Title	Habenula and ADHD: Convergence on time.
Author(s)	Lee, Young-A; Goto, Yukiori
Citation	Neuroscience and biobehavioral reviews (2013), 37(8): 1801-1809
Issue Date	2013-09
URL	http://hdl.handle.net/2433/178664
Right	© 2013 Elsevier Ltd.
Type	Journal Article
Textversion	author

Habenula and ADHD: Convergence on Time

Young-A Lee & Yukiori Goto

Primate Research Institute, Kyoto University, Inuyama, Aichi, 484-8506, Japan

Address Correspondence:
Yukiori Goto, Ph.D.
Primate Research Institute
Kyoto University
41-2 Kanrin
Inuyama, Aichi
484-8506
Japan
Phone: +81(0)568-63-0551
Fax: +81(0)568-63-0551
E-mail: goto.yukiori.5c@kyoto-u.ac.jp

Number of Pages: 43 pages
Abstract: 138 words
Text: 5,430 words
Figures: 1
Tables: 0
References: 111

Abstract

Attention deficit/hyperactivity disorder (ADHD) is a childhood-onset psychiatric condition characterized by hyperactivity, impulsivity, and attention deficit. In addition to these core symptoms, accumulating evidence suggests that ADHD may also involve alterations in circadian rhythms, sleep disturbance, and time perception. The habenula is a brain region transmitting limbic information into the midbrain monoamine systems and thereby involved in regulation of monoamine release in the target brain areas such as the striatum, where is a part of biological substrates processing time perception. Moreover, the habenula is a part of the circadian rhythm network and involved in sleep regulation. Our recent study provides a new insight that habenula lesion given in early development produces behavioral and brain alterations resembling to those observed in ADHD. We propose that the habenula may be a promising target for understanding of the pathogenesis of ADHD.

Content

1. Introduction

2. Sleep, Circadian Rhythms, and Time Perception Deficits in ADHD

    2.1 Sleep and Circadian Rhythm Deficits in ADHD

    2.2 Altered Time Perception in ADHD

3. The Role of the Habenula in Sleep, Circadian Rhythms, and Time Perception

    3.1 Neural Network Organization of the Habenula

    3.2 Habenula in Circadian Rhythms and Sleep

    3.3 Dopamine Transmission in Time Perception

    3.4 Implication of Habenula Deficit in ADHD

4. Neonatal Habenula Lesion as a Novel Animal Model of ADHD

    4.1 Behavioral Effects of Neonatal Habenula Lesion

    4.2 Physiological Changes Caused by NHL

    4.3 NHL with Nicotine Microinfusion into the Habenula

    4.4 NHL as a Novel Animal Model of ADHD

5. ADHD and Depression Linked with Habenula Deficit

6. Conclusion

Acknowledgements

References

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a childhood onset psychiatric condition, consisting of the core symptoms of hyperactivity, impulsivity, and attention deficit. These symptoms in ADHD children take characteristic developmental patterns. Thus, hyperactivity and impulsivity tend to wane as ADHD children grow into adulthood, whereas attention deficit persist even at adulthood (Spencer et al., 2007). These patterns of symptom emergence and waning through development could be an important clue to understand the biological mechanisms of this disorder. Indeed, such developmental changes of the symptoms may be associated with delayed maturation process of the brain suggested in ADHD (Shaw et al., 2007a). In contrast, however, it is unfortunate that developmental dynamics of symptom waning/persistence have been relatively ignored in most animal model studies in which behavioral and brain abnormalities are examined only in adult animals.

The pathophysiology of ADHD is suggested to involve dopamine (DA) deficits, specifically based on the observation that therapeutic treatments of ADHD are achieved with DA agonists such as amphetamine and methylphenidate. Recent genetic studies also confirm DA deficits in ADHD. For instance, Gizer et al. have reported that *DRD5* 148 bp allele is associated with ADHD children (Gizer et al., 2009). Moreover, adult ADHD subjects with the 7-repeat allele of the *DRD4* gene polymorphism have been shown to exhibit smaller volume in the dorsolateral prefrontal cortex and cerebellum (Monuteaux et al., 2008). Shaw et al. unveiled that the *DRD4* 7-repeat allele adolescent ADHD subjects was associated with a thinner right

orbitofrontal/inferior prefrontal and posterior parietal cortex (Shaw et al., 2007b). Durston et al. also reported that 4R-repeat allele of *DRD4* gene preferentially influences prefrontal gray matter volume in adolescent ADHD subjects (Durston et al., 2005). Nonetheless, alteration of DA D4 or D5 receptor expression or function with functional imaging or postmortem tissue in ADHD individuals has not been reported to date. Dopamine transporter (DAT) has been also thought to be involved in ADHD. Cook et al. have reported an association between ADHD children and the 10-repeat allele of a tandem repeat polymorphism located in the 3′ untranslated region of the *DAT* gene *SLC6A3* (Cook et al., 1995). Brown et al. have shown that adult ADHD individuals homozygous for the 10-repeat allele of *SLC6A3* exhibit hypoactivation in the anterior cingulate cortex (Brown et al., 2010). It was also reported that the 9-repeat allele in the *DAT1* gene, which is predominantly expressed in the basal ganglia, preferentially influences caudate volume in adolescent ADHD subjects (Durston et sl., 2005). Nevertheless, imaging studies investigating DAT expression in the striatum of adult ADHD subjects have reported highly controversial results with either increase (Dougherty et al., 1999; Larisch et al., 2006), decrease (Volkow et al., 2007), or no change (van Dyck et al., 2002) of expression of DAT expression.

Other catecholamines including norepinephrine (NE) has also been proposed to play a key role in the pathophysiology and pharmacotherapy of ADHD. Clinical evidence reported dysregulation of the NE system in ADHD individuals, whereas the NE transporter blocker atomoxetine and the α_{2a} noradrenergic receptor agonist guanfacine alleviate symptoms in ADHD adults and children (Pliszka, 2005; Biederman and Spencer, 1999; Hunt et al., 1995).

The habenula is a brain region linking limbic structures and midbrain monoamine systems (Bianco and Wilson, 2009; Hikosaka, 2010). Increasing attention has been given to the function of the habenula as it relates to its regulation of monoamine transmission in cognitive/affective behaviors (Hikosaka, 2010). Deficits of the habenula have been also implicated in psychiatric disorders such as mood disorders (Ranft et al., 2010; Sartorius et al., 2010; Savitz et al., 2011) and schizophrenia (Shepard et al., 2006), but not in other disorders including ADHD, to date.

In this review article, we first summarize some characteristics of ADHD associated with time processing such as disturbance of circadian rhythms and sleep patterns, and altered time perception. Then, we describe function and dysfunction of the habenula in circadian rhythms, sleep regulation, and time perception. Finally, we discuss that, along with our recent findings of neonatal lesion of the habenula producing behavioral and brain alterations resembling to those observed in ADHD, the relationship between habenula deficits and the pathogenesis of ADHD.

2. Sleep, Circadian Rhythms, and Time Perception Deficits in ADHD

2.1 Sleep and Circadian Rhythm Deficits in ADHD

Sleep disturbance was one of diagnostic criteria used for diagnosis of ADHD in DSM-III, which is, however, eliminated in the subsequent DSM editions, including up-coming DSM-V. This may be because subjective vs. objective reports of sleep problems are often inconsistent (O'Brien et al., 2003), or sleep disturbance is not a useful criterion for diagnosing purpose, as it is not specific for ADHD, but also observed in other psychiatric conditions. Nevertheless, it is estimated that approximately one third of medication-free children and adults with ADHD suffer from sleep problems (Corkum et al., 1999; Stein, 1999), and approximately half of parents who have children with ADHD have reported that their children have sleep problems (Sung et al., 2008). The sleep disturbances observed in ADHD children include unstable pattern of sleep, such as variable timing of sleep and awake (Gruber et al., 2000), difficulty on initiating sleep (e.g. delayed onset of sleep and bedtime resistance) (Corkum et al., 1999; Stein, 1999), lower sleep efficacy with increased wake bouts (Marcotte et al., 1998), and higher level of nocturnal activity (Konofal et al., 2001). Sleep-related disorders such as habitual snoring (≤ 25%), periodic limb movement disorder (~40%) and restless legs syndrome (≤ 25%) are also common in ADHD children (Chervin et al., 2002). Studies with polysomnographic measurements of sleep state in ADHD adults and children have been conducted by several research groups. These studies (Greenhill et al., 1983; Gruber et al., 2000; Khan, 1982; O'Brien et al., 2003; Sobanski et al., 2008), except those from one research group that has repeatedly reported increased period (Kirov et al., 2004), found decreased period of rapid eye movement (REM), but not non-REM, sleep in ADHD compared to age-matched normal subjects.

Sleep disturbance in ADHD may be explained by several mechanisms. For instance, the symptom such as hyperactivity would make ADHD children difficult to settle down into sleep (O'Brien et al., 2003). However, the observed patterns of sleep disturbance in ADHD subjects appear to be best explained by the deficit in the mechanism of circadian rhythms. Indeed, the endogenous circadian timekeeping mechanism is a pivotal regulator of the sleep-wake cycle, which interacts with the homeostatic system in determining onset and duration of sleep. There are several studies reporting altered circadian rhythms in ADHD subjects. Ironside et al. have shown that ADHD children exhibit significant increase of motor activity measured by actigraphy during the sleep-onset latency period, which in turn causes reduction of circadian amplitude of motor activity and phase-delay in the timing of the daily rhythms (Ironside et al., 2010). Delayed start and end of sleep period and associated delay of melatonin production onset have been also observed in ADHD adults and children (Van der Heijden et al., 2005; Van Veen et al., 2010; Bijlenga et al., 2013). The circadian clock gene, the circadian locomotor output cycles protein kaput (CLOCK), acts as a transcription factor, and plays an important role in the organization of circadian rhythms in mammals. At the intracellular level, CLOCK interacts with brain and muscle ARNT-like protein 1 (BMAL1) and forms a heterodimer that activates transcription of the genes period (PER2) and cryptochrome. Such circadian rhythm-associated molecular signaling cascade has been shown to be altered in ADHD. For instances, Kissling and colleagues have reported that the T-allele of re1801260 polymorphism of CLOCK gene is the risk factor in adult ADHD (Kissling et al., 2008). The recent study has unveiled that rhythmic expression of the clock genes BMAL1 and PER2 is

diminished, and cortisol level is phase delayed, in oral mucosa of adult ADHD subjects (Baird et al., 2012).

Collectively, these studies suggest that ADHD may be associated with disturbance of the mechanisms that regulate circadian rhythms and sleep.

2.2 Altered Time Perception in ADHD

Accumulating evidence suggests altered time perception in ADHD subjects. Time perception is an ability to perceive length of a time interval, and thought to be an important function in decision making (Wittmann and Paulus, 2008) and attention (Brown and Boltz, 2002). The type of attention deficit in ADHD is not orientation of attention, the ability to selectively allocate attentional resources to a particular location of the visual field, but the problem on sustaining attention, the subject's readiness to detect rarely and unpredictably occurring signals over prolonged periods of time, which is likely to be associated with altered recognition of time passage (Lu et al., 2012; Sarter et al., 2001). In addition, deficits in time perception could also cause impulsive behavior, the problem of withholding delayed response. Indeed, it is suggested that time perception in people with greater impulsivity is different from that in people without impulsivity (Wittmann and Paulus, 2008).

Time processing such as time estimation, duration discrimination and temporal (re-) production is also an important function in neuropsycologial performance. In particular, time estimation and reproduction are abilities to judge time under prospective and retrospective conditions, respectively, where such that a major difference between them are whether subjects aware or do not aware duration of time that they have to

judge in advance. Studies have consistently reported that ADHD children exhibit relatively intact time estimation of time intervals, but have a problem (less precisely perform) on time reproduction in the task in which subjects press the lever at a certain time interval (Meaux and Chelonis, 2003; Rommelse et al., 2007; Smith et al., 2002). The studies by Rommelse (Rommelse et al., 2007) and Meaux (Meaux and Chelonis, 2003) found that inaccurate time reproduction was observed regardless of durations of tested intervals (from 3 to 24 seconds), whereas the study by Smith (Smith et al., 2002) found that inaccuracy was present only at a longer duration (12, but not 5, seconds) in ADHD children. In addition, adolescent ADHD subjects were also found poor at discriminating durations of sensory stimuli regardless of stimulus modality (Toplak and Tannock, 2005).

Whether time perception is associated with circadian rhythms is currently unclear, with mixture of studies that support involvement or non-involvement of circadian rhythms on time perception (Tucci, 2012; Papachristos et al., 2011; Agostino et al., 2011; Cordes and Gallistel, 2008). However, among those studies suggesting that circadian rhythms can influence time perception, the study by Shurtleff et al. has reported that rats exhibit significantly longer estimation and reproduction of stimulus durations in the night than in the day time (Shurtleff et al., 1990). Similarly, in human subjects, circadian fluctuation of time reproduction is observed, with longer reproduction in the morning than in the night (Kuriyama et al., 2003; Kuriyama et al., 2005).

These studies suggest that the neural systems that process time perception and circadian rhythms interact with each other, and thereby disruption in circadian rhythms may alter time perception.

3. The Role of the Habenula in Sleep, Circadian Rhythms, and Time Perception

3.1 Neural Network Organization of the Habenula

The habenula consists of two distinct nuclei: the medial (MHb) and lateral (LHb) habenula (Fig. 1a, b; Paxinos and Watson, 2005). Although the MHb and LHb have common afferent inputs and efferent targets, the MHb and LHb are represented by largely distinct circuits. Thus, the MHb primarily receives synaptic inputs from the septum, and sends outputs through fasciculus retroflexus (FR) into the interpeduncular nuleus (IPN), which in turn projects to midbrain monoamine neurons (Bianco and Wilson, 2009; Hikosaka, 2010). In contrast, the LHb receives inputs from the hypothalamus, prefrontal cortex (PFC), and basal ganglia, and sends outputs directly to midbrain nuclei such as the ventral tegmental area (VTA) and dorsal raphe where DA and serotonin (5HT) neurons are located, respectively (Fig. 1c; Bianco and Wilson, 2009; Hikosaka, 2010). In agreement with such network organizations of the MHb and LHb, lesion of the LHb increases DA release in PFC and nucleus accumbens (NAcc; Lecourtier et al., 2008), consistent with the finding that the LHb provides

inhibitory tone on DA neurons (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). In contrast, lesion of the MHb or LHb attenuates 5HT release, whereas electrical stimulation of the LHb promotes 5HT release, in 5HT-innervated brain regions such as the PFC, striatum, and the hippocampus (Amat et al., 2001; Kalén et al., 1989; Nishikawa and Scatton, 1985), suggesting that the habenula provides excitatory tone on 5HT neurons.

In the circadian network of mammals, the suprachiasmatic nucleus of the hypothalamus (SCN) serves as a pacemarker with receiving light signals from the retina through the retinal hypothalamic tract, which in turn produces synchronized rhythms of behavior and physiological activity through alignment of circadian gene oscillation in extra-SCN neurons and peripheral tissues. Wiring of the neural circuit generating circadian rhythms involves projections of the SCN to a wide range of the brain nuclei such as the arcuate nucleus, paraventricular nucleus, lateral hypothalamic area and the brainstem including VTA. In addition, circadian rhythms in the hypothalamus and brainstem can be also regulated by other factors than light such as peptidergic hormones and nutrients (Huang et al., 2011; Bass and Takahashi, 2010). In particular, DA signaling in VTA neurons that is implicated for a reward mechanism associated with feeding could also be a regulator for circadian variation (Fig. 1d; Huang et al., 2011), and may be involved in ADHD pathology. SCN regulates pineal melatonin biosynthesis as an output of the clock. Along with other neuronal and hormonal mechanisms, a rhythmic melatonin level could regulate sleep-wake cycles and coordinate peripheral oscillator functions (Bell-Pedersen et al., 2005). Importantly, the LHb receives synaptic inputs from the SCN, the brain region thought to be the center of

circadian rhythms (Guilding and Piggins, 2007). Moreover, MHb outputs also target the pineal gland, where melatonin is synthesized (Rønnekleiv and Møller, 1979), suggesting that the habenula is a part of the circadian network.

3.2 Habenula in Circadian Rhythms and Sleep

Because of its connection with the SCN and pineal gland, habenula consists of a part of the circadian network. More than a half (~70%) of LHb neurons and lesser amount (~25%) of MHb neurons are responsive to retinal illumination (Zhao and Rusak, 2005). Moreover, these neurons exhibit circadian rhythms on spiking activity, with higher spike firing activity during day time than at night (Zhao and Rusak, 2005). This suggests that LHb may provide inhibitory influence on melatonin synthesis in the pineal gland. Indeed, habenula neurons have been shown to inhibit DA neurons, although they send excitatory outputs to the target areas (Hikosaka, 2010). LHb cells in the medial portion of the nucleus also exhibit circadian oscillation of expression of the core clock genes and proteins, per2/PER2 (Guilding et al., 2010). This circadian oscillation of gene and protein expression was not blocked by the sodium channel blocker, tetrodotoxin, indicating that rhythmic expression has intrinsic timekeeping properties (Guilding et al., 2010), which is similar to what is observed in SCN neurons (Yamaguchi et al., 2003). Similarly, Wyse and Coogan have also reported rhythmic expression with circadian rhythms of clock genes including CLOCK and BMAL1 in the habenula during adult period, and their alterations with age-associated circadian dysfunction (Wyse and Coogan, 2010). In addition, the study by Tavakoli-Nezhad and Schwartz has reported that c-fos immediate early gene expression in LHb cells also

fluctuates with circadian rhythms. They found that under the constant day light, c-fos expression in the LHb was higher during active phase (such as running in wheels), which is consistent with the c-fos expression pattern observed in the SCN (Tavakoli-Nezhad and Schwartz, 2006). However, it is important to note that expression of clock genes and proteins is also observed in peripheral tissues (e.g. fibroblasts), such that expression of these genes in the habenula does not necessarily reflect regulation mechanisms of circadian rhythms.

Lesion of the habenula or its outputs, the FR, causes sleep and circadian rhythm alterations. Studies have consistently shown decreased REM sleep without affecting non-REM sleep (Haun et al., 1992; Paul et al., 2011; Valjakka et al., 1998). Paul and colleagues have shown that transection of FR increases locomotor activity both in daytime and night (Paul et al., 2011). Hyperlocomotion observed in these animals appears to be associated with novel environments (Paul et al., 2011), whereas hyperactivity observed in ADHD children is present even in familiar environments. In particular, however, increased locomotion at night was due to decreased periods of inactivity including sleep, resulting in undifferentiated pattern of day-night circadian locomotor activity. Such habenula lesion-induced sleep pattern changes are indeed not exactly identical to the sleep problems including the most frequently observed chronic sleep onset insomnia observed in ADHD adults and children (Van Veen et al., 2010; Van der Heijden et al., 2005; Bijlenga et al., 2013), but still appear to have commonality in some aspects. FR lesion also markedly decreases the muscle atonia component during REM sleep and reduces duration of REM sleep episodes compared to normal animals (Haun et al., 1992). The study by Valjakka et al. has also reported that FR

lesion induces reduction of REM sleep to be ~80%, intermediate state of sleep to be ~30%, and quiet waking state to be ~50%, of the normal condition, but duration of non-REM sleep and active waking are not altered (Valjakka et al., 1998). Collectively, these studies suggest that the habenula and its output brain structures are the important system of sleep and circadian rhythm regulation.

3.3 Dopamine Transmission in Time Perception

Although there has been no direct evidence that the habenula may play a role in time perception, this brain region may still be involved in time perception through regulation of striatal DA release (Lecourtier et al., 2008). Indeed, accumulating evidence suggests that striatal DA transmission plays a critical role on time perception. The evidence in human subjects primarily comes from studies with patients with Parkinson's disease (PD), which is mainly caused by degeneration of nigrostriatal DA innervations, but degeneration of NE and 5HT neurons is also involved (Scatton et al., 1983). In PD patients, greater amount of variability in time estimation and reproduction and improvement by administrations of the DA/NE precursor L-DOPA has been observed (Pastor et al., 1992). It appears that such impairments are specifically in the range of second, but not millisecond, time intervals (Koch et al., 2008). In addition to PD studies, Yang and colleagues have also reported that in schizophrenia patients, strong association is found between striatal DA D2 receptor binding and the disruption of optimal time performance in finger tapping test (Yang et al., 2004).

Numerous animal studies further support the evidence of striatal DA transmission in time perception. In animals, time perception has been typically tested

with the temporal reproduction task, which involves the peak-interval procedure, with lever pressing at the fixed interval. Lesion of the nigrostriatal DA innervations has been shown to abolish fixed timing lever press (Meck, 2006). Administration of psychostimulants such as amphetamine (Maricq and Church, 1983) or DA D2 agonists (Santi et al., 2001) and DAT knockout (Meck et al., 2012) produced the leftward shift (i.e. lever pressing at shorter interval), whereas administration of antipsychotic drugs (Maricq and Church, 1983; Meck, 2006) produced the rightward shift (i.e. lever pressing at longer interval), of timing function in the test. Although some psychostimulants and antipsychotics interact with NE and 5HT receptors, Meck discovered that affinity for the striatal DA D2 receptor, but not other aminergic receptors predicted potency of these drugs on producing alterations of time perception (Meck, 1983). Collectively, these studies suggest that feeling of time passage may become slower or faster with increased or decreased striatal DA release, respectively.

3.4 Implication of Habenula Deficit in ADHD

The habenula has not been a major concern in the research field of ADHD to date. Nevertheless, the roles of the habenula in circadian rhythms, sleep regulation, and time perception are intriguing in relation to deficits of these functions in ADHD. In particular, lesion of habenula outputs decreases REM sleep (Haun et al., 1992; Paul et al., 2011; Valjakka et al., 1998), REM muscle atonia (Haun et al., 1992), and circadian amplitude of motor activity (Paul et al., 2011). In ADHD adults and children, decreased REM sleep has been shown in several studies with polysomnography (Greenhill et al., 1983; Gruber et al., 2000; Khan, 1982; O'Brien et al., 2003; Sobanski

et al., 2008). Moreover, less differentiated motor activity (Ironside et al., 2010) and higher level of nocturnal activity (Konofal et al., 2001) has been also described. Thus, these sleep problems observed in ADHD subjects are consistent with the sleep pattern alterations induced by habenula lesion. These common sleep problems observed between ADHD subjects and animals with habenula lesion may be nested in the same root: alteration of circadian rhythms. However, it is also important to note that there is no direct evidence for relation between circadian clocks and REM/non-REM transitions, such that the mechanisms other than circadian rhythms may indeed be involved. Moreover, given that the sleep problems in ADHD varies from those onset, duration, architecture, and disruption by extraneous factors such as uncontrolled motor activity, which could be mediated by distinct mechanisms, habenula deficit is most likely to be involved in only one or some, but not all, aspects of the sleep problems.

Altered time perception is another similarity between ADHD individuals and animals with habenula lesion. ADHD children exhibit altered time perception with impairment especially in time reproduction and discrimination (Smith et al., 2002). It has been suggested that time perception is associated with striatal DA release. Biochemical and electrophysiological studies indicate that the habenula is an important region for control of DA release. Electrical stimulation of the LHb has been shown to inhibit activity of DA neurons in the substantia nigra and VTA (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). Moreover, pharmacological inactivation of the habenula increases DA release in the striatum (Lecourtier et al., 2008). Thus, although direct evidence of the habenula involvement in time perception has not yet been emerged, it is no doubt that habenula deficit would compromise time perception by

altering striatal DA release. Since striatal DA release is expected to be augmented with habenula lesion, altered time perception by habenula lesion may be similar to that caused by DA agonists (i.e. feeling of slower time passage). This is consistent with what has been suggested in altered time perception in ADHD children (Smith et al., 2002).

4. Neonatal Habenula Lesion as a Novel Animal Model of ADHD

4.1 Behavioral Effects of Neonatal Habenula Lesion

We recently examined the effects of habenula lesion given at early brain development in rodents (Lee and Goto, 2011). We found that this neonatal habenula lesion (NHL) caused hyperlocomtion, impulsivity, and attention deficits in juvenile rats. However, hyperlocomotion and impulsivity diminished when animals reached adulthood, whereas attention deficit persists. Moreover, administration of low dose of amphetamine improved these behavioral changes, consistent with the symptoms and pharmacotherapeutic treatments of ADHD. It is also worth to note that NHL also causes augmented responses to amphetamine when animals with NHL reaches adulthood, which is in agreement with the reports that adult ADHD subjects are more vulnerable to psychostimulants (Faraone et al., 2007).

4.2 Physiological Changes Caused by NHL

We further explored cellular and anatomical changes associated with NHL-induced behavioral deficits (Lee and Goto, 2011). In particular, NHL induced decreased expressions of DA D3 receptor in the dorsomedial PFC and DAT expression in the NAcc core of juvenile rats. However, these alterations were not observed when animals reached adulthood. We also found that PFC volume was smaller in rats with NHL than that in normal animals, and this alteration was present both in juvenile and adult rats. Our study further suggests that decreased DA D3 receptor in the PFC is associated with impulsivity, decreased DAT expression in the NAcc is associated with hyperlocomotion, and PFC volume reduction is associated with attention deficits. Indeed, such correlations do not necessarily confirm causal links. However, these associations are also supported by the findings that 0.5 mg/kg of amphetamine administration improved hyperlocomotion, but worsened impulsivity and attention deficit, suggesting that hyperlocomotion may be caused by the alterations that are distinct from those causing impulsivity and attention deficit. Both attention deficit and PFC volume reduction were present in both juvenile and adult NHL rats, whereas hyperlocomotion and impulsivity as well as altered NAcc DAT and PFC DA D3 receptor expression were observed only in the juvenile period.

These NHL-induced alterations are partly complied with cellular and anatomical findings depicted in ADHD subjects. Human imaging studies investigating DAT expression in the striatum of adult ADHD subjects have reported highly inconsistent results with mixture of increase (Dougherty et al., 1999; Larisch et al., 2006), decrease (Volkow et al., 2007), or no change (van Dyck et al., 2002). PFC volume reduction with NHL is consistent with the findings of thinner PFC gray matter

in ADHD children, adolescents, and adults than that of age-matched normal subjects (Batty et al., 2010; Makris et al., 2007; Narr et al., 2009; Seidman et al., 2006), which also correlates with attention deficit (Makris et al., 2007; Seidman et al., 2006). Cortical DA D3 receptor expression change is not reported in ADHD subjects. Although genetic studies suggest potential DA D4 and D5 receptor deficits (Gizer et al., 2009), no anatomical or functional evidence of DA D4 and D5 receptor alteration has been provided to date. It is interesting to note that characteristic dynamics of cortical DA D3 receptor expression through development has been observed at least in rodents. Thus, cortical DA D3 receptor expression is highest during prenatal and neonatal period, and dramatically decreases toward adulthood (Demotes-Mainard et al., 1996; Gurevich and Joyce, 2000). Indeed, decreased DA D3 expression in juvenile, but not in adult, rats with NHL appeared to be associated with this characteristic developmental pattern of DA D3 receptor expression.

4.3 NHL with Nicotine Microinfusion into the Habenula

One major caveat of our finding is that NHL affected both the MHb and LHb, and therefore it was important to identify whether behavioral and physiological alterations in animals with NHL was caused by neurodegeneration in both nuclei. The MHb is one of the brain regions with the highest nicotinic receptor expression, whereas few nicotine receptors are expressed in the LHb (Clarke et al., 1984), suggesting that nicotine may yield greater influence on MHb than LHb neurons. Nicotinic receptors in the MHb are high not only in adult, but also in prenatal and neonatal periods (Winzer-Serhan and Leslie, 1997). Driven by the study showing that systemic

administration of nicotine selectively degenerates MHb neurons in adult rats (Carlson et al., 2001), we examined whether microinfusion of nicotine into the habenula of neonatal rats causes selective MHb lesion. This neonatal nicotine microinfusion (NNM) was found to produce selective MHb lesion. Our study with NNM has unveiled that hyperlocomotion, impulsivity, and attention deficit are present in juvenile rats with NNM. In contrast, however, adult rats with NNM exhibit no attention deficit, which is different from NHL in which attention deficit persist until adulthood. Moreover, amphetamine response in adult rats with NNM was attenuated, which is opposite from that in adult rats with NHL, showing augmented amphetamine response.

These NNM findings are intriguing in relation to the epidemiological studies suggesting that antenatal maternal smoking during pregnancy increases the risk of ADHD in offspring (Cornelius and Day, 2009; Linnet et al., 2003). Prenatal nicotine treatments have been also shown to produce behavioral and brain alterations in rodents (Pauly et al., 2004; Schneider et al., 2011) and primates (Slotkin et al., 2005), some of which appear to be associated with ADHD.

4.4 NHL as a Novel Animal Model of ADHD

Based on these observations, we suggest that habenula deficits occurring in early brain development may be involved in the pathogenesis of ADHD. In particular, developmental changes of altered behaviors suggest that these alterations may not be due to habenula deficit itself, since hyperactivity and impulsivity caused by NHL diminish when animals reach adulthood. On the other hand, our study suggests that altered developmental trajectory of the cortico-striatal system as consequence of

habenula deficit in early development may be associated with behavioral changes, which is consistent with the suggested pathophysiology of ADHD involving altered DAT and DA receptor function/expression in the cortex and striatum.

It is still unclear how habenula deficits may be caused during early brain development, if such deficits are really present in ADHD, since there is apparently no clear brain damage in this psychiatric condition. Brn3a is a molecule that plays an important role in neurodevelopment, and its deletion results in alterations of differentiation, migration or survival of specific neuronal populations (McEvilly et al., 1996). The study by Quina and colleagues have revealed that Brn3a is a habenula-specific marker in the forebrain, and the orphan nuclear receptor Nurr1, the product of the NR4A2 gene as the downstream of Brn3a is co-expressed with Brn3a in the habenula (Quina et al., 2009). In Brn3a mutant embryos, habenula neurons fail to innervate their targets including the IPN (Quina et al., 2009). Moreover, Brn3a knockout induces nearly complete loss of Nurr1 expression in the habenula, suggesting that Nurr1 expression depends on Brn3a in the habenula (Quina et al., 2009). These results suggest that developmental abnormalities of the habenula may involve the altered molecular signaling pathway regulated by Brn3a and its downstream, Nurr1. Interestingly, the polymorphism on the promoter region of NR4A2 gene has been identified as one of susceptible genes associated with ADHD (Smith et al., 2005), suggesting that developmental disruption of the habenula may be indeed involved in the pathology of ADHD.

5. ADHD and Depression Liked with Habenula Deficit

Abnormalities in various brain regions have been reported in ADHD subjects. Structural abnormalities, especially volumetric reductions in the PFC, somatosensory cortex, dorsal striatum, and corpus callosum are observed in ADHD subjects, although some studies have also reported no difference (Seidman et al., 2005). In contrast, however, no study has reported structurally alteration in the habenula of ADHD subjects. The habenula is a very small brain structure, and thereby it is difficult to examine this brain area with functional imaging in human subjects. Nevertheless, 3T high resolution magnetic resonance imaging enables to detect and measure the volume of the habenula by intensification of delineation between the habenula and the white matter of posterior commissure (Savitz et al., 2011; Sun et al., 2008). Recent studies have shown that the volume of the habenula is smaller in patients with mood disorders (Ranft et al., 2010; Savitz et al., 2011). Consistently, postmortem tissue study with immunohistochemical staining by Ranft et al. has also reported volumetric reductions of both medial and lateral habenula in right hemisphere of depressive patients (Ranft et al., 2010). Moreover, deep brain stimulation of the habenula yields therapeutic effects on mood disorders (Sartorius et al., 2010). In relation to these findings, it is interesting to note that major depressive disorder (MDD) is a common comorbid disorder with ADHD (Daviss, 2008; Goodman and Thase, 2009). Although it is suggested that comorbidity of MDD with ADHD may be associated with social incompatibility because of the symptoms (Daviss, 2008; Goodman and Thase, 2009), such argument appears against that fact that there are several other psychiatric disorders that involves

social deficits, but does not necessarily accompany MDD. Thus, there may be a biological explanation that ADHD subjects may be more vulnerable to mood disorders, and the habenula deficit may be one of the candidates. It is also interesting to note that MDD patients are accompanied with sleep problems (Soehner and Harvey, 2012; Harvey, 2011) as well as altered circadian rhythms (Harvey, 2011) and time perception (Kitamura and Kumar., 1983:; Sévigny et al., 2003).

6. Conclusion

Increasing attention has been recently given to the habenula as the brain region that regulates monoamine transmission such as DA, NE, and 5HT. Alterations of these neurochemical systems have been implicated in the pathophysiology of ADHD. Nonetheless, the habenula has not been considered as a target for the biological understanding of ADHD. Indeed, ADHD is most likely a multifactorial disorder, with many different causes and manifestations. Here we have argued that one of such causes involved in ADHD may be the habenula, along with a summary of studies linking function of the habenula on regulation of sleep, circadian rhythms, and time perception. Although we have not yet examined whether alterations on a sleep pattern, circadian rhythms, and time perception are caused by NHL, addressing these issues could strengthen that neurodevelopment deficit in the habenula may be involved in

ADHD. In addition, further investigation of human subjects with high resolution magnetic resonance imaging or postmortem study to examine the habenula volume may also provide more direct link between habenula deficit and ADHD pathology.

Acknowledgements

The authors are supported by Kyoto University. We thank Dr. Nobuo Masataka for supports.

References

Agostino, P.V., Golombek, D.A., Meck, W.H., 2011. Unwinding the Molecular Basis of Interval and Circadian Timing. Front Integr Neurosci. 5, 64.

Amat, J., Sparks, P.D., Matus-Amat, P., Griggs, J., Watkins, L.R., Maier, S.F., 2001. The role of the habenular complex in the elevation of dorsal raphe nucleus serotonin and the changes in the behavioral responses produced by uncontrollable stress. Brain Res. 917, 118-126.

Baird, A.L., Coogan, A.N., Siddiqui, A., Donev, R.M., Thome, J., 2012. Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. Mol Psychiatry. 17, 988-995.

Bass, J., Takahashi, J.S., 2010. Circadian integration of metabolism and energetics. Science. 330, 1349-1354.

Batty, M.J., Liddle, E.B., Pitiot, A., Toro, R., Groom, M.J., Scerif, G., Liotti, M., Liddle, P.F., Paus, T., Hollis, C., 2010. Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry. 49, 229-238.

Bell-Pedersen, D., Cassone, V.M., Earnest, D.J., Golden, S.S., Hardin, P.E., Thomas, T.L., Zoran, M.J., 2005. Circadian rhythms from multiple oscillators: lessons from diverse organisms. Nat Rev Genet. 6, 544-556.

Bianco, I.H., Wilson, S.W., 2009. The habenular nuclei: a conserved asymmetric relay station in the vertebrate brain. Philos Trans R Soc Lond B Biol Sci. 364, 1005-1020.

Biederman, J., Spencer, T., 1999. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. Biol Psychiatry. 46, 1234-1242.

Bijlenga, D., van der Heijden, K.B., Breuk, M., van Someren, E.J., Lie, M.E., Boonstra, A.M., Swaab, H.J., Kooij, J.J., 2013. Associations between sleep characteristics, seasonal depressive symptoms, lifestyle, and ADHD symptoms in adults. J Atten Disord. 17, 261-275.

Brown, A.B., Biederman, J., Valera, E.M., Doyle, A.E., Bush, G., Spencer, T., Monuteaux, M.C., Mick, E., Whitfield-Gabrieli, S., Makris, N., LaViolette, P.S., Oscar-Berman, M., Faraone, S.V., Seidman, L.J., 2010. Effect of dopamine transporter gene (SLC6A3) variation on dorsal anterior cingulate function in attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 153B, 365-375.

Brown, S.W., Boltz, M.G., 2002. Attentional processes in time perception: effects of mental workload and event structure. J Exp Psychol Hum Percept Perform. 28, 600-615.

Carlson, J., Noguchi, K., Ellison, G., 2001. Nicotine produces selective degeneration in the medial habenula and fasciculus retroflexus. Brain Res. 906, 127-134.

Chervin, R.D., Archbold, K.H., Dillon, J.E., Panahi, P., Pituch, K.J., Dahl, R.E., Guilleminault, C., 2002. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics. 109, 449-456.

Clarke, P.B., Pert, C.B., Pert, A., 1984. Autoradiographic distribution of nicotine receptors in rat brain. Brain Res. 323, 390-395.

Cook, E.H. Jr, Stein, M.A., Krasowski, M.D., Cox, N.J., Olkon, D.M., Kieffer, J.E., Leventhal, B.L., 1995. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet. 56, 993–998.

Cordes, S., Gallistel, C.R., 2008. Intact interval timing in circadian CLOCK mutants. Brain Res. 1227, 120-127.

Corkum, P., Moldofsky, H., Hogg-Johnson, S., Humphries, T., Tannock, R., 1999. Sleep problems in children with attention-deficit/hyperactivity disorder: impact of subtype, comorbidity, and stimulant medication. J Am Acad Child Adolesc Psychiatry. 38, 1285-1293.

Cornelius, M.D., Day, N.L., 2009. Developmental consequences of prenatal tobacco exposure. Curr Opin Neurol. 22, 121-125.

Daviss, W.B., 2008. A review of co-morbid depression in pediatric ADHD: etiology, phenomenology, and treatment. J Child Adolesc Psychopharmacol. 18, 565-571.

Demotes-Mainard, J., Henry, C., Jeantet, Y., Arsaut, J., Arnauld, E., 1996. Postnatal ontogeny of dopamine D3 receptors in the mouse brain: autoradiographic evidence for a transient cortical expression. Brain Res Dev Brain Res. 94, 166-174.

Dougherty, D.D., Bonab, A.A., Spencer, T.J., Rauch, S.L., Madras, B.K., Fischman, A.J., 1999. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet. 354, 2132-2133.

Durston, S., Fossella, J.A., Casey, B.J., Hulshoff Pol, H.E., Galvan, A., Schnack, H.G., Steenhuis, M.P., Minderaa, R.B., Buitelaar, J.K., Kahn, R.S., van Engeland, H., 2005. Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. Mol Psychiatry. 10, 678-685.

Faraone, S.V., Wilens, T.E., Petty, C., Antshel, K., Spencer, T., Biederman, J., 2007. Substance use among ADHD adults: implications of late onset and subthreshold diagnoses. Am J Addict. 16 Suppl 1, 24-32; quiz 33-34.

Gizer, I.R., Ficks, C., Waldman, I.D., 2009. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. 126, 51-90.

Goodman, D.W., Thase, M.E., 2009. Recognizing ADHD in adults with comorbid mood disorders: implications for identification and management. Postgrad Med. 121, 20-30.

Greenhill, L., Puig-Antich, J., Goetz, R., Hanlon, C., Davies, M., 1983. Sleep architecture and REM sleep measures in prepubertal children with attention deficit disorder with hyperactivity. Sleep. 6, 91-101.

Gruber, R., Sadeh, A., Raviv, A., 2000. Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 39, 495-501.

Guilding, C., Hughes, A.T., Piggins, H.D., 2010. Circadian oscillators in the epithalamus. Neuroscience. 169, 1630-1639.

Guilding, C., Piggins, H.D., 2007. Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? Eur J Neurosci. 25, 3195-3216.

Gurevich, E.V., Joyce, J.N., 2000. Dopamine D(3) receptor is selectively and transiently expressed in the developing whisker barrel cortex of the rat. J Comp Neurol. 420, 35-51.

Harvey, A.G., 2011. Sleep and circadian functioning: critical mechanisms in the mood disorders? Annu Rev Clin Psychol. 7, 297-319.

Haun, F., Eckenrode, T.C., Murray, M., 1992. Habenula and thalamus cell transplants restore normal sleep behaviors disrupted by denervation of the interpeduncular nucleus. J Neurosci. 12, 3282-3290.

Hikosaka, O., 2010. The habenula: from stress evasion to value-based decision-making. Nat Rev Neurosci. 11, 503-513.

Huang, W., Ramsey, K.M., Marcheva, B., Bass, J., 2011. Circadian rhythms, sleep, and metabolism. J Clin Invest. 121, 2133-2141.

Hunt, R.D., Arnsten, A.F., Asbell, M.D., 1995. An open trial of guanfacine in the treatment of attention deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 34, 50–54.

Ironside, S., Davidson, F., Corkum, P., 2010. Circadian motor activity affected by stimulant medication in children with attention-deficit/hyperactivity disorder. J Sleep Res. 19, 546-551.

Ji, H., Shepard, P.D., 2007. Lateral habenula stimulation inhibits rat midbrain dopamine neurons through a GABA(A) receptor-mediated mechanism. J Neurosci. 27, 6923-6930.

Kalén, P., Strecker, R.E., Rosengren, E., Björklund, A., 1989. Regulation of striatal serotonin release by the lateral habenula-dorsal raphe pathway in the rat as demonstrated by in vivo microdialysis: role of excitatory amino acids and GABA. Brain Res. 492, 187-202.

Khan, A.U., 1982. Sleep REM latency in hyperkinetic boys. Am J Psychiatry. 139, 1358-1360.

Kirov, R., Kinkelbur, J., Heipke, S., Kostanecka-Endress, T., Westhoff, M., Cohrs, S., Ruther, E., Hajak, G., Banaschewski, T., Rothenberger, A., 2004. Is there a specific polysomnographic sleep pattern in children with attention deficit/hyperactivity disorder? J Sleep Res. 13, 87-93.

Kissling, C., Retz, W., Wiemann, S., Coogan, A.N., Clement, R.M., Hunnerkopf, R., Conner, A.C., Freitag, C.M., Rösler, M., Thome, J., 2008. A polymorphism at the 3'-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 147, 333-338.

Kitamura, T., Kumar, R., 1983. Time estimation and time production in depressive patients. Acta Psychiatr Scand. 68, 15-21.

Koch, G., Costa, A., Brusa, L., Peppe, A., Gatto, I., Torriero, S., Gerfo, E.L., Salerno, S., Oliveri, M., Carlesimo, G.A., Caltagirone, C., 2008. Impaired reproduction of

second but not millisecond time intervals in Parkinson's disease. Neuropsychologia. 46, 1305-1313.

Konofal, E., Lecendreux, M., Bouvard, M.P., Mouren-Simeoni, M.C., 2001. High levels of nocturnal activity in children with attention-deficit hyperactivity disorder: a video analysis. Psychiatry Clin Neurosci. 55, 97-103.

Kuriyama, K., Uchiyama, M., Suzuki, H., Tagaya, H., Ozaki, A., Aritake, S., Kamei, Y., Nishikawa, T., Takahashi, K., 2003. Circadian fluctuation of time perception in healthy human subjects. Neurosci Res. 46, 23-31.

Kuriyama, K., Uchiyama, M., Suzuki, H., Tagaya, H., Ozaki, A., Aritake, S., Shibui, K., Xin, T., Lan, L., Kamei, Y., Takahashi, K., 2005. Diurnal fluctuation of time perception under 30-h sustained wakefulness. Neurosci Res. 53, 123-128.

Larisch, R., Sitte, W., Antke, C., Nikolaus, S., Franz, M., Tress, W., Müller, H.W., 2006. Striatal dopamine transporter density in drug naive patients with attention-deficit/hyperactivity disorder. Nucl Med Commun. 27, 267-270.

Lecourtier, L., Defrancesco, A., Moghaddam, B., 2008. Differential tonic influence of lateral habenula on prefrontal cortex and nucleus accumbens dopamine release. Eur J Neurosci. 27, 1755-1762.

Lee, Y.A., Goto, Y., 2011. Neurodevelopmental disruption of cortico-striatal function caused by degeneration of habenula neurons. PLoS one. 6, e19450.

Linnet, K.M., Dalsgaard, S., Obel, C., Wisborg, K., Henriksen, T.B., Rodriguez, A., Kotimaa, A., Moilanen, I., Thomsen, P.H., Olsen, J., Jarvelin, M.R., 2003. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity

disorder and associated behaviors: review of the current evidence. Am J Psychiatry. 160, 1028-1040.

Lu, S., Cai, Y., Shen, M., Zhou, Y., Han, S. 2012. Altering and orienting of attention without visual awareness. Conscious Cogn. 21, 928-938.

Makris, N., Biederman, J., Valera, E.M., Bush, G., Kaiser, J., Kennedy, D.N., Caviness, V.S., Faraone, S.V., Seidman, L.J., 2007. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb Cortex. 17, 1364-1375.

Marcotte, A.C., Thacher, P.V., Butters, M., Bortz, J., Acebo, C., Carskadon, M.A., 1998. Parental report of sleep problems in children with attentional and learning disorders. J Dev Behav Pediatr. 19, 178-186.

Maricq, A.V., Church, R.M., 1983. The differential effects of haloperidol and methamphetamine on time estimation in the rat. Psychopharmacology (Berl). 79, 10-15.

Matsumoto, M., Hikosaka, O., 2007. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature. 447, 1111-1115.

McEvilly, R.J., Erkman, L., Luo, L., Sawchenko, P.E., Ryan, A.F., Rosenfeld, M.G., 1996. Requirement for Brn-3.0 in differentiation and survival of sensory and motor neurons. Nature. 384, 574-577.

Meaux, J.B., Chelonis, J.J., 2003. Time perception differences in children with and without ADHD. J Pediatr Health Care. 17, 64-71.

Meck, W. H., 1983. Selective adjustment of the speed of internal clock and memory processes. J. Exp. Psychol. Anim. Behav. Process. 9, 171–201.

Meck, W.H., 2006. Neuroanatomical localization of an internal clock: a functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. Brain Res. 1109, 93-107.

Meck, W.H., Cheng, R.K., MacDonald, C.J., Gainetdinov, R.R., Caron, M.G., Cevik, M. Ö., 2012. Gene-dose dependent effects of methamphetamine on interval timing in dopamine-transporter knockout mice. Neuropharmacology. 62, 1221-1229.

Monuteaux, M.C., Seidman, L.J., Faraone, S.V., Makris, N., Spencer, T., Valera, E., Brown, A., Bush, G., Doyle, A.E., Hughes, S., Helliesen, M., Mick, E., Biederman, J., 2008. A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. Am J Med Genet B Neuropsychiatr Genet. 147B, 1436-1441.

Narr, K.L., Woods, R.P., Lin, J., Kim, J., Phillips, O.R., Del'homme, M., Caplan, R., Toga, A.W., McCracken, J.T., Levitt, J.G., 2009. Widespread cortical thinning is a robust anatomical marker for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 48, 1014-1022.

Nishikawa, T., Scatton, B., 1985. Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenulo-raphe pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Brain Res. 331, 81-90.

O'Brien, L.M., Ivanenko, A., Crabtree, V.M., Holbrook, C.R., Bruner, J.L., Klaus, C.J., Gozal, D., 2003. Sleep disturbances in children with attention deficit hyperactivity disorder. Pediatr Res. 54, 237-243.

Papachristos, E.B., Jacobs, E.H., Elgersma, Y., 2011. Interval timing is intact in arrhythmic Cry1/Cry2-deficient mice. J Biol Rhythms. 26, 305-313.

Pastor, M.A., Artieda, J., Jahanshahi, M., Obeso, J.A., 1992. Time estimation and reproduction is abnormal in Parkinson's disease. Brain. 115 Pt 1, 211-225.

Paul, M.J., Indic, P., Schwartz, W.J., 2011, A role for the habenula in the regulation of locomotor activity cycles. Eur J Neurosci. 34, 478-488.

Pauly, J.R., Sparks, J.A., Hauser, K.F., Pauly, T.H., 2004. In utero nicotine exposure causes persistent, gender-dependant changes in locomotor activity and sensitivity to nicotine in C57Bl/6 mice. Int J Dev Neurosci. 22, 329-337.

Paxinos G, Watson C (2005) The rat brain in stereotaxic coordinates, 5th edition. San Diego, CA: Academic Press.

Pliszka, S.R., 2005. The neuropsychopharmacology of attention-deficit/hyperactivity disorder. Biol Psychiatry. 57**,** 1385-1390.

Quina, L.A., Wang, S., Ng, L., Turner, E.E., 2009. Brn3a and Nurr1 mediate a gene regulatory pathway for habenula development. J Neurosci. 29, 14309-14322.

Ranft, K., Dobrowolny, H., Krell, D., Bielau, H., Bogerts, B., Bernstein, H.G., 2010. Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia. Psychol Med. 40, 557-567.

Rommelse, N.N., Oosterlaan, J., Buitelaar, J., Faraone, S.V., Sergeant, J.A., 2007. Time reproduction in children with ADHD and their nonaffected siblings. J Am Acad Child Adolesc Psychiatry. 46, 582-590.

Rønnekleiv, O.K., Møller, M., 1979. Brain-pineal nervous connections in the rat: an ultrastructure study following habenular lesion. Exp Brain Res, 37, 551-562.

Santi, A., Coppa, R., Ross, L., 2001. Effects of the dopamine D2 agonist, quinpirole, on time and number processing in rats. Pharmacol Biochem Behav. 68, 147-155.

Sarter, M., Givens, B., Bruno, J.P., 2001. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. Brain Res Brain Res Rev. 35, 146-160.

Sartorius, A., Kiening, K.L., Kirsch, P., von Gall, C.C., Haberkorn, U., Unterberg, A.W., Henn, F.A., Meyer-Lindenberg, A., 2010. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biol Psychiatry. 67, e9-e11.

Savitz, J.B., Nugent, A.C., Bogers, W., Roiser, J.P., Bain, E.E., Neumeister, A., Zarate, C.A., Jr., Manji, H.K., Cannon, D.M., Marrett, S., Henn, F., Charney, D.S., Drevets, W.C., 2011. Habenula Volume in Bipolar Disorder and Major Depressive Disorder: A High-Resolution Magnetic Resonance Imaging Study. Biol Psychiatry. 69, 336-343.

Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., Agid, Y., 1983. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res. 275, 321-328.

Schneider, T., Ilott, N., Brolese, G., Bizarro, L., Asherson, P.J., Stolerman, I.P., 2011. Prenatal exposure to nicotine impairs performance of the 5-choice serial reaction time task in adult rats. Neuropsychopharmacology. 36, 1114-1125.

Seidman, L.J., Valera, E.M., Makris, N., 2005. Structural brain imaging of attention-deficit/hyperactivity disroder. Biol Psychiatry. 57, 1263-1272.

Seidman, L.J., Valera, E.M., Makris, N., Monuteaux, M.C., Boriel, D.L., Kelkar, K., Kennedy, D.N., Caviness, V.S., Bush, G., Aleardi, M., Faraone, S.V., Biederman, J., 2006. Dorsolateral prefrontal and anterior cingulate cortex

volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. Biol Psychiatry. 60, 1071-1080.

Sévigny, M.C., Everett, J., Grondin, S., 2003. Depression, attention, and time estimation. Brain Cogn. 53, 351-353.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J.P., Greenstein, D., Clasen, L., Evans, A., Giedd, J., Rapoport, J.L., 2007a. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 104, 19649-19654.

Shaw, P., Gornick, M., Lerch, J., Addington, A., Seal, J., Greenstein, D., Sharp, W., Evans, A., Giedd, J.N., Castellanos, F.X., Rapoport, J.L. 2007b. Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 64, 921-931.

Shepard, P.D., Holcomb, H.H., Gold, J.M., 2006. Schizophrenia in translation: the presence of absence: habenular regulation of dopamine neurons and the encoding of negative outcomes. Schizophr Bull. 32, 417-421.

Shurtleff, D., Raslear, T.G., Simmons, L., 1990. Circadian variations in time perception in rats. Physiol Behav. 47, 931-939.

Slotkin, T.A., Seidler, F.J., Qiao, D., Aldridge, J.E., Tate, C.A., Cousins, M.M., Proskocil, B.J., Sekhon, H.S., Clark, J.A., Lupo, S.L., Spindel, E.R., 2005. Effects of prenatal nicotine exposure on primate brain development and attempted amelioration with supplemental choline or vitamin C:

neurotransmitter receptors, cell signaling and cell development biomarkers in fetal brain regions of rhesus monkeys. Neuropsychopharmacology. 30, 129-144.

Smith, A., Taylor, E., Rogers, J.W., Newman, S., Rubia, K., 2002. Evidence for a pure time perception deficit in children with ADHD. J Child Psychol Psychiatry. 43, 529-542.

Smith, K.M., Bauer, L., Fischer, M., Barkley, R., Navia, B.A., 2005. Identification and characterization of human NR4A2 polymorphisms in attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 133B, 57-63.

Sobanski, E., Schredl, M., Kettler, N., Alm, B., 2008. Sleep in adults with attention deficit hyperactivity disorder (ADHD) before and during treatment with methylphenidate: a controlled polysomnographic study. Sleep. 31, 375-381.

Soehner, A.M., Harvey, A.G.. 2012. Prevalence and functional consequences of severe insomnia symptoms in mood and anxietydisorders: results from a nationally representative sample. Sleep. 35, 1367-1375.

Spencer, T.J., Biederman, J., Mick, E., 2007. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol. 32, 631-642.

Stein, M.A., 1999. Unravelling sleep problems in treated and untreated children with ADHD. J Child Adolesc Psychopharmacol. 9, 157-168.

Sun, B., Tang, Y.C., Fan, L.Z., Lin, X.T., Li, Z.P., Qi, H.T., Liu, S.W., 2008. The pineal region: thin sectional anatomy with MR correlation in the coronal plane. Surg Radiol Anat. 30, 575-582.

Sung, V., Hiscock, H., Sciberras, E., Efron, D., 2008. Sleep problems in children with attention-deficit/hyperactivity disorder: prevalence and the effect on the child and family. Arch Pediatr Adolesc Med. 162, 336-342.

Takahashi, J.S., Hong, H.K., Ko, C.H., McDearmon, E.L., 2008. The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Genet. 9, 764-775.

Tavakoli-Nezhad, M., Schwartz, W.J., 2006. Hamsters running on time: is the lateral habenula a part of the clock? Chronobiol Int. 23, 217-224.

Toplak, M.E., Tannock, R., 2005. Time perception: modality and duration effects in attention-deficit/hyperactivity disorder (ADHD). J Abnorm Child Psychol. 33, 639-654.

Tucci, V., 2011. Sleep, Circadian Rhythms, and Interval Timing: Evolutionary Strategies to Time Information. Front Integr Neurosci. 5, 92.

Valjakka, A., Vartiainen, J., Tuomisto, L., Tuomisto, J.T., Olkkonen, H., Airaksinen, M.M., 1998. The fasciculus retroflexus controls the integrity of REM sleep by supporting the generation of hippocampal theta rhythm and rapid eye movements in rats. Brain Res Bull. 47, 171-184.

Van der Heijden, K.B., Smits, M.G., Van Someren, E.J., Gunning, W.B., 2005. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. Chronobiol Int. 22, 559-570.

van Dyck, C.H., Quinlan, D.M., Cretella, L.M., Staley, J.K., Malison, R.T., Baldwin, R.M., Seibyl, J.P., Innis, R.B., 2002. Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. Am J Psychiatry. 159, 309-312.

Van Veen, M.M., Kooij, J.J., Boonstra, A.M., Gordijn, M.C., Van Someren, E.J., 2010. Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry. 67, 1091-1096.

Volkow, N.D., Wang, G.J., Newcorn, J., Fowler, J.S., Telang, F., Solanto, M.V., Logan, J., Wong, C., Ma, Y., Swanson, J.M., Schulz, K., Pradhan, K., 2007. Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage. 34, 1182-1190.

Winzer-Serhan, U.H., Leslie, F.M., 1997. Codistribution of nicotinic acetylcholine receptor subunit alpha3 and beta4 mRNAs during rat brain development. J Comp Neurol. 386, 540-554.

Wittmann, M., Paulus, M.P., 2008. Decision making, impulsivity and time perception. Trends Cogn Sci. 12, 7-12.

Wyse, C.A., Coogan, A.N., 2010. Impact of aging on diurnal expression patterns of CLOCK and BMAL1 in the mouse brain. Brain Res. 1337, 21-31.

Yamaguchi, S., Isejima, H., Matsuo, T., Okura, R., Yagita, K., Kobayashi, M., Okamura, H., 2003. Synchronization of cellular clocks in the suprachiasmatic nucleus. Science. 302, 1408-1412.

Yang, Y.K., Yeh, T.L., Chiu, N.T., Lee, I.H., Chen, P.S., Lee, L.C., Jeffries, K.J., 2004. Association between cognitive performance and striatal dopamine binding is higher in timing and motor tasks in patients with schizophrenia. Psychiatry Res. 131, 209-216.

Zhao, H., Rusak, B., 2005. Circadian firing-rate rhythms and light responses of rat habenular nucleus neurons in vivo and in vitro. Neuroscience. 132, 519-528.

Figure Legends

Figure 1. Neuroanatomy of the habenula

(**a**) Nissl stained section representing the habenula. The blue and red dotted lines indicate the MHb and LHb. FR: fasciculus retroflexus; PV, paraventricular nucleus of the thalamus; MD, mediodorsal nucleus of the thalamus; DG, dentate gyrus; sm, stria medullaris of the thalamus. Scale bar = 100 μm.

(b) A schematic diagram illustrating a rodent coronal brain section -3.3 mm posterior from the bregma where the habenula is represented.

(c) Afferent and efferent connections of the habenula. The MHb primarily receives synaptic inputs from the septum, and sends outputs through FR into the interpeduncular nuleus (IPN), which in turn projects to midbrain monoamine neurons. In contrast, the LHb receives inputs from the hypothalamus, the prefrontal cortex, basal ganglia, and sends outputs directly to midbrain nuclei such as the ventral tegmental area (VTA) and dorsal raphe where dopamine and serotonin neurons are located, respectively. CPu, caudate and putamen; DBB, diagonal band of Broca; GPb, border region of the globus pallidus; LPO, lateral preoptic area; RMTg, the rostromedial tegmental nucleus; SNc, substantia nigra pars compacta (modified from Hikosaka, 2010).

(d) Afferent and efferent connections of the suprachiasmatic nucleus. Light reaches the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract (RHT), which in turn projects to the subparaventricular zone (SPZ) and sends output through the

dorsomedial nucleus of the hypothalamus (DMH) into the lateral hypothalamus (LHA) that is critical for wakefulness. Moreover, DMH has separated projection into the ventrolateral preoptic nucleus (VLPO) to regulate sleep and the paraventricular nucleus (PVN). PVN receives input from SCN and DMH and sends outputs through the intermediolateral nucleus (IML) and the superior cervical ganglion (SCG) into the pineal gland that regulates melatonin synthesis (modified from Takahashi et al., 2008).

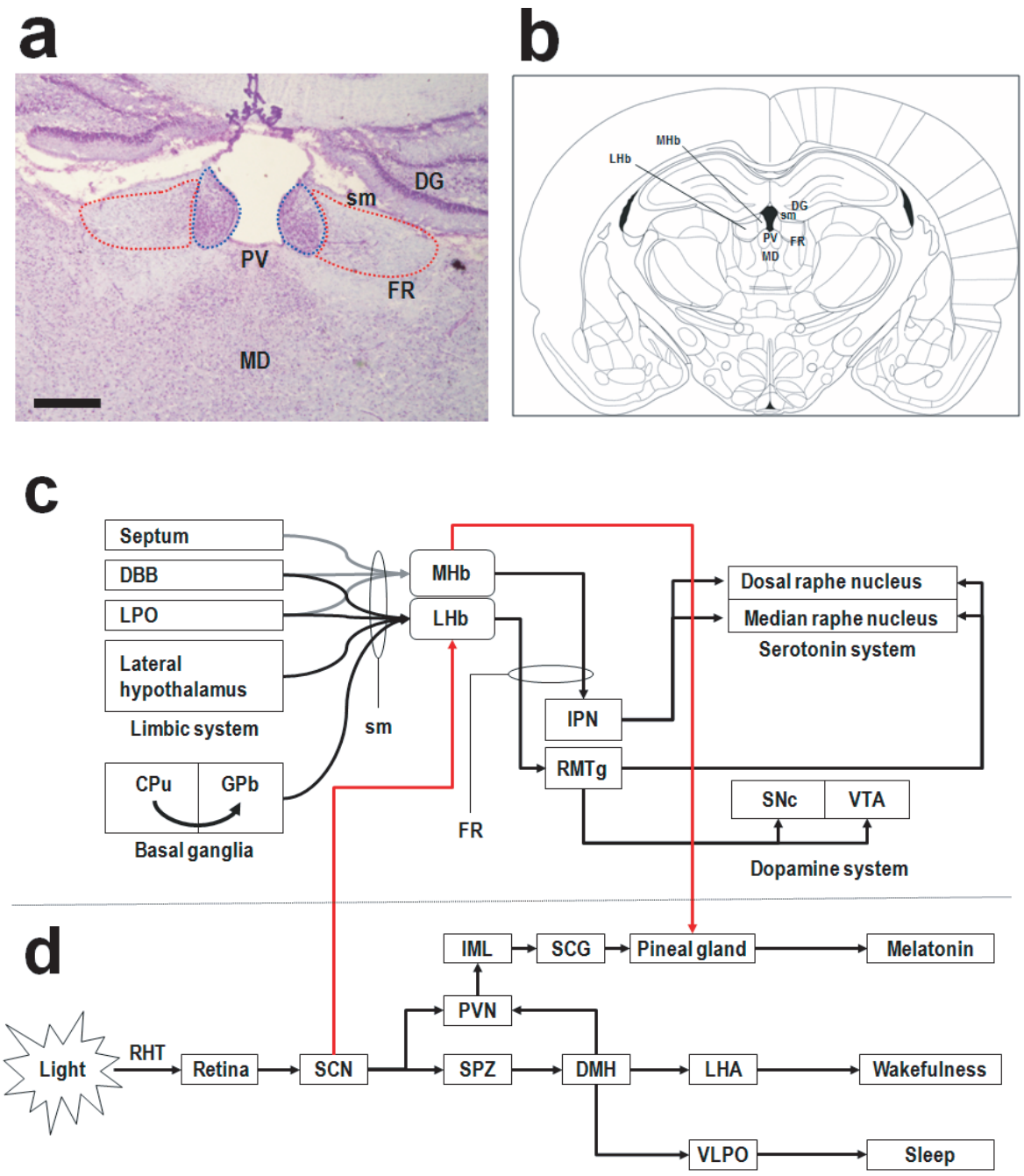

Figure 1 - Lee & Goto