

Sleep Deprivation and Gene Expression

Annie da Costa Souza and Sidarta Ribeiro

Abstract Sleep occurs in a wide range of animal species as a vital process for the maintenance of homeostasis, metabolic restoration, physiological regulation, and adaptive cognitive functions in the central nervous system. Long-term perturbations induced by the lack of sleep are mostly mediated by changes at the level of transcription and translation. This chapter reviews studies in humans, rodents, and flies to address the various ways by which sleep deprivation affects gene expression in the nervous system, with a focus on genes related to neuronal plasticity, brain function, and cognition. However, the effects of sleep deprivation on gene expression and the functional consequences of sleep loss are clearly not restricted to the cognitive domain but may include increased inflammation, expression of stress-related genes, general impairment of protein translation, metabolic imbalance, and thermal deregulation.

Keywords Sleep • Gene expression • Immediate early genes • Cognition • Memory • Inflammation • Stress • Thermoregulation

Contents

1	Introduction
2	Approaches to Study Effects of Sleep Deprivation on Gene Expression
2.1	Methods of Sleep Deprivation
2.2	Methods for the Assessment of Gene Expression and Protein Levels
3	Sleep Deprivation and Gene Expression
4	Sleep Deprivation and Early Changes in Gene Expression
4.1	c-fos
4.2	Zif-268
4.3	Arc
4.4	Homer
4.5	Nr4a

A. da Costa Souza · S. Ribeiro (✉)
Instituto do Cérebro, Universidade Federal do Rio Grande do Norte (UFRN),
Av. Nascimento de Castro 2155, Natal-RN, Brazil
e-mail: sidartaribeiro@neuro.ufrn.br

Curr Topics Behav Neurosci
DOI: 10.1007/7854_2014_360
© Springer-Verlag Berlin Heidelberg 2015



5	Sleep Deprivation and Neurotrophic Factors
6	Sleep Deprivation Changes Expression of Genes Related to Protein Synthesis
7	Changes in Serum Protein Levels After Sleep Deprivation may Indirectly Reflect Changes in Gene Expression.....
8	Sleep Deprivation and Genes Related to Cellular Stress Responses
9	Sleep Deprivation, Gene Expression, and Cognition
10	Conclusion
	References

1 Introduction

Sleep is a complex behavioral state of major importance for vertebrates (Frank 2012) and invertebrates (van Swinderen 2007; Ramon et al. 2012), which directly or indirectly affects a plurality of physiological functions (Shaw et al. 2000; Markwald et al. 2013; Kayser et al. 2014). While moderate sleep disturbance leads to stress and homeostatic imbalance (Killick et al. 2012; Pellegrino et al. 2012; Moller-Levet et al. 2013; Gonnissen et al. 2013), controlled laboratory studies in rodents have shown that prolonged sleep deprivation causes serious physiological and immunological deficits, eventually causing death (Rechtschaffen et al. 1983; Bergmann et al. 1989a; Everson et al. 1994).

Since sleep-dependent gene regulation produces long-term changes in behavior and physiology, it is important from a clinical point of view to understand how sleep deprivation affects health through the expression of specific genes (Tononi et al. 1994; Ledoux et al. 1996; Cirelli and Tononi 2000b; Tononi and Cirelli 2001; Cirelli 2002; Terao et al. 2003, 2006; Nelson et al. 2004; Cirelli et al. 2005; Maret et al. 2007; Jones et al. 2008; Thompson et al. 2010; Nitabach et al. 2011). Conversely, the investigation of sleep-dependent gene regulation has overarching implications for basic research on the mechanisms underlying cognition, neurogenesis, thermal balance, inflammation, metabolic turnover, and several other processes (Smith and Kelly 1988; Everson 1995; Taishi et al. 2001; Guzman-Marin et al. 2003, 2005, 2006; Knutson et al. 2007; Guess et al. 2009; Mullington et al. 2009; Tufik et al. 2009; van Leeuwen et al. 2009; Calegare et al. 2010; Aldabal and Bahammam 2011; Barf et al. 2012; Aydin et al. 2013). In this chapter, we review studies concerned with how sleep deprivation affects gene expression, with a focus on genes involved in neuronal plasticity, brain function and cognition.

It is important to note that several of the studies reviewed here have assessed protein levels rather than changes in gene expression per se. The transcription of mRNA from DNA and the translation of protein from mRNA are subjected to complex regulation by a variety of mechanisms (Filipowicz et al. 2008; Maas 2010; McManus and Graveley 2011). Since mRNA and protein levels related to the same gene are often separately regulated (Vogel and Marcotte 2012), protein measurements are not necessarily good indicators of gene expression. On the other hand, changes in protein levels are more indicative of an effective genomic response than

changes in the amount of mRNA transcripts. For these reasons, we opted to review the literature more broadly, while making explicit for each study reviewed whether gene expression and/or protein levels were assessed.

2 Approaches to Study Effects of Sleep Deprivation on Gene Expression

2.1 Methods of Sleep Deprivation

To study the role of sleep and the effects of sleep loss on gene expression, a wide variety of methods has been employed to deprive animals of their sleep for variable durations. While each of these methods is aimed at keeping animals awake, there are method-specific effects that need to be considered when discussing the resulting changes in gene expression, because of different impacts on specific sleep states, and different side effects.

2.1.1 Flowerpot Method (or Disk-over-water)

The flowerpot method, basis of a modified (automatized) version called disk-over-water method, was first proposed by Michel Jouvet as a reliable way to systematically deprive animals from sleep (Jouvet et al. 1964; Kushida et al. 1989; Rechtschaffen and Bergmann 1995). The method consists in putting the animal on a small platform, typically a disk, within a tank of water. In the flowerpot method, the animal has to maintain wakefulness in order to stay on top of the disk, because upon entering sleep there is a loss of muscle tone and the animal falls in the water, interrupting sleep. Specific deprivation of rapid-eye-movement sleep (REM) can be achieved by slightly increasing the area of the circular platform [in rats, from 6.5 cm of diameter (Mendelson et al. 1974) to 11 cm of diameter (Kushida et al. 1989; Youngblood et al. 1997)], thus allowing animals to traverse slow-wave sleep (SWS)—in which there is residual muscle tone (Jouvet 1967)—but not REM (Jouvet et al. 1964; Mendelson et al. 1974; Jouvet 1994). The use of larger platforms that allow for sleep serves to generate negative controls (Youngblood et al. 1997). In the disk-over-water method, early signs of sleep trigger a slow rotation of the disk, carrying the animal to a pool of water; animals learn to wake up and move away from the water, thus interrupting sleep. This method can be used for specific REM sleep deprivation or for total sleep deprivation (Bergmann et al. 1989a, b; National Research Council of the National Academies 2003). These methods are highly efficient for unsupervised sleep deprivation, but are associated with various confounding factors and high levels of stress, associated with restricted movement and the risk of falling in the water surrounding the platform. Mice are less impacted by movement restrictions in the flowerpot method because they can use the metal grids on cage tops to move around (Bergmann et al. 1989b; National Research Council of the National Academies 2003). In rats,

which typically cannot perform this behavior, several platforms are used to mitigate the stress associated with movement restriction (Alkadhi et al. 2013).

2.1.2 Treadmills and Rotating Wheels

Another common procedure to keep animals awake is the use of motorized treadmills or wheels (Guzman-Marin et al. 2005, 2006; Roman et al. 2005; Xu et al. 2010). This approach is thought to be less stressful than the flowerpot method, but the continuous forced activity, even though it is generally at a rather slow pace, may have effects unrelated to sleep loss per se. A commonly used control procedure is to have animals that walk at a faster pace for shorter periods of time, allowing them sufficient sleep (Guzman-Marin et al. 2005, 2006; Roman et al. 2005).

2.1.3 Cage Tapping and Gentle Handling

A supervised method for sleep deprivation commonly used in rodents consists of tapping the experimental cage or gently handling the animal as soon as a specific sleep state is detected (Rechtschaffen et al. 1999). This method is considered to be one of the least stressful ways of sleep deprivation, partly because animals most often remain in their home cage, and several studies have reported only minimal increases in stress hormones such as glucocorticoids (van der Borght et al. 2006; Hagewoud et al. 2010a, b, c). However, a clear disadvantage is that this method requires constant human supervision and is therefore generally used only for short sleep deprivations (Rechtschaffen et al. 1999).

2.1.4 Novel Object Presentation

This method typically consists of introducing novel objects in the experimental cage and is based on the natural tendency of rodents to explore the environment, particularly when it contains novel stimuli (Henderson 1970; Ennaceur and Delacour 1988). The disturbance caused by introducing novel objects in the cage typically induces wakefulness, as the animal is prone to spontaneously explore the objects. When an object is no longer novel, and the animal becomes drowsy, another object is introduced in the cage (Cirelli and Tononi 2000b). The main advantage of this method is that sleep is prevented due to an endogenous drive to explore a novel environment, rather than an external perturbation of the animal itself. On the other hand, well-balanced controls are nearly impossible to achieve, due to the intrinsic variability of the behavioral responses to novel object exposure (Thor et al. 1988; Dellu et al. 1996; Bevins et al. 1997; Kabbaj and Akil 2001; Pisula and Siegel 2005; Clinton et al. 2010; Duclot et al. 2011). Moreover, one caveat that must be taken into account is the fact that gene expression following a period of sleep deprivation by exposure to novel objects will confound the effects of novel object exploration with the effects of sleep loss per se.

2.1.5 Automated deprivation based on the computer analysis of neural and muscle signals

Sleep deprivation can be improved by the use of a feedback computer system for triggering cage movements depending on pre-established thresholds of neural and muscular activity (Ocampo-Garcés et al. 2000; Vivaldi et al. 2008; Wu et al. 2011). In addition to the visual inspection of behavior, electrophysiological signals such as intracerebral local field potentials (LFPs) or cortical electroencephalogram (EEG) can be used to inform the experimenter about when to interfere with the animal. For instance, once the animal begins to sleep, the EEG is characterized by waves with higher amplitude and lower frequencies in comparison with the waking state; this slow-wave activity within the delta range (<4 Hz) is characteristic of SWS. In the case of REM sleep, the presence of hippocampal theta rhythm (4–10 Hz) is one of the most reliable electrophysiological signals (Franken et al. 1991). The method is suitable for the use of yoked controls, i.e., animals recorded in parallel in which the perturbations occur at approximately the same times, but uncoupled from the wake–sleep states. Computer software can identify either SWS or REM and then prompt a mechanical perturbation of the animal, typically a sudden movement of the entire cage or recording box. Such automatic supervision is very precise and reliable, allowing for the use of yoked controls as explained above, but improved with the precise and instantaneous perturbations of both experimental and control animals (Rechtschaffen et al. 1999). The main disadvantage of the method is the more expensive and sophisticated setup.

2.2 Methods for the Assessment of Gene Expression and Protein Levels

2.2.1 In Situ Hybridization

This technique uses a complementary DNA or RNA strand to detect a certain sequence of mRNA or DNA in the tissue, which for instance may be an entire brain section. Labeling can be radioactive or antigen based, using fluorophores or chromophores (Gall and Pardue 1969; Jin and Lloyd 1997). The method is suitable for determining cell-specific and region-specific changes in gene expression directly on brain sections.

2.2.2 Reverse Transcriptase Quantitative Polymerase Chain Reaction (RT-qPCR)

One important variation of classical polymerase chain reaction (PCR) is quantitative PCR (qPCR), which precisely quantifies DNA sequences (Bustin et al. 2005). A second very important variation broadly used for gene expression detection is RTq-PCR. Instead of DNA, this method amplifies mRNA sequences using reverse

transcriptase, polymerizing cDNA sequences as a product of the reaction. This method is very sensitive and also quantitative, allowing for the assessment of the amount of mRNA of a certain gene even if it is expressed at very low levels (Shiao 2003; Bustin et al. 2005); however, the method is performed on tissue homogenates and therefore allows for less regional specificity.

2.2.3 DNA Hybridization Array (Microarray)

This method uses a plate with multiple spots that contain different DNA sequences for genes of interest. These sequences are hybridized with cDNA or cRNA extracted from a tissue sample. Hybridization levels can be detected by chemiluminescence or by the use of fluorophores. Typically, an important step before hybridization is the labeling of target sequences of the sample; mRNA is purified and submitted to RT-PCR to synthesize cDNA, which is labeled afterward with a fluorescent component (Freeman et al. 2000). The main advantage of this method is the ability to assess a very large number of genes for a single tissue sample.

2.2.4 Western Blotting

This method is used to detect and sort specific proteins in tissue homogenates using gel electrophoresis. After being separated, proteins are transferred to a membrane (e.g., nitrocellulose), treated with a protein-rich blocking reagent to avoid non-specific labeling, incubated with a primary antibody (IgG) to detect a specific protein of interest, washed and then incubated with a secondary antibody (anti-IgG) associated with a reporter molecule (e.g., horseradish peroxidase or alkaline phosphatase). Detection is performed using a chromogenic or luminescent substrate (Gallagher et al. 2004). This method detects proteins and therefore provides only an indirect measurement of gene expression.

2.2.5 Immunohistochemistry

This method uses the same principle of antibody detection described above, but in tissue sections instead of homogenate samples (Jin and Lloyd 1997). This method also detects proteins and therefore provides only an indirect measurement of gene expression.

3 Sleep Deprivation and Gene Expression

Some of the most important effects of sleep deprivation are modifications in gene expression, which can reflect the activation or suppression of cellular processes leading to changes in neuronal function and synaptic connections. The analysis of

gene expression changes provides therefore a privileged window into brain function. As described in Sect. 2, there are different methods for the sleep deprivation of animal and many ways to measure changes in gene expression profiles. Most of the studies on sleep deprivation that aim to analyze gene expression are performed in rodents (Pompeiano et al. 1992, 1997; Cirelli et al. 1995, 2006; Maloney et al. 2002; Cirelli 2006; Terao et al. 2006), but there are also important studies in flies (Wang et al. 2010), birds (Jones et al. 2008), and fish (Appelbaum et al. 2010). Sleep deprivation studies are often difficult to compare, due to the use of different deprivation methods, durations, and animal models. There is also considerable variation in the methods employed to quantify gene expression levels (Fig. 1). For instance, the decision to measure protein or mRNA may bias toward different outcomes, depending on the timescale of the experiment. Since mRNA transcriptional regulation precedes protein synthesis, experimental designs must carefully consider whether the method of choice for gene expression assessment is compatible with the temporal windows chosen.

Most of the gene expression studies use the microarray method, which allows for the simultaneous measurement of large numbers of genes [from 10,000 transcripts (Cirelli and Tononi 2000b) to more than 26,000 (Cirelli et al. 2006)]. Such screens reveal that sleep deprivation causes major changes in gene expression not only in the brain but also in the periphery. Stress response genes are frequently targeted in sleep deprivation experiments, since many methods of sleep deprivation are considered stressful due to the use of unpleasant stimuli (e.g., disk-over-water method). Sleep deprivation per se may be considered a stressful situation, irrespective of which deprivation method is used. Under this assumption, sleep loss is expected to always trigger a stress response.

Several genes expressed during spontaneous waking have their expression upregulated in the central nervous system during sleep deprivation (Cirelli et al. 2006). These genes comprise immediate early genes that encode transcription factors, growth factors, adhesion molecules, neurotransmitter receptors and transporters, and enzymes (Cirelli and Tononi 2000a, b, c). A gene screen study (Cirelli and Tononi 2000b) showed a wide range of genes whose expression is upregulated by sleep deprivation: the activity-regulated cytoskeleton-associated protein (*Arc*), the C/EBP homology protein (CHOP), the immediate early response 5 (*IER5*), the nerve growth factor-induced protein A (*NGFI-A*, homologue of *Zif-268*, *Krox-24*, *Egr-1*, and *ZENK*), the nerve growth factor-induced gene B (*NGFI-B*, also known as *Nr4a1*), the neuroblastoma ras oncogene (*N-Ras*), the signal transducer and activator of transcription (*3Stat3*), the glucose type I transporter (*Glut1*), the VGF nerve growth factor inducible (*Vgf*), brain-derived neurotrophic factor (*BDNF*), the tyrosine-related kinase B (*TrkB*, also known as *NTRK2*), the coagulation factor III (*F3*), the binding immunoglobulin protein (*BiP*, also known as *HSPA5* or *HSP70*), the endoplasmic reticulum resident protein 72 (*ERP72*, also known as *PDIA4*), the 75-kDa glucose-regulated protein (*GRP75*, also known as *HSPA9*), the 60-kDa heat-shock protein (*HSP60*), the 70-kDa heat-shock protein (*HSP70*), chromogranin C, synaptotagmin IV, the adrenergic receptors α and β , the GABA receptor B, the glutamate NMDA receptors 1A, 2A, and 3A, the glutamate AMPA receptors

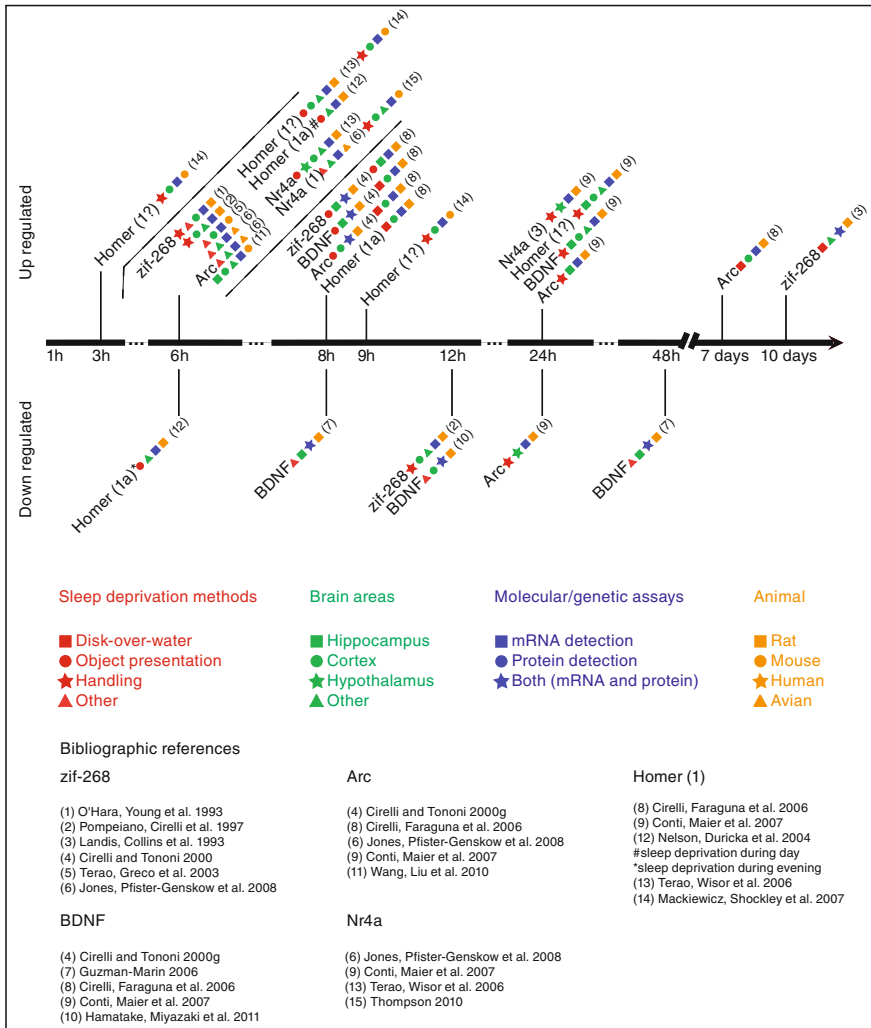


Fig. 1 Effects of sleep deprivation on plasticity-related gene expression. Symbols indicate different sleep deprivation methods, brain areas, targets of detection assays, and animal models used (respectively, polygons in red, green, blue, and orange). References listed at the bottom are referred as smaller numbers in parentheses (larger numbers or letters in parentheses refer to gene/protein family, while question marks indicate unspecified form, e.g., Homer1a, b or c)

GluR2 and GluR3, nicotinic acetylcholine receptor B, the thyroid hormone receptor beta (TRb), the glutamate/aspartate transporter (*GLAST*), and the Na/Cl transporter NTT4/Rxt1. Also upregulated are the enzymes aryl sulfotransferase, c-jun N-terminal kinase 1, serum/glucocorticoid-induced serine/threonine kinase, calmodulin, cyclin D2, LIM domain only protein 4 (LMO-4), and metallothionein 3. All these genes were systematically investigated through mRNA differential display and

cDNA microarrays, being upregulated in rats deprived of sleep for 8 h (Cirelli and Tononi 2000b). Another study from the same research group assessed the long-term effects of sleep deprivation on mRNA levels in the rat cerebral cortex. After 1 week of sleep deprivation, 75 transcripts had their levels increased in comparison with the levels found in spontaneously awake animals, as well as animals deprived of sleep for a few hours. These transcripts comprised mRNA for immunoglobulins, stress response proteins, minoxidil sulfotransferase, globins, and cortistatin. Altogether, these results indicate that sleep deprivation induces marked inflammatory and stress responses in the brain (Cirelli et al. 2006).

4 Sleep Deprivation and Early Changes in Gene Expression

Sleep deprivation upregulates the expression of several immediate early genes, as well as alternative splice variants induced by neuronal activity, whose protein products are involved in regulating a wide variety of cellular processes that ultimately influence neuronal plasticity and brain function (Tischmeyer and Grimm 1999).

4.1 *c-fos*

The immediate early gene *c-fos* gives rise to the *fos* protein that acts as a rather general transcription factor. Expression of the *fos* gene is upregulated by membrane depolarization and therefore widely used as a general marker of neuronal activity (Kovacs 1998; Cirelli and Tononi 2000c). The expression of *c-fos* is upregulated in several brain areas by spontaneous wakefulness (Pompeiano et al. 1994) as well as forced sleep deprivation (Cirelli et al. 1995). Both the mRNA and the protein levels of *c-fos* are elevated in rats when the sleep cycle is arrested, with a wide anatomical distribution that comprises the cerebral cortex, portions of the hypothalamus, the medial preoptic area, thalamic nuclei, and nuclei of the dorsal pontine tegmentum (Cirelli et al. 1995). Somewhat similar results were obtained in cats using immunohistochemistry, which revealed increased *c-fos* levels in the preoptic area and lateral hypothalamus of sleep-deprived animals (Ledoux et al. 1996). In mice subjected to sleep deprivation for 6h, *c-fos* mRNA levels were increased in the cerebral cortex, basal forebrain, thalamus, and cerebellum (Terao et al. 2003). A study of sleep deprivation in neonate rats found increased *c-fos* mRNA levels in the cerebral cortex and hippocampus at postnatal days 16, 20, and 24, with a return to basal levels after a 2-h recovery sleep period (Hairston 2004).

An anatomically comprehensive study of sleep-deprived mice used laser microdissection and cDNA microarrays to show upregulation of *c-fos* mRNA levels in visual and caudal somatosensory cortex, agranular insular cortex, orbitofrontal cortex, piriform cortex, amygdala, dorsal caudate putamen, and cerebellum, with downregulation in the ventral posteromedial nucleus of the thalamus. *C-fos*

expression was largely coincident with expression of the excitatory neuron-specific vesicular glutamate transporter 1 (Slc17a7) and overlapped with Arc and Nr4a1 expression in visual and agranular insular cortices (Thompson et al. 2010).

Sleep deprivation of non-mammalian vertebrates by and large yields similar results. In the white-crowned sparrow, c-fos mRNA levels are increased in several portions of the telencephalon after 6 h of sleep deprivation (Jones et al. 2008). In the zebrafish, sleep deprivation for 3 h or 6 h leads to c-fos mRNA upregulation in the olfactory bulb, telencephalon, diencephalon, and rhombencephalon, with a return to basal levels after recovery sleep (Appelbaum et al. 2010).

4.2 *Zif-268*

The transcription factor Zif-268 (zinc finger protein 268) is also known as NGFI-A (nerve growth factor-induced protein A), Egr-1 (early growth response protein 1), Krox-24, and ZENK (acronym of the initial letters of Zif-268, Egr-1, NGFI-A, and Krox-24). The Zif-268 protein regulates the expression of many genes involved with plasticity, mitogenesis, and differentiation, including synapsins I and II, and synaptobrevin II (Knapska and Kaczmarek 2004). Zif-268 was found to be upregulated after 6 h of sleep deprivation in the rat cerebral cortex assessed through Northern blotting (O'Hara et al. 1993). In rats submitted to sleep deprivation for up to 10 days using the disk-over-water method (Landis et al. 1993), immunocytochemistry and Northern blotting showed elevated Zif-268 expression in the dorsal raphe, lateral habenula, superior colliculus, and ventral periaqueductal gray. These neuroanatomical locations were not corroborated by a subsequent study, which applied in situ hybridization to brains of animals subjected to sleep deprivation by gentle handling for 3, 6, 12, and 24 h (Pompeiano et al. 1997). Increased mRNA levels were found in the cerebral cortex and caudate-putamen (Pompeiano et al. 1997). The same authors found that 3 h of sleep deprivation were associated with increased Zif-268 levels in the cerebral cortex but not in the locus coeruleus, while 12 or 24 h of sleep deprivation induced Zif-268 expression in the locus coeruleus, the parabrachial nuclei, and the superior and inferior colliculi (Tononi et al. 1994). A plausible explanation for the somewhat divergent findings may reside in the different amounts of sleep deprivation applied. Longer periods of deprivation may trigger self-regulation mechanisms such as the negative feedback enabled by the Zif-268 response, in which the protein recognizes consensus sequences in the promoter region of the gene, allowing for downregulation of its own expression (Christy and Nathans 1989).

More recently, a study in mice showed that sleep deprivation for 6 h followed by a recovery period of 4 h leads to the upregulation of Zif-268 mRNA levels in the cerebral cortex and basal forebrain (Terao et al. 2003). The deprivation-related increase of Zif-268 levels seems to obey very similar dynamics in the avian brain. In white-crowned sparrows, telencephalic Zif-268 mRNA levels were reported to increase 117 % after 6 h of sleep deprivation, with a 90 % increase from spontaneous waking to control (Jones et al. 2008).

4.3 *Arc*

Another immediate early gene involved in neuronal plasticity and affected by sleep deprivation is *Arc* (also known as *Arg3.1*), encoded by mRNA transported to post-synaptic dendritic terminals for local translation (Lyford et al. 1995). *Arc* participates in synaptic remodeling by regulating the dynamics of F-actin, AMPA receptors, and Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) (Bramham et al. 2010; Okuno et al. 2012).

Arc levels are upregulated in rats after both acute (8 h) (Cirelli and Tononi 2000b) and chronic (1-week) sleep deprivation, when assessed by microarrays and confirmed by (RT-qPCR) and RNase protection assay (RPA) (Cirelli et al. 2006). Another study found *Arc* mRNA levels to be upregulated in the cerebral cortex of mice and rats subjected to sleep deprivation for 6 h (Terao et al. 2006). Similar results were obtained in the cerebral cortex and hippocampus after 8 h of sleep deprivation in rats, with recovery to basal *Arc* mRNA levels after 2 h of sleep (Taishi et al. 2001). Corroborating these findings, a study with C57BL/6J mice showed higher levels of *Arc* mRNA in the hippocampus, amygdala, neocortex, and piriform cortex of sleep-deprived animals, in comparison with controls. However, increased *Arc* levels were detected even after a 4-h sleep rebound period (Thompson et al. 2010). Another study in rats using gene chip analysis and 24 h of sleep deprivation by gentle handling found a 1.2-fold decrease of *Arc* mRNA levels in the hypothalamus and a twofold increase in the hippocampus, in comparison with controls (Conti et al. 2007). A meta-analysis of datasets comprising 91 different genes found *Arc* mRNA to be upregulated in the cerebral cortex, hippocampus, olfactory bulb, and striatum of mice deprived of sleep for 6 h (Wang et al. 2010). Similar effects occur in the brain of the white-crowned sparrow, with a 66 % increase in *Arc* mRNA levels after 6 h of sleep deprivation (Jones et al. 2008).

4.4 *Homer*

Another gene of interest is *Homer1*, which is widely expressed in the brain and other tissues with two main splice variants: a short form called *Homer1a*, which is induced by neuronal activity, and long forms called *Homer1b* and *c*, which have constitutive expression (Shiraishi-Yamaguchi and Furuichi 2007). *Homer1a* inhibits the scaffolding action of the long forms, decreasing glutamatergic signaling and diminishing dendritic spines (Tu et al. 1998). Like *Arc* (Sect. 4.3), *Homer1a* is broadly upregulated in the brains of sleep-deprived rats (Cirelli et al. 2006; Maret et al. 2007). Additionally, it is expressed in spontaneously awake rats, which suggests that *Homer1a* is generally associated with wakefulness and neuronal activity (Thompson et al. 2010). *Homer1a* mRNA is upregulated in the somatosensory cortex of rats deprived of sleep for 6 h during the day (sleep period); in contrast, *Homer1a* gene expression is downregulated by sleep deprivation during

the evening (active period); similar results of a lesser magnitude were obtained for Homer1bc (Nelson et al. 2004). Homer1a is significantly overexpressed in the cerebral cortex, hippocampus, and striatum in three different mouse genotypes (Maret et al. 2007). Another study using microarray analysis and the disk-over-water method presented compatible results: Rats deprived of sleep for 8 h showed upregulated Homer1a levels in comparison with animals allowed to sleep, while sleep deprivation for 7 days yielded a non-significant tendency for transcriptional downregulation in comparison with short-term sleep deprivation (8 h) and spontaneous waking (Cirelli et al. 2006). Homer1 upregulation was detected in the basal forebrain and cerebral cortex of rats submitted to sleep deprivation by introducing novel objects and tapping the cage during 6 h (Terao et al. 2006). Another study used in situ hybridization to detect Homer1 upregulation in rats deprived of sleep for 24 h (Conti et al. 2007). An investigation of Homer1 expression after 3, 6, 9, and 12 h of sleep deprivation found transcriptional upregulation in the cerebral cortex for all these periods (Mackiewicz et al. 2007). Although these particular three studies (Conti et al. 2007; Terao et al. 2006; Mackiewicz et al. 2007) did not specify which Homer1 variation was measured, it is likely that it was Homer1a, since most of the other studies cited in this section specifically indicate Homer1a to be upregulated by sleep deprivation. A meta-analysis found Homer1a levels to be upregulated in mice after 6 h of sleep deprivation in the cerebral cortex, hippocampus, olfactory bulb, and striatum (Wang et al. 2010). Interestingly, experiments performed in *Drosophila melanogaster* showed Homer downregulation in sleep-deprived flies. Homer1a uncouples the metabotropic glutamate receptor from other Homer isoforms. *Drosophila* has only one Homer isoform, which acts in the opposite direction of Homer1a (Zimmerman et al. 2006; Mackiewicz et al. 2008).

4.5 *Nr4a*

Gene expression is highly influenced by nuclear receptors that act as transcription factors upon activation by steroid and thyroid hormones, among other ligands (Green and Chambon 1988; McKenna and O'Malley 2002). Some nuclear receptors are regulated as immediate early genes, such as the NR4A subfamily of orphan receptors that include (NGFIB/NR4a1), the nuclear receptor-related protein 1 (NURR1/NR4a2), and the neuron-derived orphan receptor 1 (NR4a3/NOR1) (Maxwell and Muscat 2006; Hawk and Abel 2011). Sleep deprivation affects Nr4a expression, which is activated by the same calcium-dependent factors that upregulate the memory-related IEG expression reviewed above (Hawk and Abel 2010). In 6 h sleep-deprived rats, Nr4a mRNA levels were found to be upregulated in the cerebral cortex, basal forebrain, and hypothalamus (Terao et al. 2006). Another study using gene chip analysis found a 100 % increase in Nr4a3 mRNA expression in the rat hypothalamus after 24 h of sleep deprivation (Conti et al. 2007). In white-crowned sparrows

deprived of sleep for 6 h, Nr4a1 mRNA levels in the telencephalon were found to be increased by 60 %, in comparison with control animals allowed to sleep (Jones et al. 2008). An assessment of Nr4a1 gene expression in mice deprived of sleep for 6 h using laser microdissection and microarray hybridization found elevated mRNA levels in the amygdala and in the primary visual, agranular insular, orbitofrontal and piriform cortices, as well as in the cerebellum and putamen; controls allowed to sleep showed increased levels of Nr4a1 and Arc in the rostral and ventral caudate–putamen, as well as in the motor and rostral somatosensory cortices; sleep-deprived mice showed Nr4a1 upregulation in the caudal dorsolateral putamen, overall a very similar profile found for Arc expression. (Thompson et al. 2010). A meta-analysis of microarray data in mouse, rat, sparrow, and fly identified the Nr4a gene family as conserved genes affected by sleep deprivation (Wang et al. 2010).

The upregulation of immediate early gene expression by sleep deprivation requires the involvement of secondary messengers. An investigation of the levels of phosphorylated cAMP response element-binding protein (p-CREB) after 3 h of sleep deprivation detected a significant and widespread increase in the cerebral cortex (Cirelli and Tononi 2000a). Another study found the mRNA levels of CaMKII to be upregulated in the cerebral cortex and basal forebrain of rats deprived of sleep for 6 h (Terao et al. 2006). In contrast, other researchers found that 48 h of sleep deprivation reduces CREB mRNA levels to the levels found in controls kept in their home cages; similar results were obtained for CaMKII (Guzman-Marin 2006). Chemical lesions of the noradrenergic system showed that the expression of Zif-268 and c-fos during wakefulness depends critically on the integrity of the locus coeruleus (Cirelli et al. 1996). The implication of this finding is that calcium-dependent immediate early gene expression, and presumably upstream events such as increases in cAMP and p-CREB levels, also requires noradrenergic modulation.

5 Sleep Deprivation and Neurotrophic Factors

The gene expression and protein levels of neurotrophic factors involved with cell growth and function (Boyd and Gordon 2003a, b) have also been shown to be affected by sleep deprivation (Cirelli and Tononi 2000a; Sei et al. 2000; Fujihara et al. 2003; Hamatake et al. 2011; Ventskova et al. 2014; Wallingford et al. 2014; Zielinski et al. 2014). Most studies were concerned with BDNF, a neurotrophin of great importance for neuronal plasticity and survival (Ghosh et al. 1994; Ventimiglia et al. 1995; Lipsky and Marini 2007; Sossin and Barker 2007). A study of rats selectively deprived of REM sleep for 6 h found BDNF protein levels to be unchanged in the hippocampus and decreased in the cerebellum and brain stem (Sei et al. 2000). A lack of hippocampal change in BDNF mRNA levels after sleep deprivation was also reported in rats subjected to full sleep deprivation for 8 h; in

contrast, the same animals showed a significant increase in BDNF mRNA levels in the cerebral cortex (Taishi et al. 2001). Rats subjected to sleep deprivation (for 8 and 48 h) by an intermittent treadmill method showed a significant decrease of mRNA and protein BDNF levels in the hippocampus, but not in the cerebral cortex (Guzman-Marin 2006). A different study of sleep deprivation in rats detected a significant increase of BDNF mRNA levels in the cerebral cortex (Cirelli and Tononi 2000a). Interestingly, BDNF mRNA levels were significantly increased in the cerebral cortex when animals were sleep deprived for 8 h by introducing new objects in the cage, but not in animals deprived of sleep for 1 week using the disk-over-water method (Cirelli et al. 2006). While this comparison is imperfect, varying both the duration and the method for sleep deprivation, it suggests that deprivation by cognitive challenge may impact gene expression quite differently from deprivation due to non-cognitive physiological challenge.

An investigation of sleep deprivation using gene chip methodology and in situ hybridization found BDNF mRNA levels to be upregulated in the piriform cortex, dorsal endopiriform nucleus, and hippocampus (Conti et al. 2007). Another study used microarrays and RT-PCR to show that BDNF mRNA levels are increased in the rat cerebral cortex after 96 h of REM sleep deprivation, with a return to basal levels after 24 h of sleep recovery (Guindalini et al. 2009). In neonate rats deprived of sleep for up to 180 min, mRNA BDNF levels were increased in the cerebral cortex at postnatal days P20 and P24 (Hairston 2004). Interpretation of the somewhat divergent results is complicated by differences in the methods employed for sleep deprivation, (e.g., the introduction of new objects *versus* intermittent locomotion on a treadmill), in the duration of the deprivation protocols, in the brain region analyzed, and in the age of the animals.

If the corpus of published studies on BDNF and sleep deprivation fails to systematically cover the parameter space, investigation of other neurotrophins is even sparser. Sei et al. compared the effects of 6 h of REM sleep deprivation on BDNF and nerve growth factor (NGF) protein levels in the rat hippocampus, cerebellum, and brainstem. NGF levels were significantly decreased in the hippocampus, but were unchanged in the cerebellum and brainstem (Sei et al. 2000). Another study showed that 6 h of total sleep deprivation was associated with a significant increase in the number of NGF-immunoreactive cortical neurons in the mice barrel field (Brandt et al. 2001). An investigation of the diurnal variations of neurotrophin-3 (NT-3) and BDNF levels in several brain regions of juvenile rats (2 weeks) detected increased BDNF levels in the dark phase and decreased levels in the light phase. NT-3 levels showed the opposite profile in the neocortex (Hamatake et al. 2011). Another study observed that intracerebroventricular injections of NT-3 and neurotrophin-4 (NT-4) in adult rabbits promote non-REM sleep in a dose-dependent manner (Kushikata et al. 2003). A great deal of additional experimentation is needed to elucidate the effect of sleep deprivation on neurotrophin expression.

6 Sleep Deprivation Changes Expression of Genes Related to Protein Synthesis

A microarray study of mice subjected to sleep deprivation for 5 h detected alterations in the hippocampal expression of 533 genes (Vecsey et al. 2012). A bioinformatics assessment pointed to a marked downregulation of translation through the insulin signaling pathway, including the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase with a major role in cell metabolism and protein synthesis (Wullschlegler et al. 2006). Sleep deprivation decreased both the absolute and the phosphorylated levels of mTOR, with a return to basal levels of expression after a 2.5 h period of sleep. The result suggests that the physiological deficits caused by sleep deprivation are in part related to the impairment of protein synthesis mediated by mTOR.

There is also evidence that sleep deprivation increases the expression of molecular chaperones involved with the folding and oligomerization of newly synthesized proteins. For instance, brain expression of the binding immunoglobulin protein (BiP), also known as the 78-kDa glucose-regulated protein (GRP-78), is significantly upregulated by sleep deprivation in *Drosophila* (Shaw et al. 2000), birds, and rodents (Cirelli and Tononi 2000b; Shaw et al. 2000; Greenspan et al. 2001; Naidoo et al. 2005; Cirelli et al. 2006; Mackiewicz et al. 2007; Jones et al. 2008). Found in the endoplasmic reticulum, BiP is a chaperone that binds to newly synthesized proteins to facilitate their folding and oligomerization. The upregulation of BiP expression by sleep deprivation likely determines the upregulation of protein levels corresponding to a plethora of different genes.

7 Changes in Serum Protein Levels After Sleep Deprivation may Indirectly Reflect Changes in Gene Expression

Given the important influence of sleep on a great number of metabolic pathways, it is not surprising that sleep deprivation induces major metabolic disarray, including changes in serum protein levels. These may reflect changes in gene expression, but may also reflect changes in the release, degradation, and turnover of these molecules. The hormones, cytokines, and other proteins whose expression levels are affected include leptin, ghrelin, the thyroid hormones T3 and T4, interleukin 6 (IL-6), TNF- α , and C-reactive protein (CRP). Combined, changes in the levels of these proteins lead to energetic imbalance, impairment of the glucose metabolism, and metabolic syndrome (Mullington et al. 2009). In particular, REM sleep deprivation increases IL-1B, IL-6, and IL-12 (P70) serum levels, as well as the liver expression of IL-1B and IL-6 receptors in rodents (Gorczynski et al. 2005; Pandey and Kar 2011). These findings corroborate and greatly extend the earlier demonstration of a modulatory role of sleep on the expression of interleukin-1 beta

(IL-1B), an important pro-inflammatory cytokine (Mackiewicz et al. 1996). REM sleep deprivation also elevates the metabolic rate by increasing expression of the UCP1 gene, which encodes a protein involved in the dissipation of mitochondrial energy as heat, instead of ATP formation (Koban and Swinson 2005). An investigation of the effects of sleep deprivation on the inflammatory response in mice detected increased levels of IL-6 and IL-10 and decreased levels of TNF-alpha in animals treated with lipopolysaccharide (Weil et al. 2009).

In humans, one night of sleep loss leads to increased levels of IL-6 and TNF-alpha (Irwin et al. 2006). Chronic sleep loss for 1 week in young adults leads to increased levels of IL-6 in both males and females, while TNF-alpha is increased only in men (Vgontzas et al. 2004). Subjects with sleep limited to 4 h per night show increased levels of IL-6, in comparison with subjects sleeping 8 h per night; no significant differences between these groups were seen for TNF or CRP (Haack et al. 2007). Sleep restriction for 5 nights induces lymphocyte activation and upregulation of IL-1, IL-6, IL-17, and CRP (van Leeuwen et al. 2009). The studies of patients with obstructive sleep apnea are not conclusive: While some report increases, other find unchanged levels (Arnardottir et al. 2009). An investigation of 70 patients found that poor sleep is associated with higher concentrations of vascular endothelial growth factor (VEGF) and that fatigue-related reduction in activity is associated with increased TNF-alpha levels (Guess et al. 2009). Night-shift workers show increased levels of IL-6 and CRP, as well as elevated counts of white blood cells, neutrophils, lymphocytes, and platelets (Khosro et al. 2011). Overall, sleep deprivation is associated with a strong inflammatory response.

8 Sleep Deprivation and Genes Related to Cellular Stress Responses

Sleep loss stresses the organism as a whole, challenging its equilibrium at multiple levels, from the molecular and cellular domains to the complex interaction of entire systems, leading to behaviors such as anxiety, fear, aggressiveness, and helplessness. Autonomic responses and activation of the hypothalamus–pituitary–adrenal (HPA) axis (Herman and Cullinan 1997; Ziegler and Herman 2002), including enhanced glucocorticoid release, lead to the transcriptional upregulation of specific genes. The mRNA levels of the serum/glucocorticoid-induced serine/threonine kinase 1 (Sgk1), which activates ion channels in response to changes in cell hydration, are increased after 8 h of sleep deprivation, but not after spontaneous waking. Sleep deprivation was achieved by multimodal sensory stimulation, which consisted of the presentation of novel objects or odors, moving the animal to another cage and tapping the cage (Cirelli and Tononi 2000b). Another study found that Sgk1 mRNA levels are increased almost twofold in the dorsal raphe nucleus and more than twofold in the locus coeruleus in rats deprived of sleep for 24 h. In this case, sleep deprivation was performed by gently handling the animals, and differential analysis of gene expression was used to assess mRNA levels (Conti et al. 2007). More recently,

several stress-related genes including Sgk, the cyclin-dependent kinase inhibitor 1A (Cdkn1a), (BDNF), secretogranin II (Scg2), prokineticin 2 (Prok2), and the heat-shock 27-kDa protein 1 (Hspb1) were shown to be upregulated in animals kept awake for 6 h by multimodal sensory stimulation (including cage rotation). To assess gene expression, seven brain regions were submitted to laser microdissection, and main genes were selected through cDNA microarray for subsequent *in situ* hybridization confirmation (Thompson et al. 2010).

Sleep deprivation also affects the expression of genes related to stress in glial cells, such as the macrophage inhibitor factor-related protein 14 (MRP14), the heat-shock protein 27 (Hsp27), and the α B-crystallin (Cryab) (Cirelli et al. 2006). MRP14 is found in microglial cells (Postler et al. 1997; Staba et al. 2002), while Hsp27 and Cryab are heat-shock proteins with a protective role in oligodendrocytes and astrocytes (Goldbaum and Richter-Landsberg 2001). Altogether, these results point to the global reach of sleep deprivation, which negatively affects the organism as a whole, while at the same time stressing individual cells quite locally.

9 Sleep Deprivation, Gene Expression, and Cognition

Sleep deprivation affects the expression of immediate early genes, genes coding for neurotrophic factors, and various other genes that directly or indirectly affect neuronal plasticity, which in turn support brain function and cognitive processes. However, the finding that many of these genes are up-regulated after sleep deprivation seems at odds with the established fact that sleep deprivation causes impairments in cognitive function. The fact that plasticity factors involved with learning and memory (Guzowski et al. 2000; Jones et al. 2001; Bozon et al. 2003) are up-regulated by sleep deprivation poses a conundrum, given the evidence that sleep deprivation produces mnemonic impairment (Pearlman 1969; Graves et al. 2003; Seugnet et al. 2011; Havekes et al. 2012; Kumar and Jha 2012). One possible explanation for these results is the notion that learning triggers gene expression in specific subsets of neurons, while sleep deprivation affects neuronal populations in a generalized manner. Such a scenario is compatible with evidence that REM sleep triggers the upregulation of Zif-268 and Arc expression in the cerebral cortex and hippocampus of rats previously exposed to novel waking experience (Ribeiro et al. 1999, 2002, 2007; Ullloor and Datta 2005). This view is also supported by results showing that the detrimental effects of sleep deprivation on contextual fear conditioning are caused by a disruption of signaling via cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). Sleep deprivation for 5 h was followed by electrophysiological recordings and stimulation of hippocampal slices in mice with or without exposure to contextual fear conditioning. Two forms of long-term potentiation (LTP) dependent on cAMP and PKA were impaired by sleep deprivation, while LTP forms independent of cAMP/ PKA signaling remained unaltered. Sleep deprivation decreased CREB phosphorylation required for Zif-268 transcriptional regulation, seemingly at variance with several studies showing increased

Zif-268 expression after sleep deprivation (Sect. 4.2). Further experiments showed that inhibitors of cyclic nucleotide phosphodiesterases (PDE) rescued cAMP-dependent plasticity and cAMP levels in sleep-deprived mice. PDE-specific cAMP breakdown was enhanced in sleep-deprived mice, and *in vivo* PDE inhibition rescued the mnemonic deficit produced by sleep deprivation (Vecsey et al. 2009).

10 Conclusion

Sleep deprivation represents a major physiological challenge, with overarching consequences for the expression of genes related to metabolism, stress, cognition, and immunity. The large number of genes whose expression is affected by sleep deprivation reflects the great complexity of the genomic response triggered by sleep. The consequences of sleep deprivation include cognitive deficits, inflammation, general impairment of protein translation, metabolic imbalance, and thermal deregulation. While several diseases include sleep disturbances among their symptoms—including psychosis, depression, and Parkinson's and Alzheimer's disease—sleep loss *per se* is a risk factor for psychiatric and neurological diseases (Frank et al. 2013; Palma et al. 2013). A better understanding of the impact of sleep deprivation on gene expression shall provide meaningful insights into both basic and applied scientific questions. It should also help mitigate the cognitive and health problems faced by those that suffer from sleep loss due to professional schedules and/or family responsibilities.

Acknowledgments Support obtained from the Pew Latin American Fellows Program in the Biomedical Sciences, Ministério da Ciência e Tecnologia e Inovação (MCTI), CNPq Universal Grant 481351/2011-6, FAPESP Neuromat (2013/ 07699-0), and a graduate fellowship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) to A.C.S. We thank D. Koshiyama for library support.

References

- Aldabal L, Bahammam AS (2011) Metabolic, endocrine, and immune consequences of sleep deprivation. *Open Respir Med J* 5:31–43
- Alkadhi K, Zagaar M, Alhaider I, Salim S, Aleisa A (2013) Neurobiological consequences of sleep deprivation. *Curr Neuroparmacol* 11(3):231–249
- Appelbaum L, Wang G, Yokogawa T, Skariah GM, Smith SJ, Mourrain P, Mignot E (2010) Circadian and homeostatic regulation of structural synaptic plasticity in hypocretin neurons. *Neuron* 68(1):87–98
- Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI (2009) Molecular signatures of obstructive sleep apnea in adults: a review and perspective. *Sleep* 32(4):447–470
- Aydin A, Selvi Y, Besiroglu L, Boysan M, Atli A, Ozdemir O, Kilic S, Balaharoglu R (2013) Mood and metabolic consequences of sleep deprivation as a potential endophenotype' in bipolar disorder. *J Affect Disord* 150(2):284–294

- Barf RP, Desprez T, Meerlo P, Scheurink AJ (2012) Increased food intake and changes in metabolic hormones in response to chronic sleep restriction alternated with short periods of sleep allowance. *Am J Physiol Regul Integr Comp Physiol* 302(1):R112–R117
- Bergmann BM, Everson CA, Kushida CA, Fang VS, Leitch CA, Schoeller DA, Refetoff S, Rechtschaffen A (1989a) Sleep deprivation in the rat: V. Energy use and mediation. *Sleep* 12(1):31–41
- Bergmann BM, Kushida CA, Everson CA, Gilliland MA, Obermeyer W, Rechtschaffen A (1989b) Sleep deprivation in the rat: II. Methodology. *Sleep* 12(1):5–12
- Bevins RA, Klebaur JE, Bardo MT (1997) Individual differences in response to novelty, amphetamine-induced activity and drug discrimination in rats. *Behav Pharmacol* 8(2–3):113–123
- Boyd JG, Gordon T (2003a) Glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor sustain the axonal regeneration of chronically axotomized motoneurons in vivo. *Exp Neurol* 183(2):610–619
- Boyd JG, Gordon T (2003b) Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. *Mol Neurobiol* 27(3):277–324
- Bozon B, Kelly A, Josselyn SA, Silva AJ, Davis S, Laroche S (2003) MAPK, CREB and zif268 are all required for the consolidation of recognition memory. *Philos Trans R Soc Lond B Biol Sci* 358(1432):805–814
- Bramham CR, Alme MN, Bittins M, Kuipers SD, Nair RR, Pai B, Panja D, Schubert M, Soule J, Tiron A, Wibrand K (2010) The Arc of synaptic memory. *Exp Brain Res* 200(2):125–140
- Brandt JA, Churchill L, Guan Z, Fang J, Chen L, Krueger JM (2001) Sleep deprivation but not a whisker trim increases nerve growth factor within barrel cortical neurons. *Brain Res* 898(1):105–112
- Bustin SA, Benes V, Nolan T, Pfaffl MW (2005) Quantitative real-time RT-PCR—a perspective. *J Mol Endocrinol* 34(3):597–601
- Calegare BFA, Fernandes L, Tufik S, D’Almeida V (2010) Biochemical, biometrical and behavioral changes in male offspring of sleep-deprived mice. *Psychoneuroendocrinology* 35(5):775–784
- Christy B, Nathans D (1989) DNA binding site of the growth factor-inducible protein Zif268. *Proc Natl Acad Sci USA* 86(22):8737–8741
- Cirelli C (2002) How sleep deprivation affects gene expression in the brain: a review of recent findings. *J Appl Physiol* 92(1):394–400
- Cirelli C (2006) Cellular consequences of sleep deprivation in the brain★. *Sleep Med Rev* 10(5):307–321
- Cirelli C, Tononi G (2000a) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J Neurosci* 20(24):9187–9194
- Cirelli C, Tononi G (2000b) Gene expression in the brain across the sleep-waking cycle. *Brain Res* 885(2):303–321
- Cirelli C, Tononi G (2000c) On the functional significance of c-fos induction during the sleep-waking cycle. *Sleep* 23(4):453–469
- Cirelli C, Pompeiano M, Tononi G (1995) Sleep deprivation and c-fos expression in the rat brain. *J Sleep Res* 4:92–106
- Cirelli C, Pompeiano M, Tononi G (1996) Neuronal gene expression in the waking state: a role for the locus coeruleus. *Science* 274(5290):1211–1215
- Cirelli C, LaVaute TM, Tononi G (2005) Sleep and wakefulness modulate gene expression in *Drosophila*. *J Neurochem* 94(5):1411–1419
- Cirelli C, Faraguna U, Tononi G (2006) Changes in brain gene expression after long-term sleep deprivation. *J Neurochem* 98(5):1632–1645
- Clinton SM, Bedrosian TA, Abraham AD, Watson SJ, Akil H (2010) Neural and environmental factors impacting maternal behavior differences in high- versus low-novelty-seeking rats. *Horm Behav* 57(4–5):463–473
- Conti B, Maier R, Barr AM, Morale MC, Lu X, Sanna PP, Bilbe G, Hoyer D, Bartfai T (2007) Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. *Mol Psychiatry* 12(2):167–189

- Dellu F, Piazza PV, Mayo W, Le Moal M, Simon H (1996) Novelty-seeking in rats—biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. *Neuropsychobiology* 34(3):136–145
- Duclot F, Hollis F, Darcy MJ, Kabbaj M (2011) Individual differences in novelty-seeking behavior in rats as a model for psychosocial stress-related mood disorders. *Physiol Behav* 104(2):296–305
- Ennaceur A, Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. *Behav Brain Res* 31(1):47–59
- Everson CA (1995) Functional consequences of sustained sleep deprivation in the rat. *Behav Brain Res* 69(1–2):43–54
- Everson CA, Smith CB, Sokoloff L (1994) Effects of prolonged sleep deprivation on local rates of cerebral energy metabolism in freely moving rats. *J Neurosci* 14(11 Pt 2):6769–6778
- Filipowicz W, Bhattacharyya SN, Sonenberg N (2008) Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat Rev Genet* 9(2):102–114
- Frank MG (2012) Sleep and brain activity. Academic Press, New York
- Frank E, Sidor MM, Gamble KL, Cirelli C, Sharkey KM, Hoyle N, Tikotzky L, Talbot LS, McCarthy MJ, Hasler BP (2013) Circadian clocks, brain function, and development. *Ann N Y Acad Sci* 1306:43–67
- Franken P, Dijk DJ, Tobler I, Borbely AA (1991) Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. *Am J Physiol* 261(1 Pt 2):R198–R208
- Freeman WM, Robertson DJ, Vrana KE (2000) Fundamentals of DNA hybridization arrays for gene expression analysis. *Biotechniques* 29(5):1042–1046, 1048–1055
- Fujihara H, Sei H, Morita Y, Ueta Y, Morita K (2003) Short-term sleep disturbance enhances brain-derived neurotrophic factor gene expression in rat hippocampus by acting as internal stressor. *J Mol Neurosci* 21(3):223–232
- Gall JG, Pardue ML (1969) Formation and detection of RNA-DNA hybrid molecules in cytological preparations. *Proc Natl Acad Sci USA* 63(2):378–383
- Gallagher S, Winston SE, Fuller SA, Hurrell JG (2004) Immunoblotting and immunodetection. *Curr Protoc Neurosci* (Chapter 5:Unit 5) 19
- Ghosh A, Carnahan J, Greenberg ME (1994) Requirement for BDNF in activity-dependent survival of cortical neurons. *Science* 263(5153):1618–1623
- Goldbaum O, Richter-Landsberg C (2001) Stress proteins in oligodendrocytes: differential effects of heat shock and oxidative stress. *J Neurochem* 78(6):1233–1242
- Gonnissen HK, Adam TC, Hursel R, Rutters F, Verhoef SP, Westerterp-Plantenga MS (2013) Sleep duration, sleep quality and body weight: parallel developments. *Physiol Behav* 121:112–116
- Gorczynski RM, Gorczynski CP, Gorczynski LY, Hu J, Lu J, Manuel J, Lee L (2005) Neutral buoyancy and sleep-deprived serum factors alter expression of cytokines regulating osteogenesis. *Acta Astronautica* 56(9–12):890–899
- Graves LA, Heller EA, Pack AI, Abel T (2003) Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. *Learn Mem* 10:168–176
- Green S, Chambon P (1988) Nuclear receptors enhance our understanding of transcription regulation. *Trends Genet* 4(11):309–314
- Greenspan RJ, Tononi G, Cirelli C, Shaw PJ (2001) Sleep and the fruit fly. *Trends Neurosci* 24(3):142–145
- Guess J, Burch JB, Ogoossan K, Armstead CA, Hongmei Z, Wagner S, Hebert JR, Wood P, Youngstedt SD, Hofseth LJ, Singh UP, Dawen X, Hrushesky WJM (2009) Circadian Disruption, Per3, and Human Cytokine Secretion. *Integr Cancer Ther* 8(4):329–336
- Guindalini C, Andersen ML, Alvarenga T, Lee K, Tufik S (2009) To what extent is sleep rebound effective in reversing the effects of paradoxical sleep deprivation on gene expression in the brain? *Behav Brain Res* 201(1):53–58
- Guzman-Marin R, Suntsova N, Stewart DR, Gong H, Szymusiak R, McGinty D (2003) Sleep deprivation reduces proliferation of cells in the dentate gyrus of the hippocampus in rats. *J Physiol* 549(Pt 2):563–571

- Guzman-Marin R, Suntsova N, Methippara M, Greiffenstein R, Szymusiak R, McGinty D (2005) Sleep deprivation suppresses neurogenesis in the adult hippocampus of rats. *Eur J Neurosci* 22 (8):2111–2116
- Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. *J Physiol* 575(Pt 3):807–819
- Guzowski JF, Lyford GL, Stevenson GD, Houston FP, McGaugh JL, Worley PF, Barnes CA (2000) Inhibition of activity-dependent arc protein expression in the rat hippocampus impairs the maintenance of long-term potentiation and the consolidation of long-term memory. *J Neurosci* 20(11):3993–4001
- Haack M, Sanchez E, Mullington JM (2007) Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 30(9):1145–1152
- Hagewoud R, Havekes R, Novati A, Keijser JN, Van der Zee EA, Meerlo P (2010a) Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. *J Sleep Res* 19(2):280–288
- Hagewoud R, Havekes R, Tiba PA, Novati A, Hogenelst K, Weinreder P, Van der Zee EA, Meerlo P (2010b) Coping with sleep deprivation: shifts in regional brain activity and learning strategy. *Sleep* 33(11):1465–1473
- Hagewoud R, Whitcomb SN, Heeringa AN, Havekes R, Koolhaas JM, Meerlo P (2010c) A time for learning and a time for sleep: the effect of sleep deprivation on contextual fear conditioning at different times of the day. *Sleep* 33(10):1315–1322
- Hairston IS (2004) Sleep deprivation effects on growth factor expression in neonatal rats: a potential role for bdnf in the mediation of delta power. *J Neurophysiol* 91(4):1586–1595
- Hamatake M, Miyazaki N, Sudo K, Matsuda M, Sadakata T, Furuya A, Ichisaka S, Hata Y, Nakagawa C, Nagata K, Furuichi T, Katoh-Semba R (2011) Phase advance of the light-dark cycle perturbs diurnal rhythms of brain-derived neurotrophic factor and neurotrophin-3 protein levels, which reduces synaptophysin-positive presynaptic terminals in the cortex of juvenile rats. *J Biol Chem* 286(24):21478–21487
- Havekes R, Vecsey CG, Abel T (2012) The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. *Cell Signal* 24(6):1251–1260
- Haw J, Abel T (2010) Role of gene transcription in long-term memory storage. In: George FK, Michel Le M, Richard MLM, Thompson A2, George F, Koob, Richard FT (eds) *Encyclopedia of behavioral neuroscience*. Academic Press, Oxford, pp 161–179
- Haw JD, Abel T (2011) The role of NR4A transcription factors in memory formation. *Brain Res Bull* 85(1–2):21–29
- Henderson ND (1970) Behavioral reactions of Wistar rats to conditioned fear stimuli, novelty, and noxious stimulation. *J Psychol* 75(2d Half):19–34
- Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20(2):78–84
- Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S (2006) Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med* 166(16):1756–1762
- Jin L, Lloyd RV (1997) In situ hybridization: methods and applications. *J Clin Lab Anal* 11(1):2–9
- Jones MW, Errington ML, French PJ, Fine A, Bliss TV, Garel S, Charnay P, Bozon B, Laroche S, Davis S (2001) A requirement for the immediate early gene Zif268 in the expression of late LTP and long-term memories. *Nat Neurosci* 4(3):289–296
- Jones S, Pfister-Genskow M, Benca RM, Cirelli C (2008) Molecular correlates of sleep and wakefulness in the brain of the white-crowned sparrow. *J Neurochem* 105(1):46–62
- Jouvet M (1967) The states of sleep. *Sci Am* 216(2):62–68
- Jouvet M (1994) Paradoxical sleep mechanisms. *Sleep* 17(8 Suppl.):S77–S83
- Jouvet D, Vimont P, Delorme F, Jouvet M (1964) Study of selective deprivation of the paradoxal sleep phase in the cat. *C R Seances Soc Biol Fil* 158:756–759

- Kabbaj M, Akil H (2001) Individual differences in novelty-seeking behavior in rats: a c-fos study. *Neuroscience* 106(3):535–545
- Kayser MS, Yue Z, Sehgal A (2014) A critical period of sleep for development of courtship circuitry and behavior in *Drosophila*. *Science* 344(6181):269–274
- Khosro S, Alireza S, Omid A, Forough S (2011) Night work and inflammatory markers. *Indian J Occup Environ Med* 15(1):38–41
- Killick R, Banks S, Liu PY (2012) Implications of sleep restriction and recovery on metabolic outcomes. *J Clin Endocrinol Metab* 97(11):3876–3890
- Knapska E, Kaczmarek L (2004) A gene for neuronal plasticity in the mammalian brain: Zif268/ Egr-1/NGFI-A/Krox-24/TIS8/ZENK? *Prog Neurobiol* 74(4):183–211
- Knutson KL, Spiegel K, Penev P, Van Cauter E (2007) The metabolic consequences of sleep deprivation. *Sleep Med Rev* 11(3):163–178
- Koban M, Swinson KL (2005) Chronic REM-sleep deprivation of rats elevates metabolic rate and increases UCP1 gene expression in brown adipose tissue. *Am J Physiol Endocrinol Metab* 289(1):E68–E74
- Kovacs KJ (1998) c-Fos as a transcription factor: a stressful (re)view from a functional map. *Neurochem Int* 33(4):287–297
- Kumar T, Jha SK (2012) Sleep deprivation impairs consolidation of cued fear memory in rats. *PLoS One* 7(10):e47042
- Kushida CA, Bergmann BM, Rechtschaffen A (1989) Sleep deprivation in the rat: IV. Paradoxical sleep deprivation. *Sleep* 12(1):22–30
- Kushikata T, Kubota T, Fang J, Krueger JM (2003) Neurotrophins 3 and 4 enhance non-rapid eye movement sleep in rabbits. *Neurosci Lett* 346(3):161–164
- Landis CA, Collins BJ, Cribbs LL, Sukhatme VP, Bergmann BM, Rechtschaffen A, Smalheiser NR (1993) Expression of Egr-1 in the brain of sleep deprived rats. *Brain Res Mol Brain Res* 17(3–4):300–306
- Ledoux L, Sastre JP, Buda C, Luppi PH, Jouvet M (1996) Alterations in c-fos expression after different experimental procedures of sleep deprivation in the cat. *Brain Res* 735(1):108–118
- Lipsky RH, Marini AM (2007) Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. *Ann N Y Acad Sci* 1122:130–143
- Lyford GL, Yamagata K, Kaufmann WE, Barnes CA, Sanders LK, Copeland NG, Gilbert DJ, Jenkins NA, Lanahan AA, Worley PF (1995) Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. *Neuron* 145(2):433–434
- Maas S (2010) Gene regulation through RNA editing. *Discov Med* 10(54):379–386
- Mackiewicz M, Sollars PJ, Ogilvie MD, Pack AI (1996) Modulation of IL-1 beta gene expression in the rat CNS during sleep deprivation. *Neuroreport* 7(2):529–533
- Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI (2007) Macromolecule biosynthesis: a key function of sleep. *Physiol Genomics* 31(3):441–457
- Mackiewicz M, Naidoo N, Zimmerman JE, Pack AI (2008) Molecular Mechanisms of Sleep and Wakefulness. *Ann N Y Acad Sci* 1129(1):335–349
- Maloney KJ, Mainville L, Jones BE (2002) c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. *Eur J Neurosci* 15(4):774–778
- Maret S, Dorsaz S, Gurcel L, Pradervand S, Petit B, Pfister C, Hagenbuchle O, O’Hara BF, Franken P, Tafti M (2007) Homer1a is a core brain molecular correlate of sleep loss. *Proc Natl Acad Sci USA* 104(50):20090–20095
- Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright Jr KP (2013) Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci USA* 110(14):5695–5700
- Maxwell MA, Muscat GE (2006) The NR4A subgroup: immediate early response genes with pleiotropic physiological roles. *Nucl Recept Signal* 4:e002

- McKenna NJ, O'Malley BW (2002) Combinatorial control of gene expression by nuclear receptors and coregulators. *Cell* 108(4):465–474
- McManus CJ, Graveley BR (2011) RNA structure and the mechanisms of alternative splicing. *Curr Opin Genet Dev* 21(4):373–379
- Mendelson WB, Guthrie RD, Frederick G, Wyatt RJ (1974) The flower pot technique of rapid eye movement (REM) sleep deprivation. *Pharmacol Biochem Behav* 2(4):553–556
- Moller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R, Lo JC, Santhi N, von Schantz M, Smith CP, Dijk DJ (2013) Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proc Natl Acad Sci USA* 110(12):E1132–E1141
- Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK (2009) Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis* 51(4):294–302
- Naidoo N, Giang W, Galante RJ, Pack AI (2005) Sleep deprivation induces the unfolded protein response in mouse cerebral cortex. *J Neurochem* 92(5):1150–1157
- National Research Council of the National Academies (2003) Guidelines for the care and use of mammals in neuroscience and behavioral research. The National Academies Press, Washington
- Nelson SE, Duricka DL, Campbell K, Churchill L, Krueger JM (2004) Homer1a and 1b levels in the rat somatosensory cortex vary with the time of day and sleep loss. *Neurosci Lett* 367(1):105–108
- Nitabach MN, Mongrain V, La Spada F, Curie T, Franken P (2011) Sleep loss reduces the DNA-binding of BMAL1, clock, and NPAS2 to specific clock genes in the mouse cerebral cortex. *PLoS One* 6(10):e26622
- Ocampo-Garcés A, Molina E, Rodríguez A, Vivaldi EA (2000) Homeostasis of REM sleep after total and selective sleep deprivation in the rat. *J Neurophysiol* 84(5):2699–2702
- O'Hara BF, Young KA, Watson FL, Heller HC, Kilduff TS (1993) Immediate early gene expression in brain during sleep deprivation: preliminary observations. *Sleep* 16(1):1–7
- Okuno H, Akashi K, Ishii Y, Yagishita-Kyo N, Suzuki K, Nonaka M, Kawashima T, Fujii H, Takemoto-Kimura S, Abe M, Natsume R, Chowdhury S, Sakimura K, Worley PF, Bito H (2012) Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKII β . *Cell* 149(4):886–898
- Palma JA, Urrestarazu E, Iriarte J (2013) Sleep loss as risk factor for neurologic disorders: a review. *Sleep Med* 14(3):229–236
- Pandey AK, Kar SK (2011) REM sleep deprivation of rats induces acute phase response in liver. *Biochem Biophys Res Commun* 410(2):242–246
- Pearlman CA (1969) Effect of rapid eye movement (dreaming) sleep deprivation on retention of avoidance learning in rats. *Rep US Naval Submarine Med Cent* 22(1):1–4
- Pellegrino R, Sunaga DY, Guindalini C, Martins RC, Mazzotti DR, Wei Z, Daye ZJ, Andersen ML, Tufik S (2012) Whole blood genome-wide gene expression profile in males after prolonged wakefulness and sleep recovery. *Physiol Genomics* 44(21):1003–1012
- Pisula W, Siegel J (2005) Exploratory behavior as a function of environmental novelty and complexity in male and female rats. *Psychol Rep* 97(2):631–638
- Pompeiano M, Cirelli C, Tononi G (1992) Effects of sleep deprivation on fos-like immunoreactivity in the rat brain. *Arch Ital Biol* 130(4):325–335
- Pompeiano M, Cirelli C, Tononi G (1994) Immediate-early genes in spontaneous wakefulness and sleep: expression of c-fos and NGIF-A mRNA and protein. *J Sleep Res* 3:80–96
- Pompeiano M, Cirelli C, Ronca-Testoni S, Tononi G (1997) NGIF-A expression in the rat brain after sleep deprivation. *Brain Res Mol Brain Res* 46(1–2):143–153
- Postler E, Lehr A, Schluesener H, Meyermann R (1997) Expression of the S-100 proteins MRP-8 and -14 in ischemic brain lesions. *Glia* 19(1):27–34
- Ramon F, Mendoza-Angeles K, Hernandez-Falcon J (2012) Sleep in invertebrates: crayfish. *Front Biosci (Schol Ed)* 4:1190–1200
- Rechtschaffen A, Bergmann BM (1995) Sleep deprivation in the rat by the disk-over-water method. *Behav Brain Res* 69(1–2):55–63

- Rechtschaffen A, Gilliland MA, Bergmann BM, Winter JB (1983) Physiological correlates of prolonged sleep deprivation in rats. *Science* 221(4606):182–184
- Rechtschaffen A, Bergmann BM, Gilliland MA, Bauer K (1999) Effects of method, duration, and sleep stage on rebounds from sleep deprivation in the rat. *Sleep* 22(1):11–31
- Ribeiro S, Goyal V, Mello CV, Pavlides C (1999) Brain gene expression during REM sleep depends on prior waking experience. *Learn Mem* 6(5):500–508
- Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye- movement sleep. *J Neurosci* 22(24):10914–10923
- Ribeiro S, Shi X, Engelhard M, Zhou Y, Zhang H, Gervasoni D, Lin SC, Wada K, Lemos NAM, Nicolelis MAL (2007) Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. *Front Neurosci* 1(1):43–55
- Roman V, Walstra I, Luiten PG, Meerlo P (2005) Too little sleep gradually desensitizes the serotonin 1A receptor system. *Sleep* 28(12):1505–1510
- Sei H, Saitoh D, Yamamoto K, Morita K, Morita Y (2000) Differential effect of short-term REM sleep deprivation on NGF and BDNF protein levels in the rat brain. *Brain Res* 877(2):387–390
- Seugnet L, Suzuki Y, Donlea JM, Gottschalk L, Shaw PJ (2011) Sleep deprivation during early-adult development results in long-lasting learning deficits in adult *Drosophila*. *Sleep* 34(2):137–146
- Shaw PJ, Cirelli C, Greenspan RJ, Tononi G (2000) Correlates of sleep and waking in *Drosophila melanogaster*. *Science* 287(5459):1834–1837
- Shiao YH (2003) A new reverse transcription-polymerase chain reaction method for accurate quantification. *BMC Biotechnol* 3:22
- Shiraishi-Yamaguchi Y, Furuichi T (2007) The Homer family proteins. *Genome Biol* 8(2):206
- Smith C, Kelly G (1988) Paradoxical sleep deprivation applied two days after end of training retards learning. *Physiol Behav* 43(2):213–216
- Sossin WS, Barker PA (2007) Something old, something new: BDNF-induced neuron survival requires TRPC channel function. *Nat Neurosci* 10(5):537–538
- Staba RJ, Wilson CL, Fried I, Engel J Jr (2002) Single neuron burst firing in the human hippocampus during sleep. *Hippocampus* 12(6):724–734
- Taishi P, Sanchez C, Wang Y, Fang J, Harding JW, Krueger JM (2001) Conditions that affect sleep alter the expression of molecules associated with synaptic plasticity. *Am J Physiol Regul Integr Comp Physiol* 281(3):R839–R845
- Terao A, Greco MA, Davis RW, Heller HC, Kilduff TS (2003) Region-specific changes in immediate early gene expression in response to sleep deprivation and recovery sleep in the mouse brain. *Neuroscience* 120(4):1115–1124
- Terao A, Wisor JP, Peyron C, Apte-Deshpande A, Wurts SW, Edgar DM, Kilduff TS (2006) Gene expression in the rat brain during sleep deprivation and recovery sleep: an Affymetrix GeneChip® study. *Neuroscience* 137(2):593–605
- Thompson CL, Wisor JP, Lee C-K, Pathak SD, Gerashchenko D, Smith KA, Fischer SR, Kuan CL, Sunkin SM, Ng LL, Lau C, Hawrylycz M, Jones AR, Kilduff TS, Lein ES (2010) Molecular and anatomical signatures of sleep deprivation in the mouse brain. *Front Neurosci* 4:165. doi: [10.3389/fnins.2010.00165](https://doi.org/10.3389/fnins.2010.00165)
- Thor DH, Harrison RJ, Schneider SR, Carr WJ (1988) Sex differences in investigatory and grooming behaviors of laboratory rats (*Rattus norvegicus*) following exposure to novelty. *J Comp Psychol* 102(2):188–192
- Tischmeyer W, Grimm R (1999) Activation of immediate early genes and memory formation. *Cell Mol Life Sci* 55(4):564–574
- Tononi G, Cirelli C (2001) Modulation of brain gene expression during sleep and wakefulness: a review of recent findings. *Neuropsychopharmacology* 25(5 Suppl):S28–S35
- Tononi G, Pompeiano M, Cirelli C (1994) The locus coeruleus and immediate-early genes in spontaneous and forced wakefulness. *Brain Res Bull* 35(5–6):589–596

- Tu JC, Xiao B, Yuan JP, Lanahan AA, Leoffert K, Li M, Linden DJ, Worley PF (1998) Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. *Neuron* 21(4):717–726
- Tufik S, Andersen ML, Bittencourt LR, Mello MT (2009) Paradoxical sleep deprivation: neurochemical, hormonal and behavioral alterations. Evidence from 30 years of research. *An Acad Bras Cienc* 81(3):521–538
- Ulloor J, Datta S (2005) Spatio-temporal activation of cyclic AMP response element-binding protein, activity-regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. *J. Neurochem.* 95(2):418–428
- van der Borgh K, Ferrari F, Klauke K, Roman V, Havekes R, Sgoifo A, van der Zee EA, Meerlo P (2006) Hippocampal cell proliferation across the day: increase by running wheel activity, but no effect of sleep and wakefulness. *Behav Brain Res* 167(1):36–41
- van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, Sallinen M, Harna M, Porkka-Heiskanen T, Alenius H (2009) Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PLoS One* 4(2):e4589
- van Swinderen B (2007) 1.28—Sleep in invertebrates. Evolution of nervous systems. HK Editor-in-Chief: Jon. Academic Press, Oxford, p 451–456
- Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li XY, Descalzi G, Kim SS, Chen T, Shang YZ, Zhuo M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. *Nature* 461(7267):1122–1125
- Vecsey CG, Peixoto L, Choi JH, Wimmer M, Jaganath D, Hernandez PJ, Blackwell J, Meda K, Park AJ, Hannehalli S, Abel T (2012) Genomic analysis of sleep deprivation reveals translational regulation in the hippocampus. *Physiol Genomics* 44(20):981–991
- Ventimiglia R, Mather PE, Jones BE, Lindsay RM (1995) The neurotrophins BDNF, NT-3 and NT-4/5 promote survival and morphological and biochemical differentiation of striatal neurons In Vitro. *Eur J Neurosci* 7(2):213–222
- Ventskovska O, Porkka-Heiskanen T, Karpova NN (2014) Spontaneous sleep-wake cycle and sleep deprivation differently induce Bdnf1, Bdnf4 and Bdnf9a DNA methylation and transcripts levels in the basal forebrain and frontal cortex in rats. *J Sleep Res*
- Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP (2004) Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* 89(5):2119–2126
- Vivaldi EA, Bassi A, Estrada J, Garrido I, Diaz J, Ocampo-Garces A (2008) On-line analysis of biosignals for the automation of total and specific sleep deprivation in the rat. *Biol Res* 41(4):439–452
- Vogel C, Marcotte EM (2012) Insights into the regulation of protein abundance from proteomic and transcriptomic analyses. *Nat Rev Genet* 13(4):227–232
- Wallingford JK, Deurveilher S, Currie RW, Fawcett JP, Semba K (2014) Increases in mature brain-derived neurotrophic factor protein in the frontal cortex and basal forebrain during chronic sleep restriction in rats: possible role in initiating allostatic adaptation. *Neuroscience* 277:174–183
- Wang H, Liu Y, Briesemann M, Yan J (2010) Computational analysis of gene regulation in animal sleep deprivation. *Physiol Genomics* 42(3):427–436
- Weil ZM, Norman GJ, Karelina K, Morris JS, Barker JM, Su AJ, Walton JC, Bohinc S, Nelson RJ, DeVries AC (2009) Sleep deprivation attenuates inflammatory responses and ischemic cell death. *Exp Neurol* 218(1):129–136
- Wu RS, Huang CC, Pan CH, Wu KC, Chen CC, Liu SK, Tang CL, Wu CH (2011) Total sleep deprivation augments balloon angioplasty-induced neointimal hyperplasia in rats. *Exp Physiol* 96(11):1239–1247
- Wulschleger S, Loewith R, Hall MN (2006) TOR signaling in growth and metabolism. *Cell* 124(3):471–484

- Xu A, Sakurai E, Kuramasu A, Zhang J, Li J, Okamura N, Zhang D, Yoshikawa T, Watanabe T, Yanai K (2010) Roles of hypothalamic subgroup histamine and orexin neurons on behavioral responses to sleep deprivation induced by the treadmill method in adolescent rats. *J Pharmacol Sci* 114(4):444–453
- Youngblood BD, Zhou J, Smagin GN, Ryan DH, Harris RB (1997) Sleep deprivation by the “flower pot” technique and spatial reference memory. *Physiol Behav* 61(2):249–256
- Ziegler DR, Herman JP (2002) Neurocircuitry of stress integration: anatomical pathways regulating the hypothalamo-pituitary-adrenocortical axis of the rat. *Integr Comp Biol* 42(3):541–551
- Zielinski MR, Kim Y, Karpova SA, McCarley RW, Strecker RE, Gerashchenko D (2014) Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression. *Neurosci Lett* 580:27–31
- Zimmerman JE, Rizzo W, Shockley KR, Raizen DM, Naidoo N, Mackiewicz M, Churchill GA, Pack AI (2006) Multiple mechanisms limit the duration of wakefulness in *Drosophila* brain. *Physiol Genomics* 27(3):337–350