5/5}$, respectively), they were statistically significant ($P < 0.05$; Fig. 3). In addition to the predicted diurnal preference difference, Lazar et al. also found associations between the $PER3^{5/5}$ genotype and earlier sleep onset ($PER3^{5/5}$ 15 min earlier than $PER3^{4/4}$), mid sleep ($PER3^{5/5}$ 17 min earlier than $PER3^{4/4}$) and wake timing ($PER3^{5/5}$ 22 min earlier than $PER3^{4/5}$) (Fig. 3). $PER3^{5/5}$ also showed lower daytime sleepiness and a larger increase in time in bed on rest days compared to other genotypes. It should be noted that, in accordance with the effects of other polymorphisms, the effect sizes were small (i.e., SD is in general 4 times larger than the difference in the means). Furthermore, Lazar et al. reported interesting genotype-dependent phenotype interactions. $PER3^{5/5}$ individuals with a delayed mid sleep time on workdays had a significantly higher body mass index (BMI) compared with the other genotypes, and $PER3^{5/5}$ individuals who slept >9 h during workdays performed worse on a fluid intelligence test compared with the other genotypes [45]. These interactions between genotype and other risk factors on outcome measures are similar to more recent reports on the interaction between diurnal preference, BMI and a polymorphism in the circadian gene *CLOCK* [46]. The study by Liberman et al. also found the 4-repeat allele to be more frequent in evening types, and the $PER3^{4/4}$ and $PER3^{5/5}$ genotypes less frequent in morning types and in evening types, respectively [44]. Of interest, Liberman et al. also used a complex circadian clock model to predict that decreased and increased phosphorylation levels associated with the $PER3^{4/4}$ and $PER3^{5/5}$ genotypes, respectively, would lead to a lengthened (24.5 h) and shortened (22.8 h) period length in those genotypes, which agrees well with the associated diurnal preference and DSPD phenotypes [44].

Other PER3 polymorphisms

The involvement of PER3 in determining diurnal preference and its contribution to CRSWDs is further supported by associations with other polymorphisms within *PER3*. Within the *PER3* promoter region, three SNPs (rs2797687, G/T; rs2794664, C/A; rs228730, G/A) and a VNTR polymorphism consisting of one or two copies of a tandem 21-nucleotide repeat have been identified and are associated with diurnal preference and DSPD [47]. A specific haplotype (TA2G) of the promoter polymorphisms was more prevalent in DSPD and also increased gene expression levels when the *PER3* promoter containing that haplotype was used to drive expression of a reporter gene construct, compared with constructs containing the other promoter haplotypes.

Within the *PER3* coding region, a specific haplotype of four missense single nucleotide polymorphisms (SNPs; rs10462020, rs228697, rs2640909, rs10462021) and the VNTR was found to be more prevalent in DSPD patients [32]. One of the SNPs (rs10462020) is close to the conserved phosphorylation sites in PER2 affected by the mutation linked with ASPD [37] and the same SNP was also linked with morning preference in a separate study [48]. Another of the DSPD haplotype SNPs (rs2640909) has also been linked with morning preference [49], while the minor allele (G) of a third (rs228697) was linked with evening preference [44,50], circadian free-running types [50], and depression [51] (see below). Interestingly, a recent study has found the opposite association with the G allele of rs228697 being associated with morning preference, and a haplotype containing the G allele and the VNTR 4-repeat also associated with morning preference [52]. In addition, homozygotes for the VNTR 4-repeat allele had an advanced urinary 6-sulfatoxymelatonin acrophase [52]. The rs228697-G/VNTR-4-repeat haplotype was also associated with worse mood in the evening, and carriers of the G allele had earlier wake times, less sleep and poorer sleep quality [52]. However, this recent study also reported reduced sleepiness in the $PER3^{5/5}$ in the morning compared to the other genotypes [52], which does agree with findings from Lazar et al. [45].

Replication failures

As the above studies indicate, the association between *PER3* genotype and diurnal preference or sleep phenotypes has not always been replicated. This may be due to a combination of factors such as different study populations and phenotyping tools (e.g., [53–56]). However, an alternative hypothesis in which interactions between social constraints, genotype and phenotypes are taken into account is worth considering. For example, it has been shown that some categories of athletes have a higher tendency to be morning types compared to controls, which has been related to a greater prevalence of competition and practice schedules in morning periods [43,56]. It has also been shown that individual sport endurance athletes (cycling, running, ironman) had a higher frequency of the $PER3^{5/5}$ genotype and morning preference compared to controls [43]. However, in a recent study, team rugby players were found to have increased morning preference compared to controls. Whereas as expected in the controls *PER3* genotype associated with morning preference, there was no association with *PER3* genotype in the rugby players [57]. The authors hypothesise that preference in rugby players is determined largely by social constraints of habitual morning athletic behaviour and not by genotype. This highlights the complexities in determining the role of gene variants in behaviour based on phenotype assessment tools that can also be confounded by social factors.

Evidence from GWAS studies

While candidate gene approaches that have specifically targeted *PER3* have undoubtedly been successful, recent large-scale genome-wide association studies (GWAS) have also highlighted *PER3*. A study of more than 89,000 individuals found an association between diurnal preference and a SNP variant (rs11121022) close to *PER3* [58]. However, rs11121022 actually lies within the adjacent *VAMP3* gene meaning that *PER3* may not be causative in this association. Another GWAS in more than 100,000 individuals found a suggestive signal (rs7545893) for diurnal preference close to the *PER3* VNTR [59]. Several SNPs in *PER3* (but not the VNTR) were associated with phenotypes associated with sleep (rs228642 with

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Table 1
Variant identification and information. The Global MAF refers to the minor allele frequency obtained from the 1000 Genomes Project Phase 3. Variants are listed according to chromosome position (5′ to 3′ of gene). Affected amino acids are indicated together with their position. Associated phenotypes are listed.

Variant	Position (Chr1)	Alleles	Global MAF	Class	Type	Amino Acid	AA Position	Phenotype	References
rs11121022	1:7776599	A/C	0.304 (C)	SNP	Intronic			Diurnal preference	[58]
rs2797687	1:7784383	G/T	0.298 (T)	SNP	Promoter			Diurnal preference, DSPD	[47]
rs2794664	1:7784384	C/A	0.298 (A)	SNP	Promoter			Diurnal preference, DSPD	[47]
[b]	1:7784385–7784405	1/2VNTR	0.010 (1)	Indel	Promoter			DSPD	[47]
rs228730	1:7784409	G/A	0.062 (A)	SNP	Promoter			DSPD	[47]
rs228729	1:7785635	T/C	0.276 (T)	SNP	Intronic			Bipolar disorder, lung cancer, gastric cancer, hepatic cancer	[94,117–119]
rs836755	1:7786467	A/C	0.442 (C)	SNP	Intronic			Bipolar disorder, sleep onset	[96]
rs11579477	1:7786940	A/G	0.005 (G)	SNP	Intronic			EEG delta power	[60]
rs7545893	1:7796207	C/A	0.120 (A)	SNP	Intronic			Diurnal preference	[59]
rs228682	1:7796286	T/C	0.311 (C)	SNP	Intronic			Depression	[91]
rs1012477	1:7798075	G/C	0.116 (C)	SNP	Intronic			Diurnal preference, prostate cancer, breast cancer	[60,115,116]
rs228642	1:7803233	C/T	0.416 (T)	SNP	Intronic			Bipolar disorder, sleep duration	[60,94]
rs228644	1:7806023	G/A	0.308 (A)	SNP	Intronic			Depression	[91]
rs228666	1:7808665	T/C	0.310 (C)	SNP	Intronic			Bipolar disorder	[94]
rs150812083	1:7809893	C/G	0.003 (G)	SNP missense	Coding	P/A	414	ASPD, PER3 stability, circadian period, SAD	[89]
rs139315125	1:7809900	A/G	0.003 (G)	SNP missense	Coding	H/R	416	ASPD, PER3 stability, circadian period, SAD	[89]
rs228669	1:7809988	T/C	0.121 (T)	SNP synonymous	Coding	S	445	Hepatic cancer	[119]
rs12137927	1:7811169	T/C	0.183 (C)	SNP	Intronic			Depression	[91]
rs2172563	1:7813983	G/A	0.183 (A)	SNP	Intronic			Bipolar disorder	[96]
rs10462020	1:7820623	T/G	0.121 (G)	SNP missense	Coding	V/G	639	Diurnal preference, DSPD, B cell lymphoma	[32,48,120]
rs2859387	1:7827188	G/A	0.483 (G)	SNP synonymous	Coding	P	745	Bipolar disorder, schizophrenia	[92]
rs228697	1:7827519	C/G	0.060 (G)	SNP missense	Coding	P/A	864 (856)[a]	Diurnal preference, DSPD, free-running type, depression, bipolar disorder	[32,44,50–52,94]
rs17031614	1:7827545	A/G	0.094 (A)	SNP synonymous	Coding	S	872	Depression	[51]
rs2859388	1:7828155	A/G	0.472 (A)	SNP	Intronic			Bipolar disorder	[94]
rs57875989	1:7829993–7830046	4/5VNTR	0.317 (5)[c]	Indel	Coding	ALSTGSPPM KNPSHPTAS	1007	Diurnal preference, DSPD, EEG power, alertness, cognition, fMRI, light sensitivity, melatonin suppression, bipolar disorder, axon structure, drug addiction, anxiety, colorectal cancer	[15,16,32,35, 41–45,52,53,64,67, 71–73,78,80–83, 93–95,97,100–102, 104,121]
rs2640909	1:7830057	T/C	0.185 (C)	SNP missense	Coding	M/T	1028	Diurnal preference, DSPD	[32,49,119]
rs10462021	1:7837073	A/G	0.121 (G)	SNP missense	Coding	H/R	1158	DSPD	[32]

ASPD, advanced sleep phase disorder; DSPD, delayed sleep phase disorder; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; Indel, insertion or deletion; PER3, Period3; SAD, seasonal affective disorder; SNP, single nucleotide polymorphism; VNTR, variable number tandem repeat.
[a] rs228697 P/A is variously referred to amino acid 864 or 856 in different publications and databases.
[b] The promoter 1/2VNTR has not been assigned a variant identification (minor allele frequency was taken from Archer et al. [47]).
[c] Minor allele frequency for UK taken from Nadkarni et al., 2005 [128].

total sleep time; rs11579477 with electroencephalogram [EEG] delta power) and chronotype (rs1012477) in patients with late-life insomnia [60]. These non-targeted GWAS studies add further support for the role of PER3 in a diverse range of phenotypes.

Underlying mechanisms linking PER3 genotype with function

The studies by Hida et al. and Turco et al. both speculated that the proline to alanine substitution associated with rs228697 could disrupt Src homology 3 binding domains that could disrupt the interaction of PER3 with other clock proteins and lead to the observed associations with diurnal preference, albeit opposite ones in each study [50,52]. Shi et al. who reported an association between rs228697 with depression, went further and showed that the proline to alanine substitution stabilized PER3 and increased its recruitment of PER2 to the repressor complex, leading to stronger repression of CLOCK/BMAL1. Expression of the alanine variant in fibroblasts also increased the period length of gene expression of a reporter construct [51], which would fit with an evening preference phenotype and its link to depression in adults [61]. Both Hida et al. and Turco et al. point out that the proline to alanine substitution will alter the hydropathy index at that amino acid site which could change the local secondary structure of the protein and potentially affect its interaction with CK1 and phosphorylation levels of the protein. Related to this, it should be noted that a hydrophobicity plot of the entire human PER3 exon 18 containing the VNTR shows very distinct alternating hydrophobic/hydrophilic domains that correspond to the VNTR repeat domains (Fig. 4). Such a regular structure could predict a series of externally facing loops in the PER3 protein in this region, presenting phosphorylation sites for CK1 with obvious implications for phosphorylation levels associated with either 4 or 5 such loop structures. Structural differences in the PER3 protein due to the VNTR in exon 18 are perhaps now even more relevant given the recent demonstration of the close interaction of PER3 with the other PERs, CRYs and CK1 in a globular protein repressor complex [2].

PER3 VNTR and sleep homeostasis

In the first electroencephalogram (EEG) sleep study comparing 14 $PER3^{4/4}$ vs. 10 $PER3^{5/5}$ participants in their twenties, several sleep

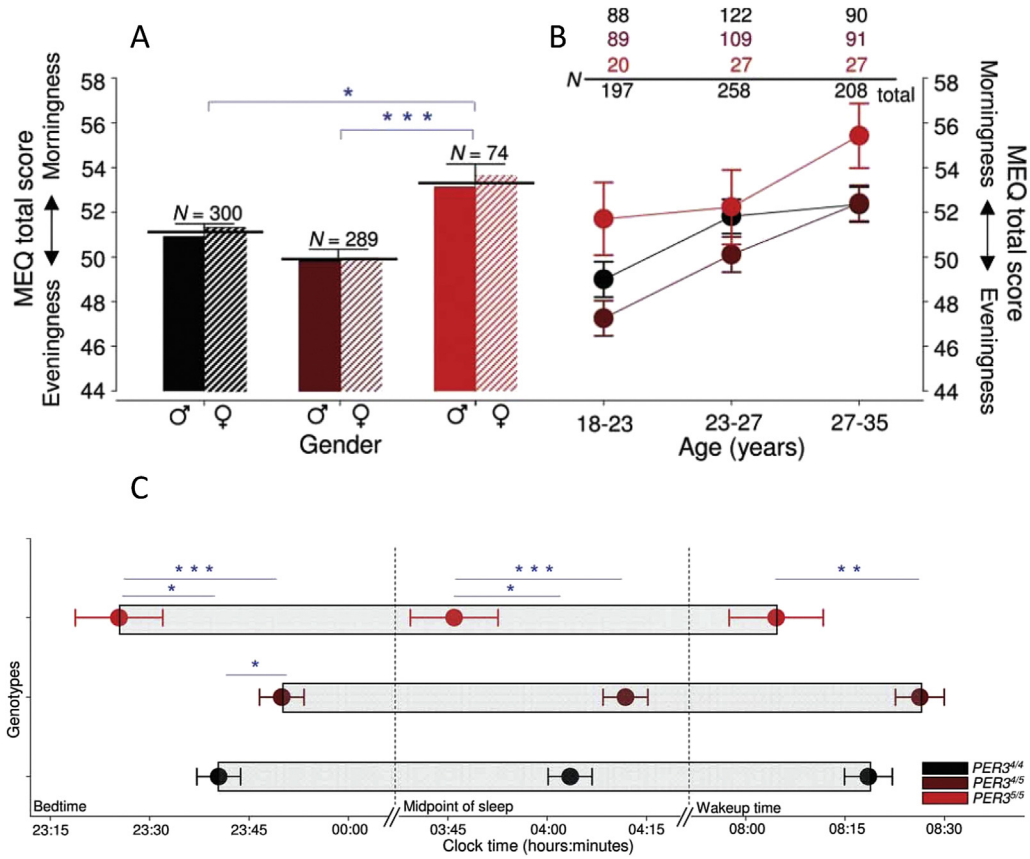

Fig. 3. The effect of the PER3 VNTR on diurnal preference and sleep–wake schedules. A) Morningness eveningness questionnaire (MEQ) diurnal preference scores (mean ± sem) in 663 individuals by genotype and sex. Diurnal preference score was higher (more morning preference) in *PER3*$^{5/5}$ compared with *PER3*$^{4/5}$ ($p = 0.001$) and *PER3*$^{4/4}$ ($p = 0.033$). There was no sex difference. B) MEQ scores (mean ± sem) for each *PER3* genotype in 663 individuals divided into three age groups each representing roughly one third of the study population. Diurnal preference was different between genotypes ($F_{2,658} = 5.45$, $p = 0.005$) and increased with age ($F_{2,658} = 15.28$, $p < 0.001$). C) Effect of PER3 VNTR on bedtime, midpoint of sleep and wakeup time as derived from averages (mean ± sem) of data collected from multiple questionnaires (see Lazar et al., 2012). Time in bed is indicated by horizontal bars. Significant differences between genotypes are indicated by horizontal lines (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). Figures adapted from Lazar et al. [45].

parameters were investigated at baseline and during recovery sleep following sleep deprivation (SD) [62]. At baseline, *PER3*$^{5/5}$ individuals fell asleep quicker and had more slow wave sleep (SWS) than *PER3*$^{4/4}$ individuals. Rapid eye movement (REM) sleep and total sleep time did not differ between the genotypes. Quantitative analyses of the EEG revealed more slow wave activity (SWA) in *PER3*$^{5/5}$ in the initial part of both baseline and recovery sleep, while SWA did not differ between genotypes in the latter part of the night. During REM sleep, alpha activity was enhanced in *PER3*$^{5/5}$, whereas during wakefulness, EEG theta activity was higher in the *PER3*$^{5/5}$ individuals. Since SWS, SWA and theta activity in wakefulness are all considered markers of the sleep homeostat, these data are in accordance with the hypothesis that *PER3*$^{5/5}$ individuals live under a higher homeostatic sleep pressure [63].

A first attempt to replicate effects of the VNTR on sleep and cognition included 52 *PER3*$^{4/4}$, 63 *PER3*$^{4/5}$ and 14 *PER3*$^{5/5}$ young adults [53]. At baseline, subjective sleepiness measures varied significantly across the three genotypes and in the maintenance of wakefulness test. The heterozygous participants were most sleepy, followed by the *PER3*$^{5/5}$ participants. At baseline, no differences were observed in sleep structure across the three genotypes, except for a tendency for sleep latency ($p < 0.1$), with the *PER3*$^{5/5}$ displaying the shortest sleep latencies. During five consecutive nights of partial sleep deprivation (PSD; 4 h time in bed), slow wave energy (SWE), expressed as a percentage of the values at baseline, varied significantly across the three genotypes such that the *PER3*$^{5/5}$ participants had a significantly stronger SWE response to PSD than the two other genotypes. Higher relative SWA values in the first non rapid eye movement (NREM) episode in *PER3*$^{5/5}$ participants were also observed during baseline sleep in another study [16].

PER3 VNTR, sleep and ageing

Whereas the previous studies were conducted in young adults, a study conducted in 26 older participants (13 of each homozygous genotype) [64] found that, at baseline, *PER3*$^{5/5}$ participants were less sleepy during daytime. At baseline, sleep efficiency was significantly lower in the *PER3*$^{5/5}$ participants and this was primarily related to more wakefulness in the second part of the night. Visually-assessed sleep structure was not different between genotypes during either baseline or during recovery sleep following total sleep deprivation (TSD). Quantitative EEG analyses revealed higher low frequency EEG activity (0.75–1.5 Hz) in a frontal derivation in NREM sleep in *PER3*$^{5/5}$ participants. In addition, frontal sigma activity (11–13 Hz) was reduced.

PER3 VNTR in mice: effects on sleep and gene expression

These human studies all indicate that the PER3 VNTR affects low frequency EEG activity in NREM sleep either both at baseline and during recovery sleep from TSD, or in response to PSD. Overall, these results in humans are consistent with a role of the PER3 VNTR

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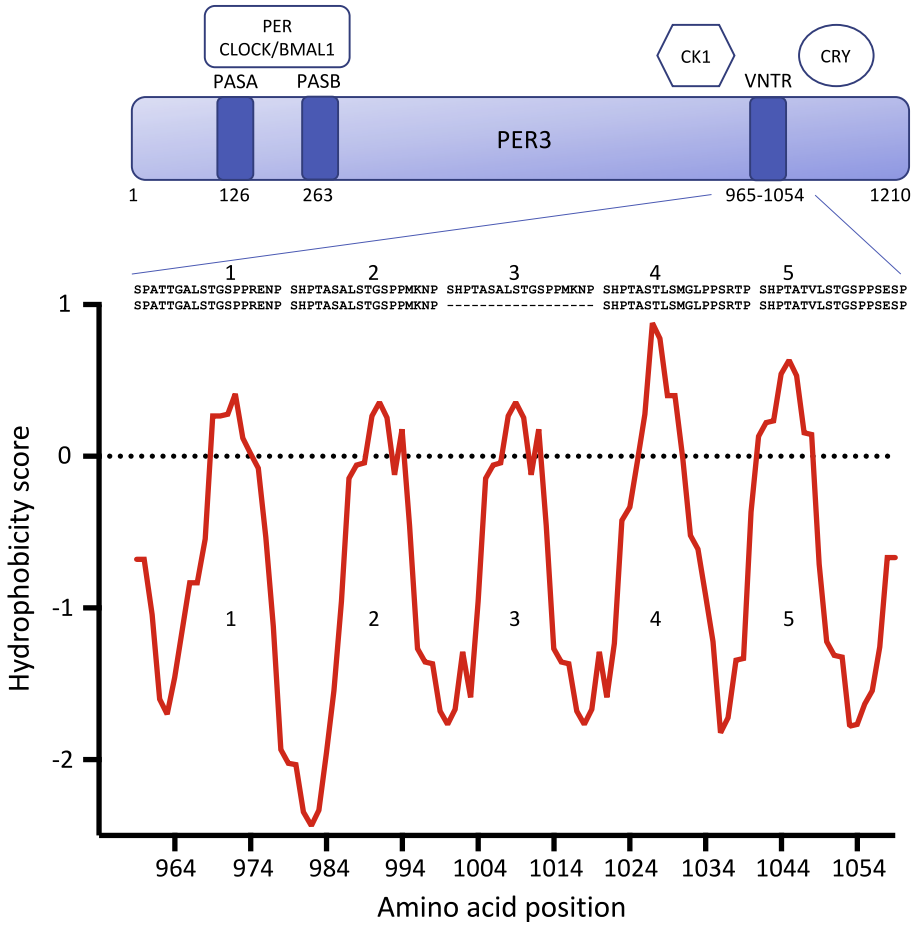

Fig. 4. Hydrophobicity plot for the human PER3 exon 18 containing the VNTR. The schematic PER3 protein shows the VNTR polymorphic region toward the C-terminal of the protein (amino acids 965–1054) in relation to binding regions for CK1 and CRY, and the PASA and PASB domains that enable binding to other proteins such as PER, CLOCK and BMAL1. The amino acid sequence for the five VNTR units is shown beneath, with the missing third unit indicated for the 4-repeat allele. The entire exon 18 amino acid sequence was submitted to ExPASy (www.expasy.org) and the Kyte & Doolittle scale was used for amino acid hydropathy scores with an averaging window of 9. Data are displayed from exon 18 amino acids positions 959 to 1060. The VNTR repeat motifs are numbered 1–5. A positive score indicates hydrophobic regions and a negative score, hydrophilic ones.

in some aspect of NREM-SWA regulation. Such effects on SWA and number of awakenings have subsequently been observed for a common variant of the human clock gene *PER2* in a carefully controlled study that included a replication sample [65]. Previously, several animal studies had demonstrated effects of various clock genes on sleep homeostasis [66]. Since the PER3 VNTR is primate-specific, the role of the PER3 VNTR is not easily investigated in mice. One approach to overcome this difficulty is to insert the PER3 VNTR in mice. Implementation of this demonstrated several effects of the human VNTR on waking EEG and sleep characteristics in mice. EEG power in the 8.5–11 Hz range in wakefulness during SD was higher in the *Per3*$^{5/5}$ mice [67]. Also, during recovery sleep, SWE lost during SD was fully recovered in *Per3*$^{5/5}$ mice but not so in *Per3*$^{4/4}$ mice (Fig. 5). These electrophysiological markers again point to an effect of the VNTR polymorphism on NREM sleep homeostasis. In addition, it was found that molecular markers of sleep homeostasis (e.g., ion channels and neurotransmitter receptors), but not circadian clock genes, were differentially affected by SD across the genotypes (Fig. 5). Microarray analysis showed that probes targeting *Homer1* transcripts were differentially regulated and probes that target the short *Homer1a* transcript, which is firmly linked to sleep homeostasis [68,69] were up-regulated in *Per3*$^{5/5}$ mice (Fig. 5). Furthermore, *Ptgs2*, which is an activity and SD-induced gene, was differentially regulated across the genotypes (Fig. 5). Since some of these genes, and *Homer1* in particular, are also strongly implicated in synaptic plasticity, these data may provide a link between sleep homeostasis and the cognitive phenotypes found in *PER3* VNTR genotypes.

Effects of PER3 VNTR on cognition depend on cognitive domain, sleep pressure and circadian phase

Several studies have indicated that *PER3* VNTR genotype may influence the effects of sleep loss on cognitive function. Young *PER3*$^{5/5}$ participants performed significantly worse in cognitive tasks than *PER3*$^{4/4}$ during SD [62]. This effect was most pronounced when performance was assessed in the late-night and early-morning hours, i.e., at a time of high sleep need when the circadian timing system does not promote wakefulness [70]. Because no differences in core physiological markers of circadian rhythmicity were found between *PER3* genotypes, it was concluded that the influence of the PER3 VNTR polymorphism on neurobehavioral performance was primarily due to differences in sleep homeostasis, the negative impact of which is strongest at an adverse circadian phase. Indeed, the impact of sleep pressure on performance depends on its interaction with circadian phase such that during sleep deprivation, the detrimental effect of high homeostatic sleep pressure is amplified by the maximal circadian sleep promotion in the early morning hours to a greater degree in *PER3*$^{5/5}$ individuals than in *PER3*$^{4/4}$ [63].

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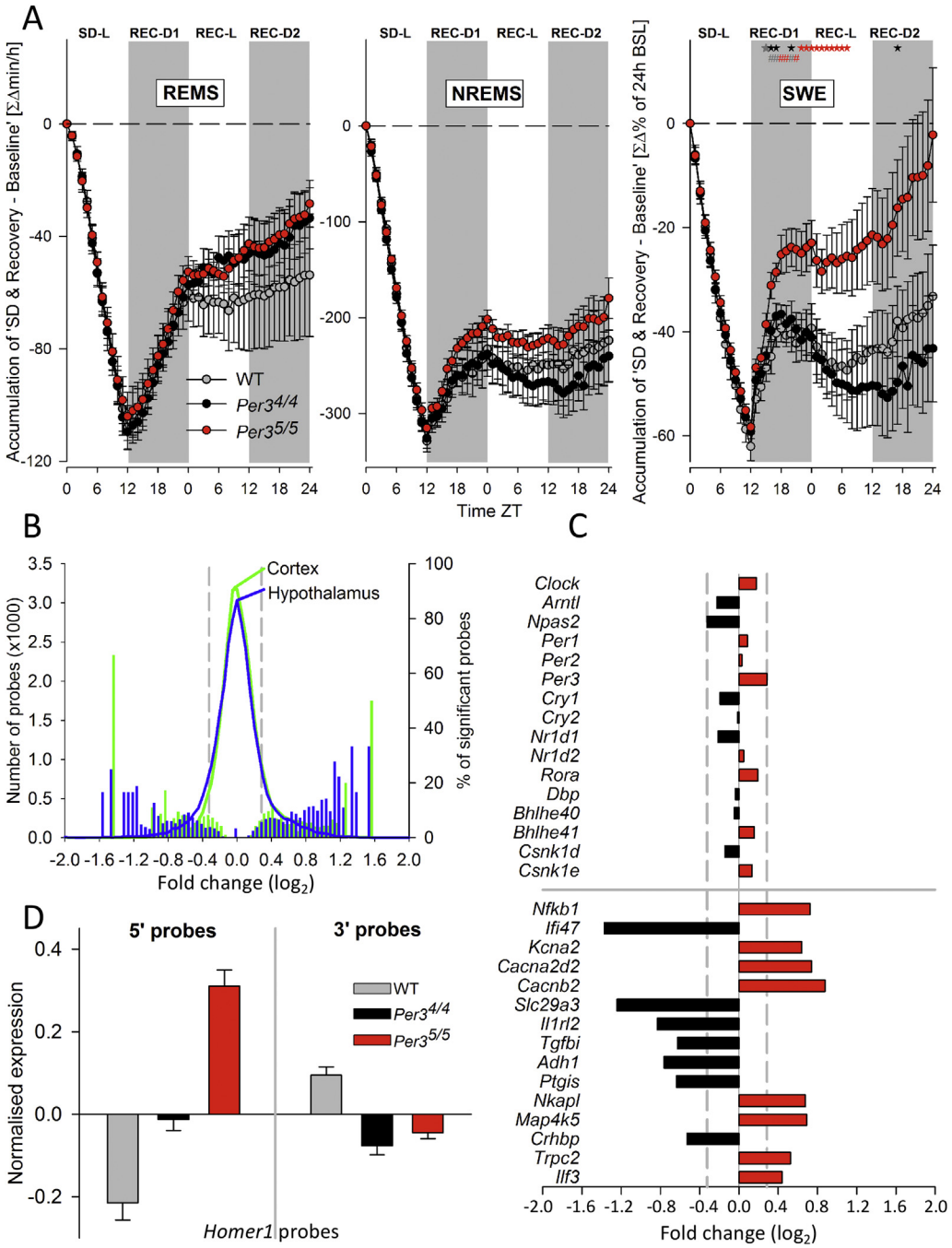

Fig. 5. A) Time courses for accumulated differences in rapid eye movement sleep (REMS) time, non REMS time, and SWE during SD and subsequent 36 h of recovery after SD. Accumulated values (mean ± sem) are relative to baseline (horizontal dashed line) for each genotype. For the SWE comparison, genotype effects are indicated for the hourly intervals (black symbols = *Per3*$^{5/5}$ higher than *Per3*$^{4/4}$; grey symbols = *Per3*$^{5/5}$ higher than WT; red symbols = *Per3*$^{5/5}$ higher than *Per3*$^{4/4}$ and WT; *P < 0.05, #P < 0.01. B) Distribution of normalised change in probe expression levels (log^2 fold change) for all probes differentially expressed between *Per3*$^{5/5}$ and *Per3*$^{4/4}$ mice after SD in cortex (green curve) and hypothalamus (blue curve). The percentage of probes that showed significant differential expression between genotypes is indicated by bars (green = cortex; blue = hypothalamus). C) Up- and down-regulated fold change in the expression of core clock genes (top) and sleep regulation-associated genes (bottom) between *Per3*$^{4/4}$ and *Per3*$^{5/5}$ mice in both tissues (black bars = down-regulated in *Per3*$^{5/5}$ vs. *Per3*$^{4/4}$; red = up-regulated in *Per3*$^{5/5}$ vs. *Per3*$^{4/4}$). Vertical dashed lines (B and C) indicate the maximum fold change for the clock gene transcripts, all non-significant. D) Mean (±sem) normalised expression across both tissues in the 3 genotypes for two probes that target the 5′ UTR (left) and two probes that target the 3′ UTR (right) of *Homer1*. Only the 5′ UTR probes target the *Homer1a* transcript. Figures adapted from Hasan et al., 2014. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). Abbreviations: REMS - rapid eye movement sleep; SWE - slow wave energy; SD - sleep deprivation; WT - wild type.

Dependency on cognitive domain

Genotypic differences in the response to sleep loss were shown to also depend on cognitive domain [71]. Performance on tests with a high load on executive function, such as the 3-back working memory paradigm, deteriorated significantly more for *PER3*$^{5/5}$ participants in the early morning hours. This result was confirmed in a TSD study following a week of either sufficient or insufficient sleep (Fig. 6) [72]. However, a partial sleep restriction study failed to observe genotype-specific effects for cognitive tests that also

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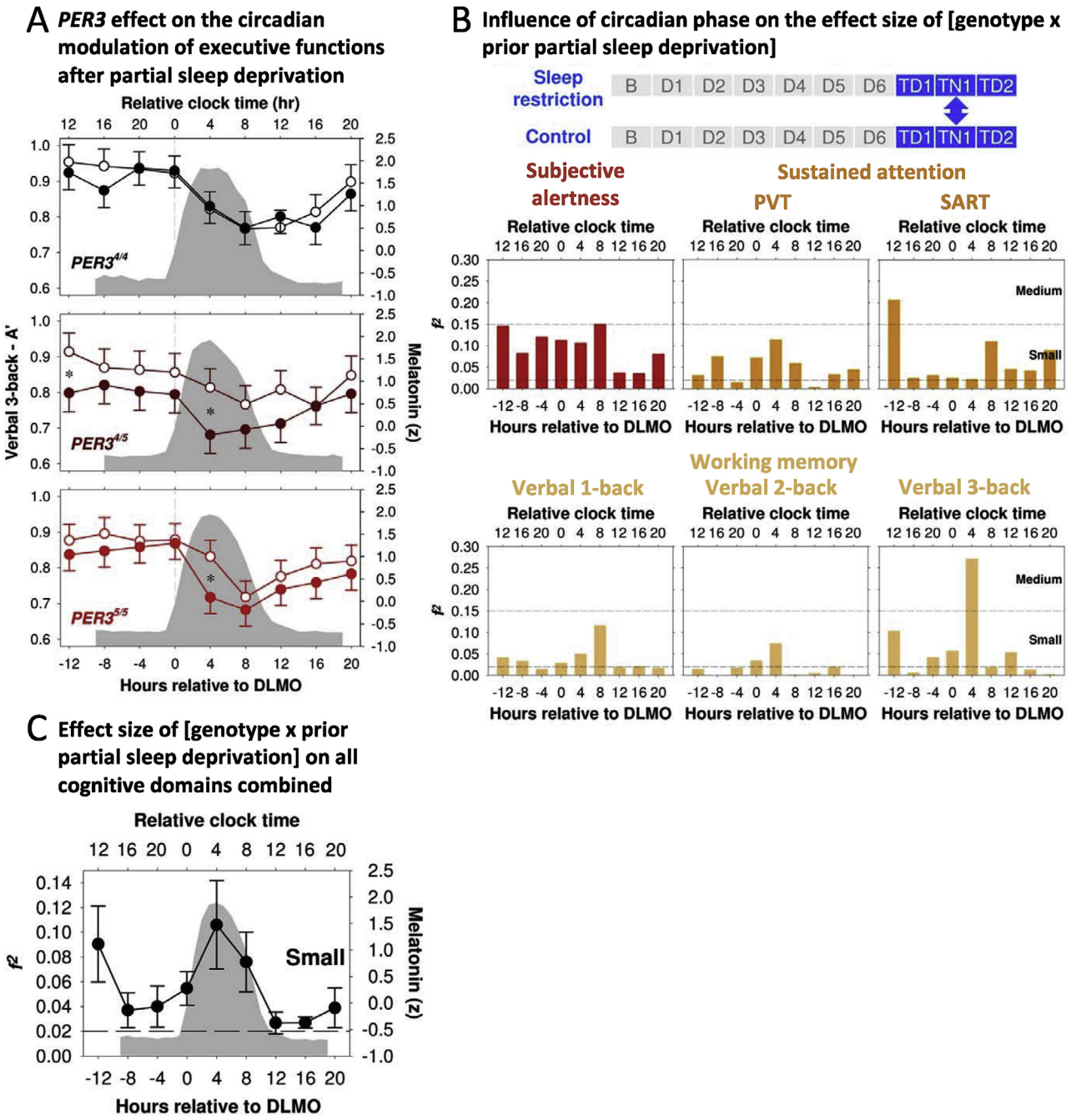

Fig. 6. Effects of *PER3* genotypes on the circadian modulation of performance during total sleep deprivation following partial sleep deprivation. A) Verbal 3-back performance during total sleep deprivation (TSD) in the sleep restriction (filled symbols) and the control conditions (open circles) separately for the three *PER3* genotypes. (DLMO: dashed grey vertical line and melatonin profile averaged between the two conditions shaded in grey). B) Effect sizes for the genotype × sleep history condition interaction during TSD for Subjective Alertness, Sustained Attention, and Working Memory, computed for each 4-h circadian melatonin bin. C) Effect size averaged across the six performance measures. Only small effect sizes are observed (above horizontal line). Error bars represent the between performance measure standard error of the mean. In panels B and C, horizontal lines indicate cut-offs for small and medium effect sizes (reprinted with permission from [72]).

measured executive function [53]. Notably, performance in this study was averaged across the day and was not assessed at the sensitive time-window of the early morning hours. In a study where sleep was restricted to 3 h time in bed for seven nights, individuals with the combined *PER3*$^{4/4}$ and the adenosine receptor *ADORA2AC/T* genotype were more resilient to detrimental effects of sleep restriction on performance in a psychomotor vigilance task (PVT) compared to individuals with the *PER3*$^{4/5}$ and *ADORA2AT/T* genotype [73].

In the past, it was suggested that SD particularly affects executive control processes [74]. However, dissociation studies and meta-analyses do not support this hypothesis and reveal that non-executive task components are more affected by SD than executive ones [72,75,76]. Furthermore, effects of circadian phase on cognition are also at least as large for alertness and attention tasks than for working memory tasks with a high executive load [77]. Importantly, however, this does not exclude the possibility that a trait-like manipulation of sleep homeostatic regulation, as *PER3*

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VNTR genotype effects were mostly observed on executive tasks under conditions of total sleep loss (Fig. 6A), while subjective alertness and vigilant attention were simultaneously shown to be largely affected in both genotypes [72]. The effect size of genotypic effects was, however, lower than the state-induced effects on alertness and sustained attention. Nevertheless, the observed small deficits (Fig. 6B) indicate that the top-down executive control of attention required to engage with a task might be ultimately affected in a trait-like manner by misalignment between circadian and homeostatic processes, notably when sleep deprived during the biological night (Fig. 6C).

PER3 and fMRI studies

In fMRI studies, *PER3* genotype was reported to affect cortical and subcortical brain activations during the performance of a 3-back task in the morning after TSD [78]. *PER3*$^{5/5}$ carriers presented widespread reductions in task-related cortical activations in the morning following sleep loss. This occurred after these participants already presented a reduced prefrontal activation in the evening before [78]. By contrast, *PER3*$^{4/4}$ participants showed only increased activations following sleep loss. These activations were present notably in the prefrontal cortex and depended on the input received from the thalamus (increased functional connectivity between thalamus and prefrontal area). This supports the notion that these brain areas play a central role in executive control during prolonged wakefulness [70,78,79]. Task duration was kept short such that the disparity in brain responses during sleep loss was detected in the absence of significant behavioural changes that could bias neuroimaging results. They are therefore likely to precede the previously reported difference in performance to the same task when it was included in a more demanding and extensive test battery [62,71].

Effects of PER3 in sleep deprivation versus ultra-short sleep–wake cycle protocols

In contrast to executive function, several studies failed to find an impact of *PER3* genetic variants on vigilant attention (PVT) following TSD [72], partial sleep restriction [53], and partial sleep restriction with subsequent TSD [72]. Yet, when combining a 40-h TSD and an ultrashort sleep–wake cycle (nap) protocol as a manipulation of sleep pressure, *PER3*$^{5/5}$ carriers produced significantly more lapses than *PER3*$^{4/4}$ participants under sleep loss, when compared to the multiple nap condition [80]. The approach applied by Maire et al. is effective in isolating homeostatic state effects, since it allows a comparison of rising (sleep deprivation) versus low (multiple naps) homeostatic levels while controlling for circadian phase. Similarly, *PER3*$^{5/5}$ carriers had more difficulties to maintain stable attentional performance over the 10-min PVT than *PER3*$^{4/4}$ carriers during night-time under high sleep pressure conditions [81]. These data suggest that *PER3*$^{5/5}$ individuals are more prone to momentary task disengagement during wakefulness when sleep need is high and particularly so during the biological night. In accordance with this hypothesis, Maire et al. observed that, during night-time, thalamic activity progressively diminished with time-on-task in *PER3*$^{5/5}$ individuals, which were also more susceptible to activate structures associated with the default mode network during disengagement [82]. Maire et al. also revealed that *PER3*$^{5/5}$ individuals produced significantly more slow eye movements and unintentional sleep episodes under SD than the *PER3*$^{4/4}$ individuals, especially during the biological night and in the beginning of the second biological day [80]. Furthermore, already in the first SD study [62], *PER3*$^{5/5}$ had higher levels of EEG theta activity, which is considered a marker of sleepiness, correlates negatively with task performance and may be a sign of disengagement.

PER3 and age-related changes in cognition and brain structure

Finally, a recent study assessed the effects of the PER3 VNTR polymorphism on age-related changes in cognition, brain structure and metabolism [83]. It was observed that reduced cognitive performance (semantic memory, cognitive interference and verbal fluency) in older *PER3*$^{5/5}$ carriers co-occurred with reduced structural and functional integrity at the cortical level and also with reductions of glucose consumption in fronto-temporo-parietal regions. Amongst others, reduced cortical thickness entailed the entorhinal cortex and lower relative metabolism was detected in the middle temporal lobe [83], both regions being of key relevance for cognitive ageing and associated declines in memory function [84].

Human behaviours are thus endangered by sleep loss, depending on when it occurs over the 24-h cycle, which cognitive component is assessed, but also the genetic background of the individual (see Fig. 7A for schematic overview). The brain mechanisms underlying differential vulnerability to sleep state manipulation remain to be further explored, but may involve thalamic and frontal cortex responsiveness (Fig. 7B). A recent study revealed that both thalamic and cortical responses underlying vigilant attention exhibit circadian rhythmicity [85]. The manifestation of the interaction between sleep need and circadian phase was, however, brain region and task specific. One could speculate then that inter-individual variability in response to sleep loss would reside in trait-like differences in brain local rhythmicity rather than in the ability or inability to recruit a given brain process.

Genetic variation in PER3 modulates the impact of light

Exposure to light is the main synchroniser of human circadian rhythms [70]. In humans, light also conveys a stimulating signal that acutely increases alertness, improves some aspects of cognitive performance, and modulates cognitive brain responses during wakefulness and affects subsequent sleep intensity [70]. Animal and human experiments have shown that these effects are most likely mediated through a pathway involving intrinsically photosensitive retinal ganglion cells (ipRGC) expressing the blue-light-sensitive melanopsin photopigment, in addition to input from rods and cones [86].

PER3, light and sleep/performance

The PER3 VNTR has been used to investigate inter-individual differences in effects of light on cognition and physiology. Suppression of melatonin and reductions in subjective and objective EEG measures of sleepiness in response to 2 h of evening exposure to blue-enriched light were more pronounced in *PER3*$^{5/5}$ vs. *PER3*$^{4/4}$ individuals [15]. Intensity of subsequent sleep, as indexed through EEG SWA, was also reduced over the occipital derivations in *PER3*$^{5/5}$, but not in *PER3*$^{4/4}$ carriers [15]. This reduction in the visual occipital cortex could putatively represent a use-dependent effect as *PER3*$^{5/5}$ also perceived blue-enriched light as brighter than *PER3*$^{4/4}$ [15]. All these data suggest that the *PER3*$^{5/5}$ genotype confers increased light sensitivity in humans. In animal studies, a reduced masking effect of light was observed in PER3-deficient mice during the rest phase (light) but not the active phase (dark) of the circadian cycle [14,87].

PER3 VNTR, light and fMRI studies

A neuroimaging study revealed that brain responses to an auditory working memory task increased in response to short (1 min) exposure to blue light in the morning hours following a

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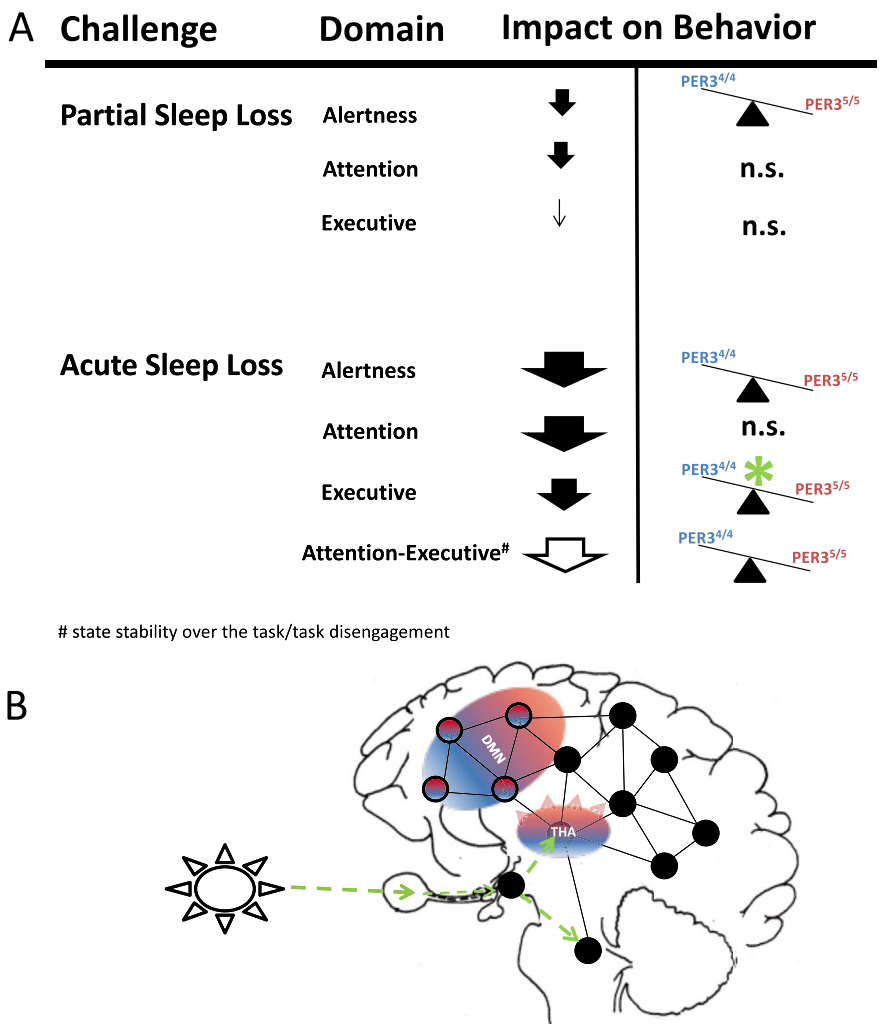

Fig. 7. Putative scenario of the impact of sleep–wake manipulation and the PER3 VNTR polymorphism on human cognition. A) Impact of sleep homeostatic challenge (partial vs. acute sleep loss) according to cognitive domain (subjectively assessed alertness, vigilant attention as assessed by a psychomotor vigilance task and executive function as assessed by the N-back paradigm). Independent of genotype the impact of sleep loss on behaviour is most pronounced for alertness and vigilant attention. Black bars schematically represent effect sizes as reported in Lo et al. (2012). The PER3 polymorphism modulates subjective alertness under partial sleep loss and alertness and executive function during acute sleep loss (balances on the right side; n.s. = not significantly different between the genotypes in the study that tested the hypothesis). State instability as assessed by momentary task disengagement or time-on-task might reflect executive control in attentional tasks (attention-executive) and thereby represent a potential tool to explore both state and trait effects on performance (Maire et al., 2014 [80], 2015 [82]). Finally, light has been shown to modulate the genotype-dependent impact on executive brain function following acute sleep loss (green star; Vandewalle et al., 2011). B) The PER3 VNTR polymorphism affects task-related activation in thalamic, prefontal as well as in midline regions encompassing the default mode network (DMN). Under sleep loss, *PER3*$^{5/5}$ individuals show decreased prefrontal and thalamic activity during task engagement (Vandewalle et al., 2009 [78]) and activity increases in key regions of the default mode network during momentary task disengagement (Maire et al., 2015). By contrast, *PER3*$^{4/4}$ show increased thalamic and prefrontal activation following acute sleep loss. The thalamus (THA) seems to play a central role in mediating the impact of high sleep pressure on cognition, particularly via its connections with the prefrontal cortex (blue-red dots). Light can impact on the cortical circuitry underlying task performance, putatively via subcortical and thalamic connexions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

night without sleep in *PER3*$^{5/5}$, as compared to *PER3*$^{4/4}$ individuals [16]. This implies that the *PER3*$^{5/5}$ individuals who were previously shown to present widespread decreased brain activation while performing the same working memory task [78], benefit more from light exposure. In the morning hours following a normal night of sleep, an impact of blue light on cognitive brain responses was detected in *PER3*$^{4/4}$ individuals and not in *PER3*$^{5/5}$ [16]. Task and light exposure durations were again kept short, so distinct light-dependent brain responses were observed without concomitant significant performance differences. The *PER3* genotype-dependent brain responses under blue light exposure are presumably occurring prior to emerging behavioural differences, but this remains to be formally tested.

This genotype-dependent impact of light on cognitive brain activity may reside in the differential association of *PER3* genotype with diurnal preference [35] with light benefiting relatively more those who are more inclined to be evening types (i.e., the *PER3*$^{4/4}$). No impact of light on cognitive brain responses was detected in the evening hours, close to melatonin secretion onset, in either genotype [16]. This may appear contradictory with the fact that evening light can suppress melatonin and affect sleepiness in the evening, particularly so in *PER3*$^{5/5}$ [15]. However, as compared to *PER3*$^{4/4}$, *PER3*$^{5/5}$ individuals could still be more influenced by a 2 h exposure to blue-enriched light [15], while neither genotype showed a significant impact of 1 min blue light exposures [16]. Likewise, both genotypes may be less affected by light in the evening as compared to other circadian times both using 1 min [16] or 2 h exposures, but such longer exposure durations have not yet been tested at different circadian phases. We infer that, around the evening wake maintenance zone, alertness is already most affected by the

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endogenous circadian drive for wakefulness [70], such that an external stimulant such as light would be less potent. Overall, the acute impact of light on cognition and physiology seems to depend on sleep need, circadian phase and *PER3* VNTR genotype.

PER3 and light-dependent phenotypes in mice and humans

Per3 KO mice show normal entrainment to the light–dark cycle as well as normal phase delays or advances to a single pulse of light [14]. A slower re-entrainment to a shifted light–dark cycle [14] and to abrupt changes in photoperiod [87] were reported in *Per3* KO mice. Decrease in circadian period lengthening under constant light conditions, as well as poor entrainment to a 3.5 h–3.5 h ultradian light–dark cycle were also reported in *Per3* KO mice [14]. Animal data suggest therefore that the long-term impact of light on circadian rhythmicity seems to be *Per3* genotype-dependent, likely through a decreased sensitivity to light in the absence of the *Per3* gene. The long-term circadian impact of light has not yet been considered in humans with respect to PER3 VNTR. Given that the genotype influences melatonin suppression by light [15] and that the impact of light on circadian phase is influenced by sleep need [88], it is likely that the human PER3 VNTR also affects the way light entrains and/or phase shifts circadian rhythmicity. Because PER3 is expressed in light-sensitive tissues (cf. above), its polymorphisms could affect light sensitivity *per se*, but could also determine how much benefit light can bring with respect to current sleep need and circadian phase status. Whether and how the genotype-dependent light effects may relate to the association of *PER3* VNTR genotype with diurnal preference remains to be established.

Further evidence for a role of PER3 in determining the response to light stems from two rare human missense variants in PER3 (P415A, rs150812083; H417R, rs139315125) which have been associated with ASPD [89]. The variants destabilise PER3 and reduce its ability to stabilise PER1 and PER2, leading to reduced repression of CLOCK/BMAL1-driven *Per2* expression (Fig. 1) [89]. When the combined variants were expressed in mice, onset of locomotor activity was delayed on a 4:20 h light:dark cycle, and a longer circadian period in constant light conditions was observed [89]. Although this is in contrast to the shorter period seen in *Per3* KO mice under the same conditions [14], both studies point toward altered light-sensing phenotypes in these different *Per3* models. Thus, although the PER3 VNTR was initially thought to not significantly affect circadian parameters, these data suggest that PER3 variants may interact with the light environment to create circadian phenotypes, including sleep timing phenotypes. Indeed, the $PER3^{5/5}$ genotype was reported to be associated with an advanced melatonin phase in older volunteers [64].

PER3 and mental disorders and their symptoms

In this section, we will discuss papers that have investigated associations between PER3 and mental disorders, or symptoms indicative of mental disorders. Many of the data were collected prior to the publication of the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V; 2013), and therefore use the term ‘mood disorder’, even though in DSM-V mood disorders are separated into ‘depressive and related disorders’ and ‘bipolar and related disorders’. Wherever possible we have adopted the DSM-V terminology.

Circadian alterations are thought to contribute to depressive disorders such as seasonal affective disorder (SAD) as well as other mental disorders [90]. This may explain why genetic variation in *PER3* is associated with depressive disorders and symptoms [91,51,92], schizophrenia [93] and bipolar disorder [92–97].

Depressive and bipolar disorders, and schizophrenia

Three intronic *PER3* SNPs (rs12137927, rs228644, rs228682) have been associated with decreased reporting of depressive symptoms in older male and female adults [91]. A synonymous (rs17031614) and a missense (rs228697) SNP were associated with major depressive disorder in males and females, with the DSPD-associated rs228697 also being significant in a female-only subset [51]. A *PER3* SNP (rs2859387) was associated with bipolar disorder and schizophrenia [93], while a haplotype of 5 SNPs (4 intronic, rs228729, rs228642, rs228666, rs2859388; 1 non-synonymous, rs228697) and the exon 18 VNTR showed suggestive links with bipolar disorder [95]. Epistatic interaction effects have been found between a *PER3* SNP (rs2172563) and two *BMAL1* SNPs in bipolar disorder, and also between a *PER3* SNP (rs836755) and difficulties to fall asleep in those patients [92]. The $PER3^{5/5}$ genotype has been associated with bipolar disorder [96] and earlier onset age for the disease [94], as well as a poorer response to antidepressant treatment after SD and an increased sleep duration during recovery after treatment and SD [97].

PER3, light and depressive disorders

The familial cases of ASPD associated with two rare *PER3* SNPs (rs150812083, rs139315125), which also led to circadian phenotypes in mouse models, were also suffering from SAD and mild to moderate depression [89]. Furthermore, *Per3* KO mice show alteration in the responses to repeated exposure to dim light at night (dLAN) i.e., extension of low light levels into the biological night [98]. dLAN exposure is increasingly common and is thought to induce a depressive like state through alteration of circadian rhythmicity in humans [99]. While *Per3* KO mice undergo the typical alterations in cortisol secretion and brain derived neurotrophic factor (BDNF) gene expression over the course of the first few weeks of exposure, they show transient abnormal alteration in mood and activity onset/offset during the first weeks of dLAN. This transient phenomenon may not be causally related to the longer term dLAN-induced mood alteration, but may be one of the determining factors for the reported link between PER3 polymorphisms and depression prevalence in humans.

PER3, bipolar disorders and brain structure

Diffusion tensor imaging studies have been used to measure mean diffusivity (MD), radial diffusivity (RD) and fractional anisotropy (FA) in white matter (WM) fibres and tracts, and these measures relate to myelination and axon structure. The technique was used to study WM in bipolar disorder patients genotyped for clock gene polymorphisms [100]. The study found that $PER3^{4/4}$ had increased RD and reduced FA in WM tracts compared to $PER3^{5/5}$ and indicates that *PER3* genotype may influence brain axon myelination [100], which potentially could be related to reported differences in sleep EEG power spectra.

PER3, addiction and anxiety symptoms

The *PER3* VNTR 4-repeat allele has been linked with heroin dependence in a Chinese population [101], and $PER3^{4/4}$ homozygotes have been reported to suffer more severe insomnia in alcohol-dependent patients compared with controls [102]. A study in mice has shown that polymorphisms in *Per3* and expression levels of *Per3* are associated with differences in expression of genes related to schizophrenia, and to alcohol and stress responses [103]. *Per3* expression levels correlated with anxiety and addiction phenotypes, and alcohol treatment increased expression levels of *Per3*

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in the hippocampus [103]. Polymorphisms within *PER3* have also been linked with anxiety in humans. Liberman et al. showed that the carriers of the rs228697 G allele and the VNTR 4-repeat allele had higher levels of anxiety and that evening types, which associated with both alleles, were more anxious than morning types [44]. The *PER3* VNTR has also been shown to interact with sleep duration for an association with anxiety in women such that $PER3^{4/4}$ individuals with short sleep duration were at greater risk of anxiety and mood disturbance [104].

PER3 and cancer

The cell cycle controls cell division and proliferation. Uncontrolled cell proliferation can lead to cancer. The cell cycle is regulated by the interaction of cyclins with cyclin-dependent kinases and phosphatases and these complexes act as checkpoints for different steps of the cycle. The circadian clock and the cell cycle are coupled such that the expression and post-translational modification of many elements at different points in the cell cycle are regulated by the molecular clock. The circadian transcription factor heterodimer CLOCK/BMAL1 activates expression of the kinase WEE1, which gates transition from growth phase 2 to mitosis. CLOCK/BMAL1 inhibits the expression of MYC, which gates transitions from quiescent stage to growth phase and then to DNA replication. Because of this tight coupling, it is possible that disruption to circadian rhythms could impact on the development and progression of cancer, and that circadian rhythms could become disrupted during cancer (for review, see [105]).

PER3 expression in cancer

Expression levels of PER3 are altered in a range of cancers. In colorectal cancer, the expression of the negative regulators PER1 and PER3 have been found to be down-regulated, while expression of the positive regulators CLOCK and BMAL1 was up-regulated [106]. Decreased expression of PER2 and PER3 was linked with more aggressive colorectal tumours and worse prognosis [107]. Overexpression of PER3 was found to reduce chemoresistance and tumour renewal ability in colorectal cancer cells [108]. PER3 expression levels were also reduced in colon cancer compared with normal tissue, and patients with PER3-negative tumours had reduced survival times [109]. In addition, PER3 was found to be downregulated in colorectal cancer while miR-103, which is increased in many cancers, was upregulated in the same cells and shown to suppress PER3 expression [110]. By contrast, overexpression of PER3 repressed tumour proliferation and invasion via regulation of cell cycle genes. Likewise, the expression of PER3 was downregulated in acute lymphoid leukaemia and recovery of PER3 expression was associated with better clinical outcome [111]. In squamous cell carcinoma, downregulated PER3 expression correlated with more advanced cancer stages and larger, more invasive tumours [112]. Similarly, PER3 expression was reduced in non-small cell lung cancer and reduced expression was associated with shorter survival times [113]. Finally, higher expression levels of PER3 were found to correlate with increased metastasis-free survival times and improved prognosis in patients with breast cancer [114]. Together, these data show that down-regulation of PER3 is associated with poor cancer outcomes, while overexpression of PER3 contributes favourable outcomes.

Polymorphisms within PER3 can potentially affect its expression levels and function. Therefore, it should be expected that PER3 polymorphisms are associated with cancer phenotypes and outcomes. An intronic SNP (rs1012477) in *PER3* was associated with reduced risk of aggressiveness in prostate cancer [115] and also a reduced risk of breast cancer in women performing three consecutive nights of shift work [116]. Another intronic *PER3* SNP (rs228729), which was also linked with bipolar disorder, has been identified as a risk factor for non-small cell lung cancer [117] and was associated with overall survival rates in gastric cancer [118] and hepatocellular carcinoma patients, where the SNP also predicted recurrence-free survival [119]. The latter study also showed an association between two additional SNPs (rs2640908, rs228669) with overall survival rates for the cancer. The *PER3* coding-region missense SNP V647G (rs10462020) that was associated with DSPD and hypothesised to affect phosphorylation of PER3 by CK1 [32], was associated with increased overall survival in large B-cell lymphoma [120]. The 5-repeat allele of the *PER3* VNTR polymorphism (rs57875989) was associated with increased incidence of colorectal adenoma formation [121].

PER3 alterations in cancer: cause or consequence?

Circadian disruption could be a consequence of cancer but could also be a contributory factor in cancer development, potentially through DNA methylation. The circadian transcriptome of core clock genes and clock-controlled genes is regulated by rhythmic epigenetic chromatin modifications via histone acetylation and methylation, and the methylation of DNA in promoter regions [122]. Disruption to the balance of this epigenetic landscape could lead to disturbances in the rhythm of the circadian transcriptome. A genome-wide study of DNA methylation in lymphocytes found reduced levels of methylation in nightshift workers compared to dayworkers [123]. Twenty-one hyopmethylated loci were identified in clock genes in the night-shift workers, with the three largest differences found in the gene body of *PER3*. Gene body hypomethylation can lead to lower expression levels and reduced expression of *PER3* was found in lymphocytes of rotating nightshift nurses [124]. Hypomethylation of the *PER3* promoter was also more frequent among patients with colorectal adenomas [125]. In hepatocellular carcinomas (HCCs), a genome-wide profiling study of promoter methylation identified hypermethylation of *PER3* in the HCCs compared to controls together with reduced expression levels of *PER3* [126]. Gene promoter hypermethylation is associated with gene silencing and the study showed that treatment designed to inhibit methylation restored *PER3* expression in the HCCs. These data point toward an additional epigenetic modulation of PER3 expression that could contribute to cancer.

Practice points

Per3 is one of the most robustly rhythmic genes in a wide range of tissues in animals and also in tissues investigated in humans.

Outside of the SCN, PER3 plays a significant role in determining circadian period and phase.

Polymorphisms within *PER3* (especially the primate-specific VNTR) have been associated with diurnal preference, sleep homeostasis, cognition, light sensitivity, axonal structure, CRSWDs, mental health disorders, and cancer.

In addition, although not covered here, there are very recent data suggesting that PER3 may also have a role to play in metabolic functions with links to obesity (e.g., [127]).

PER3 genotype can therefore act as a predictive biomarker for a wide range of phenotypes and disease conditions.

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Research agenda

Although *PER3* is often not considered a core clock gene, it is one of the most robustly rhythmic genes. Variants of *PER3* have been investigated extensively and linked to a wide variety of phenotypes. The latter may in part be due to early positive findings which then led to an 'over-investigation' of *PER3* in candidate gene approaches. Alternatively, PER3 may play an important role in driving temporal organisation, in particular in non-SCN tissues.

For many of the reported associations it should be kept in mind that sample sizes were often relatively small, and failures to replicate may not have been reported. It is reassuring that GWAS studies have identified associations between *PER3* variants and some phenotypes, but more and larger studies are needed. It should also be noted that more progress needs to be made in understanding the underlying molecular mechanisms and translating these to clinical applications.

Phenotyping could also be more comprehensive and include diverse sleep–wake protocols, including not only sleep restriction and sleep deprivation under constant routine conditions and iterative napping, but also using sleep extension, daytime napping, ad libitum sleep and changes in the phase angle between sleep and circadian rhythmicity (i.e., as in jet-lag, shift work). *PER3* genotype-dependent light sensitivity should also be characterised by means of irradiance response curves to light and different monochromatic and polychromatic light spectra.

Some of the phenotypes associated with *PER3* variants may be interrelated through a common mechanism. For example, associations with diurnal preference, depression and seasonal affective disorders may all be mediated by effects of PER3 on light sensing and transduction processes and their rhythmic modulation. Likewise, effects on cognition, sleep EEG, and response to sleep loss may be mediated by effects on neuroanatomy or sleep–wake dependent changes in neural networks in conjunction with circadian modulation of these networks. The associations between PER3 variants and cancer may simply point to a general role for PER3 in peripheral circadian organisation, which in turn could interact with the cancer processes. For none of the phenotypes associated with PER3 variants have molecular mechanisms mediating the associations been identified, although the effects of the PER3 VNTR knock in on sleep homeostasis and activity related genes in mice may be considered a first step. Research aimed at a better understanding of molecular mechanisms is warranted.

The PER3 VNTR polymorphism might contribute to shape the cognitive ageing trajectory of an individual, through its action on major sleep–wake regulatory processes, but further evidence including longitudinal studies on larger cohorts is needed.

Comprehensive phenotyping, including simultaneous assessments of EEG, sleep and cognition, as well as functional and structural imaging of variants of other clock genes may provide new insights into the widespread effects of circadian processes in health and disease.

Conflict of interest

The authors report no conflicts of interest with respect to the content of this review.

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* The most important references are denoted by an asterisk.

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