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When brain clocks lose track of time: Cause or Consequence of neuropsychiatric disorders

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Abstract

Patients suffering from neuropsychiatric disorders often exhibit a loss of regulation of their biological rhythms which leads to altered sleep/wake cycle, body temperature rhythm and hormonal rhythms. Whereas these symptoms have long been considered to result from the pathology of the underlying disease, increasing evidence now indicates that the circadian system may be more directly involved in the etiology of psychiatric disorders. This emerging view originated with the discovery that the genes involved in the generation of biological rhythms are expressed in many brain structures where clocks function – and perhaps malfunction. It is also due to the interesting phenotypes of clock mutant mice. Here we summarize recent reports showing that alteration of circadian clocks within key brain regions associated with neuropsychiatric disorders may be an underlying cause of the development of mental illness. We discuss how these alterations take place at both systems and molecular levels.

Introduction

Neuropsychiatric disorders represent the second largest cause of morbidity and premature mortality worldwide. They include major depressive disorder, anxiety, schizophrenia, bipolar disorder, obsessive-compulsive disorder, alcohol and substance abuse, and attention-deficit hyperactivity disorder. One prevalent symptom often associated with these mental illnesses is a disruption of biological rhythms with deregulation of the sleep/wake cycle, body temperature rhythm and hormonal rhythms. Whereas these biological rhythm dysfunctions have been considered to mainly result from the pathology of the mental illnesses, increasing data now show that the circadian system may be more directly involved in disease etiology. Indeed, genes involved in the generation of biological rhythms (i.e., “clock genes”) are expressed in many brain structures where they fine tune biological and physiological functions to be optimal at the most appropriate times of day. Alteration of clock gene expression within the brain regions associated with neuropsychiatric disorders can lead to development of mental illnesses. We discuss here how these alterations take place at both the molecular and system levels.

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1. Clock genes are expressed in many brain structures

1.1 Communication between the central clock and the peripheral clocks

The mammalian circadian system is organized into cell-autonomous molecular oscillators not only in many brain locations but also throughout the body, where they temporally control biological and physiological functions. Cell-autonomy refers to the fact that these clocks continue to run when disconnected to the system, i.e, when incubated *in vitro*. At the molecular level, all of these oscillators appear to rely on the same mechanism, i.e., transcriptional feedback loops [reviewed in 1,2]. The transcription factor BMAL1 acts as a dimer with either CLOCK (CLK) or Neuronal PAS domain protein 2 (NPAS2) to activate the transcription of many genes including the transcriptional repressors *Period* (*Per1*, *Per2* and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*) (figure 1). The PERs and CRYs are expressed, post-translationally modified, and feedback to inhibit their own transcription. Rhythmic degradation of the repressor proteins leads to a new round of BMAL1/CLK or BMAL1/NPAS2-mediated transcription. This major feedback loop is accompanied by regulatory interlocked loops, which involve for example the BMAL1 target gene *Nr1d1* (*Rev-erbα*), mediating transcriptional oscillations of *Bmal1*. These transcriptional rhythms, which are believed to occur similarly in all clock-cells, cycle with a period of about 24h; hence the term circadian.

The brain location that has been studied in the most detail is the suprachiasmatic nucleus (SCN) of the hypothalamus, which contains the mammalian master circadian clock (figure 1). The SCN integrates daily environmental signals such as the light:dark cycle (via direct retinal input) and as a master clock, acts as a conductor and orchestrates these other ("peripheral") rhythms so that they are in an appropriate phase relationship with each other and with the SCN as well as with the daily environmental variations that feed into the SCN [reviewed in 3,4]. The SCN uses a combination of neuronal connections and paracrine signals (e.g., prokineticin 2) to control, directly or indirectly, many endocrine (e.g., melatonin and glucocortcoid rhythms) and behavioral output rhythms (rest activity cycle, daily rhythm of body temperature) [reviewed in 4; figure 1]. In turn, these rhythms act as synchronizing cues.

Importantly, animals with ablated SCN are behaviorally arrhythmic and exhibit a desynchronization and/or loss of these rhythmic signals. Indeed, lesions of the SCN do not abolish all circadian rhythms but instead cause phase desynchrony between the tissues of an individual animal [5].

The circadian clock has been studied in considerable detail in many non-brain tissues, especially in the liver where the clock plays a major role in metabolism. Results show that it is responsible for the rhythmic expression of up to 10% of all mRNAs, most of them being involved in metabolic functions. As a consequence, many biological functions within non-brain tissues are rhythmically regulated, which account for physiology optimized to the best time of the day. The synchronization of circadian gene expression to environmental cues is complex and relies on many different factors that function as systemic cues [reviewed in 6].

1.2 Clock genes are expressed within structures relevant for psychiatric disorders

Expression of clock genes within brain structures relevant for psychiatric disorders, such as the hippocampus, the prefrontal cortex, the ventral tegmental area (VTA) and the amygdala, has been described [4,7–9]. Although details of this expression are beyond the scope of the present review, we will highlight some relevant functional aspects.

First and more broadly (i.e., beyond the confines of the nervous system and psychiatric disorders), there is extensive evidence indicating that morbidity associated with the

circadian system is due to a deregulation of peripheral rather than central oscillator function (i.e., SCN-independent). For example, the arthropathy developed by *Bmal1*−/− mice (ossification of ligaments and tendons) is not induced by deregulation of gene expression within the SCN but rather where the ossification occurs [10]. Likewise in the central nervous system, links between deregulation of circadian rhythms and psychotic disorders are likely due to problems within the peripheral clocks in the hippocampus, prefrontal cortex, amygdala or VTA rather than within the SCN.

Second, the phase of circadian oscillations differs among peripheral oscillators and even within some subdivisions of the same structure. This is for example the case of PER2 rhythmic expression in the amygdala, which peaks in the evening in the central nuclear region (CEA) but in the morning in the basolateral region (BLA) [11]. Moreover, these structure and substructure-specific phases are almost identical in each animal. This strongly suggests that circadian gene expression within peripheral oscillators is set so that they best suit the biological and physiological functions they subserve.

Finally, the phase of circadian rhythms within peripheral clocks is determined, at least in part, by organ-specific synchronizers downstream of the SCN. They include many molecules and systems like hormones, neuronal connections, paracrine signals, metabolites and body temperature (figure 1). It is interesting to speculate that the circadian phase in peripheral oscillators is determined by the phase of the synchronizer as well as the sensitivity of each structure to the different synchronizers. This would depend in turn on the relative expression of each specific “receptor”. For example, higher expression of glucocorticoid receptors or *Hsf1* (heat shock transcription factor 1) may confer higher sensitivity to cortisol or temperature, respectively.

Many experiments have examined the effects of “synchronizers” on rhythmic gene expression within different oscillators. In addition to tissue-specificity, one additional characteristic arose: the SCN exhibits low sensitivity to tissue-specific synchronizers (figure 1). Indeed, clock gene expression within the SCN is insensitive to glucocorticoid [12], melatonin [13], temperature [14], food entrainment [15] and its own paracrine signal prokineticin 2 [16,17].

The relative insensitivity of the SCN to tissue-specific synchronizers contrasts with the plethora of strong effects observed within other brain structures, including those important for the development of neuropsychiatric disorders. For example, glucorticoids may be important for the entrainment and function of the hippocampus and amygdala, since these two structures are highly enriched in glucocorticoid receptors [18]. Indeed, *Per1* expression in the hippocampus can be directly induced by a pulse of corticosterone in rats [19], and clamping the daily levels of corticosterone suppresses *Per1*-mediated luciferase expression in the dentate gyrus of *Per1-luciferase* rats [20]. Moreover, PER2 rhythms in the CEA, but not in the BLA and dentate gyrus, disappear in adrenalectomized rats [11]. Many other reports also indicate that forebrain clock gene expression is affected by various stimuli [e.g., 21,22,23] and overall show that the synchronization of these oscillators is complex and incorporates many factors (figure 1).

Altogether, these results demonstrate that the rhythmic signals orchestrated by the SCN set the phases of peripheral clocks, including those in the brain. The importance of this synchronization process is highlighted by the problems arising in its absence.

2. Internal desynchronization alters brain functions

Aspects of modern life such as shift work lead to activity or food intake during what should be the resting phase. This causes internal signals to be generated at inappropriate circadian

times, which results in turn in a conflictual timing between the internal signals and the still properly timed external (environmental) signals generated by the SCN [reviewed in 24]. In the most pronounced cases, all circadian rhythms of hormones, neuronal outputs and metabolites throughout the body are desynchronized [25].

Studies aiming at creating animal models of night work have reported this phenomenon. For instance, rats forced to be active for 8 hours during their sleeping phase (light phase), 5 days a week for 4 weeks, exhibit alterations of many endogenous rhythms [26 *]. In addition to the forced shift in their activity, rats also shift their food intake. This translates into a disappearance of normal glucose rhythms, an out-of-phase rhythm of triacylglycerols as well as the appearance of an additional corticosterone peak at the beginning of their “work” period during the day -- in addition to the normal endogenous peak occurring at the beginning of the night [26 *]. Strikingly, this shift work schedule is accompanied by alterations of rhythms in several hypothalamic structures but not the SCN [27 *].

In a more recent paper, Karatsoreos and collaborators produced internal desynchronization by exposing mice to a 10h-light:10h-dark(LD10:10) schedule for several weeks. Mice are unable to entrain their activity rhythms to such a light:dark regime and therefore exhibit circadian locomotor behavior reflecting their endogenous period of about 24h [28 **]. Although hormonal rhythms were not assayed, their alteration may be responsible for the decreased complexity of the neurons in the medial prefrontal cortex; they show a prominent shortening of apical dendrites. Mice subjected to this protocol also manifested behavioral defects known to be dependent on the prefrontal cortex, as they exhibit a reduced ability to modify a learned behavior and also have a decreased latency to enter a novel environment [28 **]. Strikingly, these are similar to behaviors observed in animal with medial prefrontal cortex lesions [29].

These and other data converge on a model in which internal desynchronization results from conflicts between SCN-driven environmental rhythms and internal rhythms. It affects the entrainment of peripheral clocks and results in altered gene expression within forebrain structures (see below). Interestingly, the internal desynchronization observed after SCN ablation [5; see above] can be overcome by treating the animals with stimulation that provide a strong and rhythmic internal signal. For example, restricted food access or methamphetamine exposure can synchronize the circadian phase of peripheral brain regions of SCN-lesioned arrhythmic mice [30 *]. It is also noteworthy that treatments of mice [31] and human [32] aimed at reinforcing biological rhythms reduce the neuropathological symptoms associated with some psychotic disorders. This presumably occurs by reinforcing peripheral oscillations and implies that some disorders are intimately linked to circadian difficulties, which may even be a more proximate cause of these symptoms.

3. Alteration of sleep in neuropsychiatric disorders: a wider role of clock genes?

Sleep is controlled by the interaction of two components: a circadian component, which controls the timing of sleep, and a homeostasis component, which reflects sleep need [reviewed in 33]. Deterioration of sleep is often associated with neuropsychiatric disorders like depression [34], bipolar disorders [35], schizophrenia [36] and attention deficit hyperactivity disorder [37]. The relationship between sleep and these illnesses appears intimate. Indeed, treatments aimed at ameliorating disease often improve sleep quality. Moreover, sleep deprivation has a spectacular but transient antidepressant effect in humans [reviewed in 38]. It remains unresolved whether the deterioration of sleep associated with mental illnesses is another consequence of circadian dysfunction or whether it is a different

manifestation of the disorder. Further research should provide insight into the links between sleep and mental illness, and the possible role of circadian clocks.

4. Association of clock gene polymorphims/SNPs with psychotic disorders

Single-nucleotide polymorphisms (SNPs) in clock genes have been associated with almost all neuropsychiatric disorders [reviewed in 39,40]. Although this may constitute additional evidence linking the circadian clock to psychotic disorders, this remains uncertain as the literature often reports conflicting results. SNPs in clock genes represent only a small fraction (~5–10%) of all SNPs linked to neuropsychiatric disorders and the effects they have on gene expression are still unknown because experimental validation is lacking. These issues should be addressed in the future.

5. Mutations/alterations of gene expression of clock genes and psychotic disorders

Cloning of mammalian clock genes almost 15 years ago was quickly followed by the generation of knockout mice in which their biological functions were assayed. Circadian phenotypes were addressed first and indicated that clock genes are necessary and sufficient for the generation of biological rhythms [reviewed in 1]. Follow up experiments, however, revealed a much broader role of these genes: knock-out mice were more prone to develop a wide range of illnesses including metabolic diseases, cancer, arthropathy, and hypertension. These results collectively highlight the importance of clock gene expression within peripheral clocks as well as how their impairment can lead to physiological disorders. Strikingly, clock mutant mice also develop symptoms similar to those seen in human neuropsychiatric disorders. We will discuss below the three best-characterized examples.

5.1 *Clock* and mania-like behavior

The first clock-mutant mouse was reported after a *N*-ethyl-*N*-nitrosourea mutagenesis screen [41]. Characterization of the point mutation revealed the generation of a dominant negative protein within the gene *Clock* in which exon 19 was skipped, hence $CLK_{\Delta}{}^{19}$ [42]. In addition to circadian [41], metabolic [43], reproductive [44] and sleep disorders [45], $Clk_{\Delta}{}^{19}$ mice also exhibit behavioral alterations that are symptomatic of mania-like behavior in human [46]. They 1) are hyperactive, 2) sleep less than wild-type littermates, 3) show reduced anxiety and depression-like behavior, 4) show less helplessness, and 5) exhibit an increased propensity for drug abuse [46].

Importantly, most of these effects seem to depend on *Clk* function within the VTA. Indeed, rescue of $Clk_{\Delta}{}^{19}$ with functional CLK protein only in this region restores wild-type hyperactivity and anxiety-related behavior [46]. In addition, specific RNA interference knockdown of *Clk* only in the VTA of wild-type mice causes many of the above-mentioned symptoms, such as a hyperactive response to novelty and less anxiety-related behavior [47 **]. These effects appear to be accompanied by increased dopaminergic response since both the $Clk_{\Delta}{}^{19}$ mutation and the *Clk* knockdown enhance the firing rates of dopaminergic cells in the VTA [46,47 **].

The role of CLOCK as a transcription factor seems to be important for these behavioral changes, as the *Clk* knockdown within the VTA also leads to changes in the expression of several genes. Importantly, many of them encode for channels and channel-associated proteins as well as genes involved in the dopamine synthesis, regulation or metabolism. Expression of these genes may therefore make major contributions to the behavioral and physiological defects observed in both $Clk_{\Delta}{}^{19}$ and VTA-specific *Clk* knockdown mice [47 **]. It is however still unknown whether these genes are directly or indirectly regulated by

CLK. Some of them are, such as the gene monoamine oxidase A (*Maoa*), which encodes an enzyme that degrades amine neurotransmitters like dopamine [48]. MAO activity in the VTA and the nucleus accumbens (NAC) is decreased in $Per2^{Brdm1}$ mutant mice and dopamine levels increased [48].

A recent paper reported altered neuronal functions in the NAC of Clk_{Δ}^{19} mice, which may also contribute to aspects of the mania-like behavior [49 **]. The authors show that the phase coupling of low-gamma to delta oscillations in the NAC is negatively correlated with the extent to which wild-type mice explore a novel environment. Clk_{Δ}^{19} mice, which become hyperactive when placed in a novel environment, exhibit a profound alteration of this phasic entrainment. These physiological and behavioral phenotypes may be explained by the complex changes in dendritic morphology of NAC neurons as well as reduced GluR1 expression in the mutant relative to wild-type mice [49 **]. Importantly, chronic lithium treatment, which is frequently prescribed to patients suffering from bipolar disorder, suppresses the exploratory drive of Clk_{Δ}^{19} mice and ameliorates several of these morphological effects as well as neurophysiological deficits.

Because there is no NAC-specific study, it is not clear whether these effects are due to *Clk* loss-of-function within the NAC or whether they originate elsewhere, for example with the altered dopaminergic signaling from the VTA. In any case, these papers highlight the numerous molecular, cellular and physiological alterations within the mesolimbic brain regions of Clk_{Δ}^{19} mice, which may be directly responsible for the development of mania-like behaviors.

5.2 Clock genes and sensitivity to drug of abuse

Neuropsychiatric disorders carry with them an increased risk of drug abuse. Co-occurrence of both serious mental illness and substance dependence, or abuse, was found in 4 millions adults in the USA in 2002 (source from the National Drug Intelligence Center). The mania-like behavior phenotype of Clk_{Δ}^{19} mice along with their sensitivity to drug of abuse [50] is reminiscent of this co-occurrence. The relationship between clock genes and drugs of abuse is even more widespread and extends to *Drosophila* where it was first observed [51]. Since this has been recently reviewed in detail [52,53], we will just summarize here the major conclusions.

First, many circadian mutant mice exhibit an altered response to drugs of abuse such as alcohol, cocaine, metamphetamine and morphine. In the case of cocaine for example, Clk_{Δ}^{19} [50] and *mPer2* [54] mutant mice have a hypersensitized reponse. *mPer1* [54] and *Npas2* [53] knockout mouse respond in the opposite way, i.e., they lack a sensitized behavioral response. Understanding why different clock gene mutants display opposite cocaine sensitivity should provide insight into how clock genes are involved in drug addiction.

Second, chronic or acute administrations of drugs of abuse such as cocaine can directly induce clock genes expression (mainly *Per1* and *Per2*) within the striatum [22,55], nucleus accumbens [56] and hippocampus [22]. There are obvious similarities with the classical light-induced expression of *Per1* and *Per2* within the SCN [e.g., 4], making it tempting to speculate that drug-induced *Per1* and/or *Per2* expression in peripheral clocks may perturb the timing of downstream gene expression.

Third, effects on clock gene expression are also observed after withdrawal of drugs of abuse. For example, expression of *Per1* and *Per2* after morphine withdrawal in rats seems to be out-of-phase within several mesolimbic structures despite no phase change within the SCN [23]. The phase alterations could explain, at least in part, why $Per2^{Brdm1}$ mutant mice show attenuated withdrawal symptoms compared to wild-type [57].

In conclusion, these results demonstrate that drugs of abuse can affect clock gene expression and therefore induce out of phase molecular oscillations within the mesolimbic system. Because clock genes regulate the expression of many output genes (see below), they may have an important role in the etiology of addiction. This may be relevant to the finding that *Per2*^{Brdm1} mutant mice show an alteration of their glutamatergic system, which may be responsible for the increase in alcohol intake in this strain [58].

5.3 Alteration of memory formation and consolidation in clock-impaired animals

Patients suffering from emotional and affective disorders often exhibit a reduced ability to access specific memories of life events [reviewed in 59]. These memory defects involve the mesolimbic system and particularly the hippocampus, which plays an important role in the consolidation of information from short-term to long-term memory.

Several reports have highlighted the importance of the circadian system in hippocampal-dependent memory function [reviewed in 60,61]. For example, lesions of the SCN or light-induced phase-shifts (i.e., jet-lag) impair hippocampus-dependent long-term memory [62–64]. Long-term potentiation (LTP), which is the long-term enhancement in synaptic response occurring after strong, repetitive stimulation, may be linked to these defects; LTP amplitude varies with the time of the day in rodents [65]. Moreover, and despite some conflicting results [66], clock gene mutant mice exhibit defects in hippocampus-dependent memory formation [67–70]. Similarly, wild-type hamsters rendered arrhythmic (by a combination of nighttime light treatments for two consecutive nights) also show altered hippocampus-dependent long-term spatial learning [71]. Importantly, a recent paper demonstrated that hippocampal circadian oscillations are directly required for memory formation and persistence: local pharmacological inhibition of circadian rhythms of MAPK activity only within the hippocampus blocks long-term memory formation [72 **].

Dentate gyrus neurogenesis constitutes another notable aspect of the circadian control of the hippocampus biology. Neurogenesis is associated with learning and memory and the number of newborn hippocampal neurons increases after a hippocampus-dependent learning task [reviewed in 73]. Interestingly, the well-described effect of exercise (e.g., wheel-running activity) on neurogenesis is modulated by the circadian system. Indeed, running activity significantly increases cell proliferation, cell survival, and the total number of new neurons only when animals have access to the wheel for 3hrs in the middle of the dark (active) period [74]. Experimental jet-lag (a 6hrs phase advance every 3 days for 25 days) results in internal desynchronization and also inhibits cell proliferation and neurogenesis in adult hamsters [75 **]. The effect on cell proliferation is dependent on a jet-lag increase in glucocorticoids levels. This circadian disruption results in pronounced deficits in learning and memory, which parallel the marked reductions in hippocampal cell proliferation and neurogenesis. Significantly, deficits in hippocampal-dependent learning and memory also persisted well after the cessation of jet lag, suggesting long-lasting negative consequences on brain function [75 **]. Although long-lasting internal desynchronization has not yet been shown to affect neurogenesis in humans, this may reveal new links between circadian biology and learning and memory mechanisms. Because glucocorticoids have been strongly involved in the regulation of memory in humans [reviewed in 76], they may represent the primary target for further investigation.

6. Regulation of gene expression by clock genes

Whether it occurs because of internal desynchronization or because of a mutation, misexpression or mistiming of clock genes within brain clocks likely affects the expression of many downstream genes, called clock-controlled genes (figure 1). In turn, these changes may account for some of the symptoms observed in patients suffering from psychotic

disorders. The current model for the generation of molecular rhythms posits that clock genes interact in transcriptional feedback loops to generate rhythms of about 24hrs and entrain widespread expression of rhythmic transcripts (figure 1; see also §1.1). This has been recently reviewed in detail [e.g., 77,78,79].

Despite considerable work in multiple systems, the molecular events leading to the generation of circadian rhythms are still not very well understood. Moreover, the current model of feedback loops is probably over-simplified with many more regulatory mechanisms yet to be described. One general question also arises: are the symptoms observed after circadian challenge only due to improper rhythmic transcription (i.e., disappearance or improper expression of rhythmic transcripts)? Or are they resulting from a more widespread alteration in gene expression that extends beyond rhythmic transcription? Until now, most of the genome-wide studies investigating dysfunction of peripheral clocks have mainly considered rhythmic transcripts. Future experiments should address whether this kind of analysis is the most relevant.

7. Conclusions

The discovery that autonomous clocks exist in virtually all organs of the human body has led to the concept that biological rhythms within these tissues were important to optimize biological functions with daily environmental fluctuations. However, malfunctions of these peripheral clocks are associated with more than just improper temporal organization. The brain clocks are no exception, as deregulation of oscillators within the mesolimbic system is associated with many symptoms observed in patients suffering from neuropsychiatric disorders. Importantly, this deregulation occurs at both the systems and molecular levels.

It is apparent that brain clock dysfunction leads to a wide range of symptoms. Our current understanding will undoubtedly be deepened by recent advances in mammalian genetic tools, which now allow better temporal and spatial controls of gene expression. Importantly, the emerging notion that well-synchronized internal rhythms reduce the incidence and severity of symptoms associated with human mental illnesses holds considerable therapeutic promise and may even contribute to an enhanced understanding of disease etiology.

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2 stars, of outstanding interest:

1 star, of special interest:

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Highlights

- Deregulation of brain clocks is associated with neuropsychiatric disorders
- Deregulation occurs at both the system and molecular levels
- Misexpression of the gene *Clk* in the mesolimbic system induces mania-like behavior
- Mutation of clock genes affect sensitization to drugs of abuse and addiction
- Deregulation of clocks in the hippocampus alters memory formation and consolidation

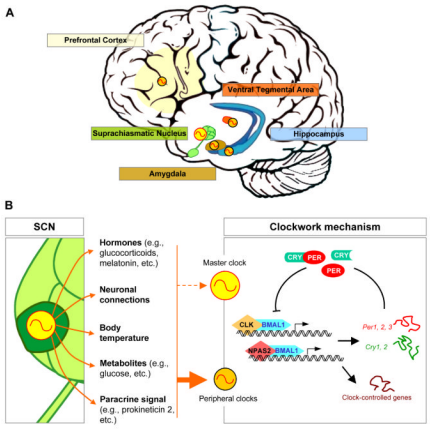

Figure 1. Multi-levels organization of the circadian system in the human brain

A/ Clocks are found in many different cerebral structures, including those involved in the neuropsychiatric disorders. These are called peripheral clocks (orange), and contrast with the master circadian clock (yellow) located in the suprachiasmatic nucleus (SCN) of the hypothalamus.

B/ As a master clock, the SCN generates and synchronizes many biological rhythms such as hormones, neuronal connections, body temperature, metabolites and paracrine signals. These circadian signals in turn entrain the molecular clockwork within peripheral clocks, so that their biological and physiological functions are optimal at the most appropriate times of day (plain, thick arrow). The SCN is, in contrast, resistant to most rhythmic signals it synchronizes (dashed, thin arrow).

The molecular clockwork in humans relies on transcriptional feedback loops in which the transcriptions factors BMAL1, CLK and NPAS2 rhythmically activate the expression of their transcriptional repressors *Per* and *Cry* genes, as well as many other “clock-controlled genes”. Clock-controlled genes are the output of the clocks and contribute to their rhythmic physiology.

External factors that desynchronize rhythmic signals within peripheral oscillators, as well as genetic mutation of clock genes, provoke improper clock function, which impacts on overall gene expression. Such a clock malfunction within brain oscillators accounts for some of the symptoms observed in patients suffering from neuropsychiatric disorders.