ELSEVIER

Progress in Neurobiology 81 (2007) 237–250

progress in Neurobiology

www.elsevier.com/locate/pneurobio

The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia

Claude Gottesmann [a,*], Irving Gottesman [b]

[a] *Département des Sciences de la Vie, Faculté des Sciences, Université de Nice-Sophia Antipolis, Nice, France*
[b] *Department of Psychiatry, University of Minnesota Medical School, University of Minnesota, Minneapolis, MN, USA*

Received 28 September 2006; received in revised form 14 December 2006; accepted 10 January 2007

Abstract

Animal models are a promising method to approach the basic mechanisms of the neurobiological disturbances encountered in mental disorders. Depression is characterized by a decrease of REM sleep latency and an increase of rapid eye movement density. In schizophrenia, electrophysiological, tomographic, pharmacological and neurochemical activities are all encountered during REM sleep. Mental retardation and dementia are characterized by rather specific REM sleep disturbances. Identification of the genetic support for these abnormalities (endophenotypes) encountered during REM sleep could help to develop specific treatments.

Keywords: Mental illness; Paradoxical sleep; Dreaming

Contents

1. Introduction

Great progress has been made in the treatment of severe mental diseases. The major innovation came from psychopharmacology which by the 1950s, launched the release of chronically hospitalized patients from psychiatric institutions. These chemical forms of treatment were first identified empirically. Although the roots of *Rawolfia serpentina* used as a tranquillizer, had been known since Antiquity, the corresponding chemical agent, reserpine (serpasil), was introduced into the modern pharmacopoeia only in 1954 (Fouks et al., 1954), before being rapidly abandoned because of major hypotensive influences (Freis, 1954). In fact, the current psychopharmacology began slightly earlier, in 1951, when

Abbreviations: 5-HT, serotonin; MHPG, 3-methoxy 4-hydroxy phenyl glycol

* Corresponding author at: 22 parc Lubonis, 06000 Nice, France. Tel.: +33 4 93 81 34 04; fax: +33 4 93 81 34 04.
E-mail address: claude.gottesmann@unice.fr (C. Gottesmann).

0301-0082/$ – see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.pneurobio.2007.01.004

Henri Laborit (Laborit and Huguenard, 1951) working on artificial hibernation for surgical procedures, identified the tranquillizing impact of 4560 R.P (chlorpromazine) and suggested its use to Jean Delay (Delay et al., 1952) for agitated patients. Chlorpromazine thus became the first specific antipsychotic treatment. The next great progress occurred in 1957 when two clinicians discovered antidepressive compounds. First, N. Kline (Loomer et al., 1957), while dining with tuberculosis surgeons, learned that the patients became euphoric after iproniazide (a later discovered inhibitor of monoamine oxydases). Then, R. Kuhn (Kuhn, 1958–1959) realized that imipramine (later identified as monoamine reuptake inhibitor), a molecule close to chlorpromazine, was also efficient against depression.

In spite of recent progress in the typically symptomatic treatment of psychiatric diseases, the underlying mechanisms of the latter remain to be discovered. Indeed, as with schizophrenia, these diseases are multifactorial with an appreciable polygenic component (Gottesman and Shields, 1967). Hence, researchers are looking for criteria which are characteristic of mental diseases and provide complementary information about their distal genetic roots. One of the most frequent approaches concerns «endophenotypes» (Gottesman and Shields, 1973). These criteria, which can be «neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological» (Gottesman and Gould, 2003) are «measurable components invisible to the naked eye along the pathway between disease and distal genotype» (Gottesman and Gould, 2003). Endophenotypes represent relatively elementary functional phenomena of any behavior and are also encountered in mental diseases where they can help identify the responsible gene(s) (Hasler et al., 2006).

Endophenotypes should posses some specific criteria. The endophenotype: (a) must be associated with illness in the general population, (b) must be observable despite the fact that the patient may be in partial or complete remission, (c) should be heritable, (d) should segregate with illness within families, (e) should be observed at a higher rate among unaffected family members compared to the general population (Gottesman and Gould, 2003; Berrettini, 2005).

Of course, nowadays, the best means of research involves valid partial animal models of the different psychiatric diseases (Gould and Gottesman, 2006).

We would like to show that a specific sleep stage, namely, the rapid eye movement REM (dreaming) stage, provides a good model for psychiatric endophenotypes. This sleep stage, which also occurs in birds (Klein et al., 1964; Ookawa and Gotoh, 1964; Ookawa and Gotoh, 1965; Tradarti, 1966), is already present in primitive mammals, in partial (Siegel et al., 1996; Siegel et al., 1999; Nicol et al., 2000) or complete (Nicol et al., 2000) form. In all other mammals, it is mainly characterized by cortical rapid low voltage activity, often indissociable from the waking electroencephalogram (EEG) (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957; Dement, 1958; Jouvet et al., 1959), rapid eye movements generally occurring in bursts (Aserinsky and Kleitman, 1953) and inhibition of muscular activity (Jouvet and Michel, 1959; Berger, 1961). In addition, though mainly studied in animals but also described in humans (McCarley et al., 1983; Miyauchi et al., 1987), phasic waves called ponto-geniculo-occipital (P.G.O.) spikes (Jouvet and Michel, 1959; Mikiten et al., 1961; Hobson, 1964; Michel et al., 1964) and eye movement potentials (E.M.P.) (Michel et al., 1964; Gottesmann, 1966, 1967a,b, 1969) occurs in association with the eye movements (see Callaway et al., 1987; Gottesmann, 1997).

Dreaming is the nearly specific unique mental activity of REM sleep. Indeed, while some dreams have been described during slow wave sleep in addition to the main thought-like mental activity (Foulkes, 1962; Bosinelli, 1995), dreaming is now considered to occur necessarily during underlying REM sleep neurobiological processes even if some electrophysiological criteria are covert (Takeuchi et al., 1999; Nielsen, 2000; Takeuchi et al., 2001). This mental activity is supported by both activating and inhibitory, antagonist yet complementary forebrain processes, mainly supported by the brainstem, the inhibitory processes being significantly decreased during REM sleep as compared to waking (see Gottesmann, 1999, 2005a).

We will consider the relationship which can be established between REM sleep neurobiological criteria and psychiatric diseases. We will successively analyse REM sleep disturbances in depression, schizophrenia and mental retardation-dementia, the last disorders being long considered to constitute the only true neurological syndromes.

2. Results

2.1. Depression

It is likely that Gresham et al. (1965) undertook the first sleep study of depressive patients and found more REM sleep in the first third of the night. Shortly afterwards, Green and Stajduhar (1966) and Hartmann et al. (1966) found a decrease of REM sleep latency at sleep onset, and an increased percentage of REM sleep. Very interestingly, Green and Stajduhar observed a decrease of REM sleep after electroshock treatment (which confirmed results obtained the same year in animals (Cohen and Dement, 1966; Cohen et al., 1967)), and the subjects were cured by this application. Today, the reduced latency of REM sleep appearance which expresses a pressure of this sleep stage, is well established. More recent findings have shown that there is also an increase of eye movement density, thus of the number of rapid eye movements per period of REM sleep, particularly during the first part of night, while the increased eye movements usually appear in the last part of the night during longer-lasting REM sleep periods (Rush et al., 1986). In addition, there are, during sleep, homolaterally theta–delta and bilaterally beta–delta EEG coherence abnormalities in subjects at high depressive risk (Fulton et al., 2000). All REM sleep abnormalities favor development of later depressive episodes (Giles et al., 1988b), and even unaffected relatives show reduced REM sleep latency and increased eye movement density (Giles et al., 1988a; Giles et al., 1993; Giles et al., 1998; Modell et al., 2005). The heritability of these REM sleep characteristics concords well with the endophenotype criteria

(Gottesman and Gould, 2003; Berrettini, 2005). The same symptoms are observed in remitted patients (Lauer et al., 1995) and borderline persons with mood disorders even without previous clear-cut depressive episodes (Battaglia et al., 1999). REM sleep disturbances continue life-long (Goetz et al., 2001), particularly the rapid eye movement density which perhaps more than REM sleep latency, appears to be a biological marker of depression (Lauer et al., 1991; Clark et al., 2000). This increase of rapid eye movement density and shortened REM sleep stage occurrence is associated with a tendency for plasma cortisol to shift to the beginning of the night (Rao et al., 1996). This phenomenon confirms that in depression there is a disturbance of the corticosteroid function, even possibly a key to its pathogenesis (Ising et al., 2005; Keck et al., 2005).

Whatever the precise origin of depression disturbances, the above described results show that there is a disturbance of the circadian cycle. Indeed, as early as in 1979, Wehr et al. (1979) observed advanced sleep phase criteria in depression, such as the 3 h advanced urine level of $^{3}OCH_{3}{}^{4}OH$-phenylglycol (MHPG), the specific metabolite of noradrenaline. After a 6 h advanced sleep time schedule prescribed to the patients, 4/7 recovered from depression. This finding could account for the reduced REM sleep latency and rapid eye movements pressure in depression, since the noradrenergic neurons of the pontine locus coeruleus have to become silent to allow REM sleep occurrence (Hobson et al., 1975; Aston-Jones and Bloom, 1981a; Mallick et al., 2002, 2005). And, indeed, behavioral (Vogel et al., 1973) as well as pharmacological suppression of REM sleep by inhibition of monoamine oxydases (Toyoda, 1964; Dunleavy and Oswald, 1973) improved depression. There was a parallel evolution of mood improvement and lowering of REM sleep and it was concluded that REM sleep deprivation is the mechanism by which antidepressive compounds improve depression (Gillin et al., 1978; Vogel, 1983). Moreover, recent results show that increased rapid eye movement density could be a marker for poor response to sleep deprivation (Clark et al., 2000). Interestingly, in contrast with the specific REM sleep pressure in depression, the tendency to a global sleep deficit in this disease could be an endogenous compensatory process which is possibly an attempt to increase the central level of noradrenaline and serotonin (Adrien, 2002).

For years, serotonin rather than noradrenaline disturbances were thought to be more heavily involved in depression, and both monoamine oxydase inhibition and monoamine reuptake inhibition act on both noradrenaline and serotonin. Serotonergic neurons of the dorsal (McGinty et al., 1974; McGinty and Harper, 1976) and medial (Rasmussen et al., 1984) raphe nuclei are also silent during REM sleep and their firing in dorsal raphe nucleus is reduced in the chlomipramine model of endogenous depression (Yavari et al., 1993). The serotonergic receptors involved were studied and it was shown that 5-HT_{1A} receptor agonists given peripherally similarly inhibit REM sleep in normal and depressed patients (Gillin et al., 1996) as well as in mice (Boutrel et al., 1999), whereas they increase REM sleep when perfused in the dorsal raphe nucleus (Portas et al., 1996). The depression-like behavior in adult knock-out mice without 5-HT transporters can be reversed by early life treatment with 5-HT_{1A} antagonists (Alexandre et al., 2006). The 5-HT_{1B} receptor is also involved in REM sleep generating processes since 5-HT_{1B} knock-out mice show an increase of REM sleep (Boutrel et al., 1999). Recent results have shown that the 5-HT_{7} receptor is also involved in REM sleep regulation since antagonists specifically disturb sleep by increasing REM sleep latency and decreasing its total amount during the day-time (Thomas et al., 2003). Finally, 5-HT_{3} receptors which favor ion fluxes are inhibited by most antidepressive compounds (Eisensamer et al., 2005).

There are also cholinergic disturbances in depression as shown by REM sleep generating mechanisms. Indeed, as early as 1960, Jouvet's team showed in animals that atropine (muscarinic blocker) suppressed and eserine (anticholinesterasic compound) increased REM sleep (Jouvet and Michel, 1960a,b). This conclusion was reinforced by local infusion of acetylcholine (Cordeau et al., 1963; Hernandez-Peon et al., 1963) or cholinomimetics (George et al., 1964). This crucial function of acetylcholine (see Jouvet, 1975; Jones, 1991, 2004; Baghdoyan, 1997) was slightly diminished by the later discovery of a final glutamatergic step in REM sleep generating processes (Onoe and Sakai, 1995; Datta and Siwek, 1997; Datta et al., 2001; Sakai and Crochet, 2003). Indeed, kainate infusion in the peri-locus coeruleus α induced REM sleep even in the animal under atropine (Onoe and Sakai, 1995; Sakai and Crochet, 2003). However, in humans, hypersensitivity to acetylcholine characterizes depression. As a matter of fact, intravenous injection of physostigmine (an anticholinesterase compound) (Sitaram et al., 1978a), or arecoline (a cholinergic agonist) (Sitaram et al., 1978b), decreases REM sleep latency while scopolamine (a muscarinic blocker) inhibits REM sleep (Sitaram et al., 1978b). These results observed in normal subjects are exacerbated in depressive patients, confirming the supersensitivity of the cholinergic system in this disease. Moreover, this characteristic persists in patients who have recovered (Sitaram and Gillin, 1980; Sitaram et al., 1980). This increased sensitivity (Lauer et al., 1990) seems to be a biological marker of depression (Sitaram et al., 1982). Another argument is that inhibitory compounds of monoamine reuptake bind on cholinergic receptors (Raisman et al., 1979), amitriptyline having the highest affinity (Stanton et al., 1993), and there is a relative predominance of central cholinergic tone over adrenergic tone in affective illness (Risch et al., 1981). However, later studies showed that although there is sensitivity to REM sleep induction by arecoline in twins, which suggests a genetic variation in muscarinic receptors (Numberger et al., 1983), there is an overlap between normal and depressive subjects regarding cholinergic supersensitivity (Numberger et al., 1989). Consequently, the cholinergic criterion is not the best endophenotype to characterize mood disturbances.

It has to be emphasized that other factors are involved in both depression and REM sleep disturbances. For example, intravenous administration of galanin improves depressive symptoms as tested by the Hamilton depression scale, and increases REM sleep latency (Murck et al., 2004).

It is necessary to mention the problem of reduced REM sleep latency in another sleep disorder, namely, narcolepsy. This fact

was already alluded by Vogel et al. (1966) and clearly described first by Rechtschaffen et al. (1963), prior to being definitively established by several groups (Hishikawa and Kaneko, 1965; Cadilhac et al., 1966; Gastaut et al., 1966; Suzuki, 1966; Vincent et al., 1966) (for details see Gottesmann, 2001, 2005b). An animal model of narcolepsy with reduced REM sleep latency (in fact cataplexy fits) was described in dogs (Foutz et al., 1979; Kilduff et al., 1986; Aldrich, 1991). Several studies have shown that the narcoleptic syndrome is characterized by: (1) an increase of muscarinic receptors in the brainstem (Kilduff et al., 1986), (2) an increase of α_2-receptors in locus coeruleus (Fruhstorfer et al., 1989), (3) a deficit of hypocretin/orexin (Thannickal et al., 2000; Overeem et al., 2002). This peptide has been shown to activate the locus coeruleus (Bourgin et al., 2000), the silence of which is necessary to REM sleep occurrence (Hobson et al., 1975; Aston-Jones and Bloom, 1981a). There are some relationships between depression and narcolepsy since narcoleptic treatments (modafinil) (added to antidepressive compounds) improve depression symptoms (DeBastita et al., 2004) and antidepressant withdrawal, in some cases, induce narcoleptic symptoms although without any abnormality of the hypocretin/orexin central level (Nissen et al., 2005). Moreover, in some bipolar disorders, narcoleptic hallucinations indicate a more severe disease (Douglass, 2003). Finally, daily amplitude variations of hypocretin/orexin are lower in depressive patients (3%) than in controls (10%), and the central level tends to be higher than in normal subjects (Salomon et al., 2003) -while a decrease of this peptide could be expected to explain REM sleep pressure. Thus, there are similar sleep disorders in depression and narcolepsy but only few shared biological and psychological disturbances. Consequently, REM sleep pressure is not a specific endophenotype of depression.

Vogel et al. (2000) recently reported the interesting observation that in rats, several criteria of REM sleep decrease with ontogenic evolution (tonic REM sleep, phasic REM sleep -twitches-, mean REM sleep duration and the number of REM sleep periods), while other criteria increase (REM sleep latency and the percentage of non-sleep onset REM sleep periods). In endogenous depression, REM sleep characteristics are the same as in neonate rats. Thus, states Vogel, «the ontogeny of REM sleep suggests a developmental process that may be altered in humans predisposed to endogenous depression, and may account for the (life-long) REM sleep abnormalities of the disorder» (p. 453) (Vogel et al., 2000). This could be first related to disturbances of the circadian clock connected to genetic disorders (Mansour et al., 2006; Nievergelt et al., 2006). Although several studies were devoted to sleep genetic support (Tafti et al., 1999; Cirelli, 2005; Terao et al., 2006), the specific distal gene(s) support of REM sleep remains open to discussion, although the cyclic AMP-response element binding protein (CREB) gene is involved in both REM sleep and in depression (Zubenko et al., 2003).

Conclusion: The main endophenotype encountered in all animal behavioral models of depression involves REM sleep pressure (Overstreet, 1993; Dugovic et al., 2000; Popa et al., 2005). In humans, it constitutes a vulnerability marker of depression (Hasler et al., 2004) (although, once again, there seems to be some overlap with normal subjects (Benson and Zarcone, 1993)). One of the basic phenomena responsible for this disorder is, of course, the hypersensitivity of cholinergic processes. However, although antidepressive compounds have an anticholinergic influence, mood shifts seem to be mainly related to a monoaminergic deficit. It is not because acetylcholine is involved in REM sleep generating processes and possibly in apoptosis phenomena observed in the anterior cingulate cortex and hippocampus (Benes et al., 2005), that this transmitter is very involved in the mood changes characteristic of depression. As we will later see, although acetylcholine is obviously crucial for correct mental functioning (Perry et al., 1999; Sarter and Bruno, 2000), its decrease is involved in schizophrenic symptoms such as hallucinations (Collerton et al., 2005). Today, it is not yet clear that the future identification of the genetic support of rapid eye movement density and reduced REM sleep latency will be able to offer a valid explanation for the mood disorders characteristic of depression.

2.2. *Schizophrenia*

Behaviorally, a decrease of REM sleep latency in schizophrenia was sometimes described (Feinberg et al., 1964; Goldman et al., 1996; Lauer et al., 1997) but was also questioned (Ganguli et al., 1987). Consequently, REM sleep latency is not a significant specific criterion (endophenotype) to characterize this disease. A more original finding concerned the specific absence of REM sleep rebound after REM sleep deprivation (Zarcone et al., 1969, 1975). However, there are several significant characteristics shared by REM sleep and schizophrenia.

2.2.1. *Electrophysiology*

The classical EEG (0.5–25 c/s) constitutes an initial but not powerful candidate endophenotype. REM sleep in normal subjects as well as in psychotics, is characterized by low amplitude rapid EEG often indissociable from active waking, thus lacking alpha rhythm. The difference in schizophrenia is that during waking one observes only a small amount of alpha rhythm (Stassen et al., 1999). Consequently, waking in schizophrenic patients and REM sleep in normal subjects show a similar strongly activated EEG. This already points to a deficit of habituation processes related to a decrease of forebrain inhibitory processes in both cases (see below).

A more important phenomenon is shown by the newly discovered gamma rhythm. This was first identified in vigilant and motionless cats (Bouyer et al., 1981). It was then described as being centered on 40 c/s in waking humans and appears to be reduced in Alzheimer patients (Ribary et al., 1991). Finally, it was observed during REM sleep in humans (Llinas and Ribary, 1993) and in animals (Franken et al., 1994; Maloney et al., 1997). An already unexpected finding in humans, there was no reset of this rhythm during REM sleep by peripheral stimulations contrary to waking, thus indicating a disconnection from sensory inputs. Still more importantly, it was

observed that gamma rhythm, synchronized over the whole cortex during waking, becomes uncoupled during REM sleep, particularly between the perceptual areas and the frontal and prefrontal cortex (Perez-Garci et al., 2001). This was an additional proof of intracerebral disconnections confirmed by a loss of gamma rhythm coherence between cortex and hippocampus (Cantero et al., 2004; Massimini et al., 2005). This phenomenon needs to be compared with the well-established intracerebral disturbed connections described in schizophrenia (Young et al., 1998; Peled et al., 2000; Meyer-Lindenberg et al., 2001, 2005).

Central responsiveness also shows strong similarities in REM sleep and schizophrenia. When two identical sensory stimuli are delivered in humans at 500 ms intervals, the N_{100} component of the second evoked potential is much lower in normal subjects. Today, this phenomenon is called prepulse inhibition. In the past it was simply named the recovery cycle of responsiveness. In contrast, in schizophrenic patients, the N_{100} component is not or much less reduced which has to be interpreted as a deficit in central inhibitory processes. The surprising fact is that, during REM sleep in psychotics as well as in controls, the amplitude of the second evoked N_{100} is not reduced, associating both kinds of subjects in the same abnormal disinhibition (Kisley et al., 2003). Another somewhat related phenomenon concerns the distinction between self- and external stimulation. In normal subjects, self-stimulation is dissociated from external stimulation. This is not the case in schizophrenia. It has very recently been shown that this distinction also disappears on emerging from REM sleep dreaming (Blagrove et al., 2006).

It cannot be overlooked that two early electrophysiological results already heralded the current and probable explanation of abnormal mentation during REM sleep. First, Evarts (Evarts, 1964; Evarts, 1965) recorded in monkey's cortical pyramidal neurons during sleep–waking stages. He observed that during waking the cells discharged regularly and at a high rate. During the following slow wave sleep the spikes were less numerous with less regular distribution, and during REM sleep he observed very high frequency cell discharges, but in large bursts of firing alternating with long silences. The author postulated that during waking the regular firing is the consequence of frequency-limiting processes involving inhibitory influences which disappear during REM sleep. The second team, of Demetrescu et al. (Demetrescu et al., 1966), used a complex paradigm of 4 consecutive evoked potentials induced at different latencies in the cortex by stimulation of the lateral geniculate nucleus. Their results showed that during waking both high rate activating and inhibitory influences act at cortical level. They both decreased during quiet waking, still further during slow wave sleep and they were minimal prior to REM sleep onset. During REM sleep, the activating influences reappeared while the inhibitory ones remained at their lowest level. Already, at that time, the present first author pointed out that the opposition between the activated and controlled cortex during waking and the activated but disinhibited cortex during REM sleep could explain the illogical mentation of dreaming (Gottesmann, 1967b, 1970, 1971).

The first experiment associating electrophysiology and neurochemistry was performed by McGinty et al. (McGinty et al., 1974; McGinty and Harper, 1976). These authors recorded the neurons of the mesencephalic dorsal raphe nucleus which is a serotonergic structure (Dahlstrom and Fuxe, 1964). These neurons fired at highest rate during waking although the frequency of discharges was low. These neurones decreased their firing rate during slow wave sleep and became silent during REM sleep. The same phenomenon was described a year later for the noradrenergic neurons of the pontine locus coeruleus nucleus (Hobson et al., 1975; Aston-Jones and Bloom, 1981a). Moreover, it was shown that these neurons begin to fire again in the few second preceding arousal (Aston-Jones and Bloom, 1981a). These two kinds of neurons send axon terminals to the whole cortex (Dahlstrom and Fuxe, 1964; Fuxe, 1965; Fuxe et al., 1968) where these monoamines are mainly released not at synaptic level, but diffusely at varicosity level (Descarries et al., 1975, 1977) with a resulting somewhat long-duration (tonic) influence, because of the absence of immediate elimination by synaptic reuptake or enzyme destruction. The important fact is that these two neuromodulators mainly inhibit cortical neurons (Krnjevic and Phillis, 1963; Frederickson et al., 1971; Nelson et al., 1973; Foote et al., 1975; Reader et al., 1979; Araneda and Andrade, 1991; Manunta and Edeline, 1999). However, paradoxically, they increase the signal-to-noise ratio of neuron functioning thus increasing their efficiency (Foote et al., 1975; Aston-Jones and Bloom, 1981b; McCormick, 1992). Consequently, their silence during REM sleep induces a general disinhibition process and a loss of the control of cortex functioning. It should be stressed that schizophrenia is also characterized by a deficit of serotonin (Silver et al., 2000; Van Hes et al., 2003) and noradrenaline (Friedman et al., 1999; Linner et al., 2002), and new neuroleptics are characterized by inhibition of the reuptake of both neuromodulators. Finally, the fact that the noradrenergic neurons (perhaps also the serotonergic ones?) fire again already prior to behavioral arousal, could favor the forgetting of dreams. Freud (Freud, 1900) wrote about psychological censorship and compared the memory forgetting processes with the child's game involving a «mystic writing-pad» (Freud, 1925). In fact, it seems rather that this (at least) noradrenergic early reappearance rather constitutes a physiological censorship (Gottesmann, 2006a,b) with the psychological consequence of avoiding an overload of irrational mental contents on waking (Crick and Michison, 1983). When this waking protection process fails, holographic-like dream pictures generated by biophotons erupt into the waking consciousness (Bokkon, 2005) and a door opens onto schizophrenia in predisposed subjects with the possible integration of hallucinatory dreaming activity in the functioning of the waking mind (Kelly, 1998).

2.2.2. *Tomography*

Blood flow studies have shown that the main forebrain structures involved in mentation are strongly activated during REM sleep (Madsen et al., 1991; Maquet et al., 1996; Braun et al., 1997, 1998; Maquet, 2000) and several limbic structures involved in affective processes are even more activated than during waking (Maquet et al., 1996; Nofzinger et al., 1997). This

can explain the affective involvement in dreams, particularly since the amygdala is strongly activated in REM sleep (Maquet and Franck, 1997). However, the frontal cortex (Madsen et al., 1991) and particularly the dorsolateral prefrontal and the posterior cingular cortex are deactivated during REM sleep (Maquet et al., 1996; Braun et al., 1997) (although there is a slight discrepancy in that there seems to be an increase of glucose utilization in the dorsolateral prefrontal cortex (Nofzinger et al., 1997)). It is of importance that the dorsolateral prefrontal cortex is also specifically deactivated in schizophrenia, particularly when cognitive performances are decreased (Weinberger et al., 1986; Fletcher et al., 1998). There is also a decrease of glucose uptake (Buschbaum et al., 1982). In addition, it is of interest that joint deactivation of dorsolateral and posterior cingular cortex was up to now observed only in piano playing, particularly when the musicians «lose themselves» when completely absorbed in intense performances (Parsons et al., 2005) (for example, is it allowed to think of Glenn Gould playing J.S. Bach, particularly the last recorded performance of Goldberg variations?). This behavior, during which the artist is in a transe-like state shows some resemblance to dreaming and schizophrenia where there is a loss of contact with reality.

However, another important structure is deactivated. Indeed, while the visual associative areas are activated during REM sleep particularly at the commencement of the ventral stream, which certainly contributes to the rich visual hallucinatory activity (Madsen et al., 1991; Braun et al., 1998), the primary visual area is deactivated (Braun et al., 1998). This is an index of disconnection from sensory inputs which is reinforced by the finding in animals of a presynaptic depolarization (Wall, 1958) in the thalamic relay nuclei, which is another cause of inhibition of sensory inputs (Iwama et al., 1966; Dagnino et al., 1969; Ghelarducci et al., 1970; Steriade, 1970; Gandolfo et al., 1980). In schizophrenia, one of the current hypotheses to explain the hallucinatory activity also involves lowering of sensory constraints (Behrendt and Young, 2005). Finally, this sensory disconnection could also explain the increased threshold to pain during psychotic episodes (Griffin and Tyrrell, 2003).

2.2.3. *Pharmacology and neurochemistry*

There are two main hypotheses related to schizophrenia involving disturbances of dopamine and glutamate, more generally suggesting a glutamate-monoamine imbalance (Pralong et al., 2002).

First, dopamine involvement. In nucleus accumbens, an excess of this neuromodulator is considered to be at least partly responsible for the positive symptoms (hallucinations, delusions, bizarre thought processes) (MacKay et al., 1982). On the other hand, a deficit in the prefrontal cortex is thought to cause the negative symptoms, among them the decrease or loss of reflectiveness (Abi-Dargham and Moore, 2003). Both kinds of symptoms are also observed in REM sleep. While dopamine agonists such as amphetamine induce both psychotic disturbances (Buffenstein et al., 1999) and nightmares (Thompson and Pierce, 1999), neuroleptics, which block the action of dopamine, suppress psychotic symptoms and dreaming, particularly nightmares (Solms, 2000; Jakovljevic et al., 2003).

Using microdialysis and capillary electrophoresis, our laboratory studied the release of dopamine in the medial prefrontal cortex and nucleus accumbens of rats. In the latter structure dopamine release was maximal during REM sleep, although the difference was not significant when compared to waking (Léna et al., 2005), which is in general accordance with schizophrenia (MacKay et al., 1982). This significant release of dopamine could be related firstly to the fact that the dopaminergic neurons are the only monoaminergic neurons which continue to discharge during REM sleep (Miller et al., 1983; Trulson and Preussler, 1984), and that they could discharge by spike bursts (Grace, 1991) which release more dopamine (Gonon, 1988; Chergui et al., 1994). Our result is in accordance with the increase of dopaminergic neuron c-Fos activity in the ventral tegmental area during REM sleep (Maloney et al., 2002). In addition, prefrontal deactivation favors dopamine release in nucleus accumbens (Brake et al., 2000; Takahata and Moghaddam, 2000; Jackson et al., 2001). In the prefrontal cortex there was a significant decrease during REM sleep as compared to waking, which is exactly the situation with schizophrenia as perceived today (Abi-Dargham and Moore, 2003). This decrease also seems to be related to prefrontal deactivation (Takahata and Moghaddam, 2000) and could explain the loss of reflectiveness during dreaming. Finally, this decrease of dopamine release during REM sleep is in accordance with the putative inverted u-shaped curve that links prefrontal dopamine stimulation of D_1 receptors and appropriate cognitive functioning (Meyer-Lindenberg and Weinberger, 2006).

The second hypothesis postulates a deficit of glutamate functioning. Indeed, these neurotransmitter antagonists induce psychotic symptoms (Grace, 2000; Heresco-Levy, 2000) while also generating vivid dreaming (Reeves et al., 2001). A glutamate deficit in nucleus accumbens seems to result from the lowering of hippocampus glutamatergic output which inhibits its prefrontal release in nucleus accumbens (Grace, 2000). Hence, the glutamatergic influence of medial nucleus of amygdala could predominate generating disturbances of emotional processes. This occurs in schizophrenia as well as during dreaming because of strong amygdala activation during this sleep stage (Maquet and Franck, 1997).

We measured glutamate concentration in both structures (Léna et al., 2005). In nucleus accumbens, the level was significantly lower during REM sleep as compared to waking, exactly as is thought to be the case in schizophrenia. In the prefrontal cortex we found no change during sleep–waking stages. This result is crucial since it has been reported that there is no change of glutamate transporter mRNA expression in schizophrenic patients (Lauriat et al., 2005). However, at both levels, there could be a weakening of glutamate synaptic strength and synaptic destabilization by glial disfunctioning (Moises et al., 2002).

In addition we tested noradrenaline release. In the prefrontal cortex, this neuromodulator is issued from neurons located in the locus coeruleus. There was a significant decrease of noradrenaline during REM sleep as compared to waking and slow wave sleep. It is interesting to notice that there was

maintenance of a given level in spite of the silence of corresponding neurons. This is certainly the result of its diffuse release (Descarries et al., 1977). In nucleus accumbens, noradrenaline is mainly issued from the medulla oblongata and only slightly from locus coeruleus (Delfs et al., 1998). However, the concentration was, here again, significantly lower during REM sleep. Once again, there is a noradrenaline deficit in schizophrenia (see above) and this neuromodulator facilitates cognitive processes (Lapiz and Morilak, 2005). We already emphasized the serotonergic silence during REM sleep and its deficit in schizophrenia. Serotonergic antagonists like LSD 25 induce psychotic symptoms, while decreasing serotonergic neuron firing (Aghajanian et al., 1968), and increase REM sleep (Toyoda, 1964; Muzio et al., 1966).

Acetylcholine is another major neurotransmitter. Its functioning at cortical level is crucial for normal cognitive processes (Perry et al., 1999; Sarter and Bruno, 2000). A decrease in concentration of acetylcholine is considered to underlie the occurrence of hallucinatory activity during waking (Collerton et al., 2005) and there is a decrease of muscarinic receptors in the cortex of untreated schizophrenic patients (Raedler et al., 2003). Finally, α-7 agonists of the nicotinic receptor provide a potential treatment for the P50 suppression deficit (Olincy et al., 2006) observed in schizophrenic patients and their relatives (Siegel et al., 1984; Clementz et al., 1998; Braff et al., 2007), and there is improvement of both psychiatric symptoms and P50 inhibition after clozapine (Nagamoto et al., 1999) which increases acetylcholine efflux in the prefrontal cortex (Huang et al., 2006). During REM sleep, the cortical release of acetylcholine has long been shown to be high (Jasper and Tessier, 1971). However, more recent research demonstrated that, although in nucleus basalis which projects on the cortex the release is highest during REM sleep (Vasquez and Baghdoyan, 2001), in the cortex the release is lower as compared to active waking, reaching only the level of relaxed waking (Marrosu et al., 1995). This decrease could also contribute to the occurrence of hallucinatory activity during dreaming.

Conclusion: All the electrophysiological, tomographic, pharmacological and neurochemical characteristics of REM sleep are specifically encountered in schizophrenia and constitute candidates endophenotypes of this disease. Consequently, REM sleep and its architecture could become a worthy neurobiological model of this mental disorder.

Several neurological diseases show a decrease of REM sleep. However, apart from manic episodes, which are characterized by global insomnia, there are mental diseases where there is a more specific deficit of REM sleep, namely disorders with insufficient cognitive functions.

2.3. Mental retardation and dementia

Although mental retardation («oligophrenia») is a congenital deficit of cognitive potentialities and dementia a later regression of these abilities, these two disorders can be considered in the same paper. REM sleep occurs with high amounts during childhood (Muzio et al., 1966), and its suppression in animals impairs learning and memory (Hennevin et al., 1995; Smith, 1995). Jouvet advanced the hypothesis that, just as computer programs have to be periodically adjusted, the genetic programming of behavior is reset during REM sleep and that this sleep stage deficit induces disfunctioning of the intellectual faculties (Jouvet, 1992). It has been shown that mental retardation, whatever its etiology, is characterized by a decrease of REM sleep with less eye movement density and an increase of the «intermediate phase» (Grubar, 1983) described by several authors (Goldsteinas and Lairy, 1965; Goldsteinas et al., 1966; Lairy et al., 1968). This stage, usually of short duration (1–5% of total sleep) (Goldsteinas et al., 1966), gives rise to the association of cortical spindles and K complexes characteristic of slow wave sleep, which are interspersed with more or less long periods of flat EEG. There are no eye movements. Lairy also considered that this intermediate phase corresponded to 20 s without eye movements at onset and outcome of REM sleep (Lairy et al., 1968). A particular mental activity occurs during this stage. It is not visual, and the mental content, which is difficult to obtain at arousal in spite of behavioral waking because of the difficulty in establishing contact, is associated with a «feeling of indefinable discomfort, anxious perplexity and harrowing worry» (p. 269) (Lairy et al., 1968). Other authors (Larson and Foulkes, 1969) reported that, in this sleep period mental contents are «inconsistent with the hypothesis of an intensification of mental activity or cerebral vigilance at pre-REM EMG suppression» (p 552). These early data, which have so far not been repeated, already contradicted the hypothesis of Steriade (Steriade et al., 1989), suggesting that vivid dreams should occur during this sleep period because of high amplitude isolated ponto-geniculo-occipital (P.G.O.) spikes occurring in cats and corresponding to phasic central activation of the cortex (Kiyono and Iwama, 1965; Satoh, 1971). In addition, in humans the peripheral vegetative characteristics of this stage were those of slow wave sleep (stages II and III) except for the electrodermogram which was often abolished as during REM sleep (Hawkins et al., 1962; Tokizane, 1964; Broughton et al., 1965; Johnson and Lubin, 1966). In mental retardation, this intermediate phase was extended at the expense of REM sleep. The significance of these disturbances is perhaps to be found in animal research. Indeed, independently from this human clinical finding, an «intermediate stage» had been shown in rats prior to REM sleep (Gottesmann, 1964, 1967b; Weiss and Adey, 1965; Depoortere and Loew, 1973; Gaillard et al., 1977; Lancel et al., 1996). This stage is characterized by high amplitude spindles in the frontal cortex, an index of deep slow wave sleep, and by low frequency theta rhythm in the dorsal hippocampus, an index of REM sleep. It was later identified in cats (Gottesmann et al., 1984) and mice (Glin et al., 1991). Interestingly, it is reproduced in rats (Gottesmann et al., 1980) and cats (Gottesmann et al., 1984) by an acute intercollicular transection (cerveau isolé preparation of Bremer (Bremer, 1935)) which, during several hours, induces continuous high ampitude cortical spindles and low frequency theta rhythm. This transitional stage would therefore seem to correspond to a transient physiological disconnection of the

forebrain from the brainstem. This conclusion is strengthened by the fact that thalamocortical responsiveness during the intermediate stage is the lowest of all sleep–waking stages (Gandolfo et al., 1980; Gottesmann et al., 1984). In fact, during the intermediate stage, the brainstem influences are not totally suppressed since the cortical neurons begin already to increase their firing prior to REM sleep (McCarley and Hobson, 1971a), but this cell slight activation is too low to modify the EEG field activities. Finally, this sleep period is suppressed by low doses of barbiturates which induce a long-lasting intermediate stage at the expense of REM sleep (Gottesmann, 1964; Gottesmann et al., 1984), while suppressing the pontine activation which is nearly specific of REM sleep (Gottesmann, 1967a,b, 1969; McCarley and Hobson, 1971b; Moroz et al., 1977; Vertes, 1977) (for synthesis see Gottesmann, 1996). Thus, in mental retardation there is a disturbance of basic REM sleep generating processes and of simultaneous brainstem ascending activating and inhibitory influences crucial for cognitive processes.

Similarly, REM sleep is lower in Alzheimer patients who manifest degeneration of the cholinergic system of the brain (Christos, 1993). Animal models of this disease show reduced REM sleep amounts and neuron disturbances in the brainstem structures involved in REM sleep-generating processes (pedunculopontine nucleus) (Zhang et al., 2005). Moreover, acetylcholine involvement in both REM sleep and cognition has been confirmed by two recent studies which have shown in Alzheimer patients that donepezil (an anticholinesterase compound) increases REM sleep, reduces EEG slow frequencies while increasing waking alpha rhythm, and tends to improve cognitive functions (Mizuno et al., 2004; Moraes et al., 2006).

Conclusion: REM sleep deficit in young people and the elderly seems to be an endophenotype of mental retardation and dementia, although this characteristic has to be considered with caution since both diseases may stem from different etiologies. The mesopontine cholinergic nuclei (pedunculopontine and dorsolateral tegmental nuclei), in addition to controlling basic REM sleep-generating processes, project to forebrain nucleus basalis the cholinergic neurons of which activate the cortex, and the importance of acetylcholine for mentation was already underlined (Perry et al., 1999; Sarter and Bruno, 2000).

3. General conclusion

The sleep–waking cycle is a fundamental biological rhythm since all types of behavior (feeding, sexual, social) are grafted upon it. It is rather unexpected that the old phylogenetic structures of the brainstem should sustain the forebrain structures responsible for generating higher integrated activities such as waking and sleep mentation.

This paper shows that, although increased rapid eye movement density and decreased REM sleep latency are systematically associated with depression, the connection with mental disturbances characteristic of depression is rather tenuous. Consequently, identification of the genic support of these REM sleep disturbances will not necessarily contribute to a significantly better understanding of the ultimate mechanisms of mood disturbances.

In contrast, the main electrophysiological, tomographic, pharmacological and neurochemical characteristics of REM sleep are also encountered in schizophrenia and this sleep stage could be adopted as a new component in a neurobiological model of this mental disease. This finding is of particular interest since it is based on physiological criteria, without the usual central applied stimulations, lesions or drugs. The discovery of the gene(s) of each of these REM sleep activities could greatly help to identify the abnormalities underlying schizophrenia and assist in the development of appropriate therapies.

From the clinical standpoint, Kant expressed very clearly how the schizophrenic characteristics of REM sleep mentation erupt into waking consciousness (and a recent animal study confirmed that REM sleep patterns can appear in the waking state during hyperdopaminergic functioning (Dzirasa et al., 2006)). The fact that, during waking, the forebrain structures are in a physiological state of REM sleep could be explained to the patients outside the psychotic episodes. Indeed, the description of this brain functioning abnormality would probably relieve the subject's stress by reducing the emotional charge linked to the disturbances (Griffin and Tyrrell, 2003). Such a psychotherapeutic approach, together with pharmacological treatment, could contribute to fuller recovery.

Finally, a fuller understanding of genetic disturbances responsible for the so-far identified neonate (Zhang et al., 2005) or later cholinergic neuron apoptosis could open up a new domain for the treatment of cognitive disorders of young people and for the growing number of patients suffering from Alzheimer's disease.

Consequently, REM sleep neurobiological characteristics represent an unexpected and original set of highly significant endophenotypes of mental diseases, and notably of schizophrenia. Elucidation of each of their genic supports in animal models (Gould and Gottesman, 2006) offers a highly promising avenue of research into early treatment of mental disorders.

Acknowledgments

I thank Professor George Morgan for improving the English of the manuscript (C.G.).

References

Abi-Dargham, A., Moore, H., 2003. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. Neuroscientist 9, 404–416.

Adrien, J., 2002. Neurobiological bases for the relation between sleep and depression. Sleep Med. Rev. 6, 341–351.

Aghajanian, G.K., Foot, W., Sheard, M., 1968. Lysergic acid diethylamide: sensitive neuronal units in the midbrain raphe. Science 161, 706–708.

Aldrich, M.S., 1991. The neurobiology of the narcolepsy–cataplexy syndrome. Int. J. Neurol. 25–26, 29–40.

Alexandre, C., Popa, D., Fabre, V., Bouali, S., Venault, P., Lesch, K.P., Hamon, M., Adrien, J., 2006. Early-life blockade of 5-HT1A receptors normalizes sleep and depression-like behavior in adult knock-out mice lacking the serotonin transporter. J. Neurosci. 17, 5554–5564.

Araneda, R., Andrade, R., 1991. 5-Hydroxytryptamine2 and 5-hydroxytryptamine 1A receptors mediate opposing responses on membrane excitability in the association cortex. Neuroscience 40, 399–412.

Aserinsky, E., Kleitman, N., 1953. Regularly occurring periods of eye motility, and concomitant phenomena during sleep. Science 118, 273–274.

Aston-Jones, G., Bloom, F.E., 1981a. Activity of norepinephrine-containing neurons in behaving rats anticipates fluctuations in the sleep–waking cycle. J. Neurosci. 1, 876–886.

Aston-Jones, G., Bloom, F.E., 1981b. Norepinephrine-containing locus coeruleus neurons in behaving rat exhibit pronounced responses to non-noxious environmental stimuli. J. Neurosci. 1, 887–900.

Baghdoyan, H.A., 1997. Cholinergic mechanisms regulating REM sleep. Sleep Sci.: Basic Res. Clin. Prac. Monogr. Clin. Neurosci. 88–116.

Battaglia, M., Strambi, L.F., Bertella, S., Bajo, S., Bellodi, L., 1999. First-cycle REM density in never-depressed subjects with borderline personality disorder. Biol. Psychiat. 45, 1056–1058.

Behrendt, R.P., Young, C., 2005. Hallucinations in schizophrenia, sensori impairment and brain disease: an unified model. Behav. Brain Sci. 27, 771–787.

Benes, F.M., Matzilevitch, D., Burke, R.E., Walsh, J., 2005. The expression of proapoptisis genes is increased in bipolar disorder, but not in schizophrenia. Mol. Psychiat. 11, 1–11.

Benson, K.L., Zarcone, V.P.J., 1993. Rapid eye movement sleep eye movements in schizophrenia and depression. Arch. Gen. Psychiat. 50, 474–482.

Berger, R., 1961. Tonus of extrinsic laryngeal muscles during sleep and dreaming. Science 134, 840.

Berrettini, W.H., 2005. Genetic bases for endophenotypes in psychiatric disorders. Dial Clin. Neurosci. 7, 95–101.

Blagrove, M., Blakemore, S.J., Thayer, B.R.J., 2006. The ability to self-tickle following rapid eye movement sleep dreaming. Conscious Cogn. 15, 285–294.

Bokkon, I., 2005. Dreams and neuroholography: an interdisciplinary interpretation of development of homeotherm state in evolution. Sleep Hypnosis 7, 61–76.

Bosinelli, M., 1995. Mind and consciousness during sleep. Brain Res. 69, 195–201.

Bourgin, P., Huitron-Resendiz, S., Spier, A.D., Fabre, V., Morte, B., Criado, J.R., Siutcliffe, J.G., Henriksen, S.I., Lecea de, L., 2000. Hypocretin-I modulatesz rapid eye movement sleep through activation of locus coeruleus neurons. J. Neurosci. 20, 7760–7765.

Boutrel, B., Franc, B., Hen, R., Hamon, M., Adrien, J., 1999. Key role of 5-HT1B receptors in the regulation of paradoxical sleep as evidenced in 5-HT1B knock-out mice. J. Neurosci. 19, 3204–3214.

Bouyer, J.J., Montaron, M.F., Rougeul, A., 1981. Fast fronto-parieta rhythms during combined focused attentive behavior and immobility in cat: cortical and thalamic localizations. Electroenceph Clin. Neurophysiol. 51, 244–252.

Braff, D.L., Freedman, R., Schork, N.J., Gottesman, I.I., 2007. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophr. Bull. 33, 21–32.

Brake, W.G., Flores, G., Francis, D., Meaney, M.J., Srivastava, L.K., Gratton, A., 2000. Enhanced nucleus accumbens dopamine and plasma corticosterone stress responses in adult rats with neonatal excitotoxic lesions to the medial prefrontal cortex. Neuroscience 96, 687–695.

Braun, A.R., Balkin, T.J., Wesensten, N.J., Carson, R.E., Varga, M., Baldwin, P., Selbie, S., Belenky, G., Herscovitch, P., 1997. Regional cerebral blood flow throughout the sleep–wake cycle: an ^{15}O PET study. Brain 120, 1173–1197.

Braun, A.R., Balkin, T.J., Wesensten, N.J., Gwardry, F., Carson, R.E., Varga, M., Baldwin, P., Belenky, G., Herscovitch, P., 1998. Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 279, 91–95.

Bremer, F., 1935. Cerveau ''isolé'' et physiologie du sommeil. C.R. Soc. Biol. 118, 1235–1241.

Broughton, R.J., Poiré, R., Tassinari, C.A., 1965. The electrodermogram (Tarchanoff effect) during sleep. Electroenceph Clin. Neurophysiol. 18, 691–708.

Buffenstein, A., Heaster, J., Ko, P., 1999. Chronic psychotic illness from amphetamine. Am. J. Psychiat. 156, 662.

Buschbaum, M.S., Ingvar, D.H., Kessler, R., Waters, R.N., Cappelletti, J., Van Kammen, D.P., King, A.C., Johnson, J.L., Manning, R.G., Flynn, R.W., Bunney, W.E.J., Sokoloff, L., 1982. Cerebral glucography with positron tomography, use in normal subjects and in patients with schizophrenia. Arch. Gen. Psychiat. 39, 251–259.

Cadilhac, J., Baldy-Moulines, M., Delange, M., 1966. Sommeil diurne et sommeil nocturne dans la narcolepsie. Riv. Neurol. 36, 94–107.

Callaway, C.W., Lydic, R., Bagdoyan, H.A., Hobson, J.A., 1987. Pontogeniculooccipital waves: spontaneous visual system activity during rapid eye movement sleep. Cell Mol. Neurobiol. 7, 105–149.

Cantero, J.L., Atienza, M., Madsen, J.R., Stickgold, R., 2004. Gamma EEG dynamics in neocortex and hippocampus during human wakefulness and sleep. Neuroimage 22, 1271–1280.

Chergui, K., Suaud-Chagny, M.F., Gonon, F., 1994. Non-linear relationship between impulse flow. Dopamine release and dopamine elimination in the rat in vivo. Neuroscience 62, 641–645.

Christos, G.A., 1993. Is Alzheimer's disease related to a deficit or malformation of rapid eye movement (REM) sleep? Med. Hypotheses 41, 435–439.

Cirelli, C., 2005. A molecular window on sleep: changes in gene expression between sleep and wakefulness. Neuroscientist 11, 63–74.

Clark, C., Dupont, R., Golshan, S., Gillin, J.C., Rapaport, M.H., Kelsoe, 2000. Preliminary evidence of an association between increased REM density and poor antidepressant response to partial sleep deprivation. J. Affect Disord. 59, 77–83.

Clementz, B.A., Geyer, M.A., Braff, D.L., 1998. Poor P50 suppression among schizophrenic patients and their first-degree relatives. Am. J. Psychiat. 155, 1691–1694.

Cohen, H.B., Dement, W.C., 1966. Sleep: suppression of rapid eye movement phase in the cat after electroconvulsive shock. Science 154, 396–398.

Cohen, H.B., Duncan II, R.F., Dement, W.C., 1967. Sleep: the effect of electroconvulsive shocks in cats deprived of REM sleep. Science 156, 1648–1746.

Collerton, D., Perry, E., McKeith, I., 2005. A novel perception and attention deficit model for recurrent visual hallucinations. Brain Behav. Sci. 28, 737–757.

Cordeau, J.P., Moreau, A., Beaulnes, A., Laurin, C., 1963. EEG and behavioral changes following microinjections of acetylcholine and adrenaline in the brain stem of cats. Arch. Ital. Biol. 101, 30–47.

Crick, F., Michison, G., 1983. The function of dream sleep. Nature 304, 111–114.

Dagnino, N., Favale, E., Loeb, C., Manfredi, M., Seitun, A., 1969. Presynaptic and postsynaptic changes in specific thalamic nuclei during deep sleep. Arch. Ital. Biol. 107, 668–684.

Dahlstrom, A., Fuxe, K., 1964. Evidence for existence of monoamine-containing neurons in the central nervous system. Acta Physiol. Scand. 62 (Suppl. 232), 3–55.

Datta, S., Siwek, D.F., 1997. Excitation of the brainstem pedunculopontine tegmentum cells induces wakefulness and REM sleep. J. Neurophysiol. 77, 2975–2988.

Datta, S., Spoley, E.E., Patterson, E.H., 2001. Microinjection of glutamate into the pedunculopontine tegmentum induces REM sleep and wakefulness in the rat. Am. J. Physiol. 280, R752–R759.

DeBastita, C., Lemke, A., Solvason, H., Ghebremichael, R., Poirier, J., 2004. A prospective trial of modafinil as an adjunctive treatment of major depression. J. Clin. Psychopharmacol. 24, 87–90.

Delay, J., Deniker, P., Harl, J.M., 1952. Traitement des états d'excitation et d'agitation par une méthode médicamenteuse dérivée de l'hibernothérapie. Ann. Med. Psychol. 110, 267–273.

Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G.S., 1998. Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res. 806, 127–140.

Dement, W., Kleitman, N., 1957. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroenceph Clin. Neurophysiol. 9, 673–690.

Dement, W.C., 1958. The occurrence of low voltage fast electroencephalogram patterns during behavioral sleep in the cat. Electroenceph Clin. Neurophysiol. 10, 291–296.

Demetrescu, M., Demetrescu, M., Iosif, G., 1966. Diffuse regulation of visual thalamo-cortical responsiveness during sleep and wakefulness. Electroenceph Clin. Neurophysiol. 20, 450–469.

Depoortere, H., Loew, D.M., 1973. Motor phenomena during sleep in the rat: a mean of improving the analysis of the sleep–wakefulness cycle. In: Jovanovic, U. (Ed.), The Nature of Sleep. Gustav Fisher, Stuttgart, pp. 101–104.

Descarries, L., Beaudet, A., Watkins, K.C., 1975. Serotonin nerve terminals in the adult rat neocortex. Brain Res. 100, 563–588.

Descarries, L., Watkins, K.C., Lapierre, Y., 1977. Noradrenergic axon terminals in the cerebral cortex of rats. III. Topometric ultrastructural analysis. Brain Res. 133, 197–222.

Douglass, A.B., 2003. Narcolepsy: differential diagnosis or etiology in some cases of bipolar disorder and schizophrenia. CNS Spectr. 8, 120–126.

Dugovic, C., Solberg, L.C., Redei, E., Van Reeth, O., Turek, F.W., 2000. Sleep in the Wistar–Kyoto rat, a putative genetic animal model for depression. Neuroreport 11, 627–631.

Dunleavy, D.L.F., Oswald, I., 1973. Phenelzine, mood response, and sleep. Arch. Gen. Psychiat. 28, 353–356.

Dzirasa, K., Ribeiro, S., Costa, R., Santos, L.M., Lin, S.-C., Grosmark, A., Sotnikova, T.D., Gainetdinov, R.R., Caron, M.G., Nicolelis, M.A.L., 2006. Dopaminergic control of sleep–wake states. J. Neurosci. 26, 10577–10589.

Eisensamer, B., Uhr, M., Myer, S., Gimpl, G., Deiml, T., Rammesz, G., Lambert, J.J., Zieglgänsberger, W., Holsboer, F., Ruppecht, R., 2005. Antidepressants and antipsychotic drugs colocalize with 5-HT_3 receptors in raft-like domains. J. Neurosci. 25, 10198–10206.

Evarts, E.V., 1964. Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey. J. Neurophysiol. 27, 152–171.

Evarts, E.V., 1965. Neuronal activity in visual and motor cortex during sleep and waking. In: Aspects anatomo-fonctionnels de la physiologie du sommeil. CNRS ed., Paris, pp. 189–212.

Feinberg, I., Koresco, R.L., Gottlieb, F., Wender, P.H., 1964. Unusually high dream time in an hallucinating patient. Am. J. Psychiat. 121, 1018–1020.

Fletcher, P.C., McKenna, P.J., Frith, C.D., Grasby, P.M., Friston, K.J., Dolan, R.J., 1998. Brain activation in schizophrenia during a graded memory taski studied with functional neuroimaging. Arch. Gen. Psychiat. 55, 1001–1008.

Foote, S.L., Freedman, R., Oliver, A.P., 1975. Effects of putative neurotransmitters on neuronal activity on monkey auditory cortex. Brain Res. 86, 229–242.

Fouks, L., Laine, Grimaud, Dariotis, 1954. La fin des thérapeutiques de choc et l'avènement de nouvelles thérapeutiques psychiatriques actives. Ann. Médico-Psychol. 112, 764–768.

Foulkes, W.D., 1962. Dream reports from different stages of sleep. J. Abnormal Soc. Psychol. 65, 14–25.

Foutz, A., Mitler, M.M., Cavalli-Sforza, L.L., Dement, W.C., 1979. Genetic factors in canine narcolepsy. Sleep 1, 280–286.

Franken, P., Djik, D.J., Tobler, I., Borbely, A.A., 1994. High-frequency components of the rat electrocorticogram are modulated by the vigilance states. Neurosci. Lett. 167, 89–92.

Frederickson, R.C.A., Jordan, L.M., Phillis, J.W., 1971. The action of noradrenaline on cortical neurons: effects of pH. Brain Res. 35, 556–560.

Freis, E.D., 1954. Mental depression in hypertensive patients treated for long periods with large doses of reserpine. N. Engl. J. Med. 251, 1006–1008.

Freud, S., 1900. The interpretation of dreams. The Hogart Press, London, 1955.

Freud, S., 1925. A note upon the " mystic writing-pad", standard ed., vol. 19. The Hogart Press, London, pp. 227–232.

Friedman, J.I., Adler, D.N., Davis, K.L., 1999. The role of norepinephrine in the physiopathology of cognitive disorders: potential applications to the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease. Biol. Psychiat. 46, 1243–1252.

Fruhstorfer, B., Mignot, E., Bowersox, S.S., Nishino, S., Dement, W., Guilleminault, C., 1989. Canine narcolepsy is associated with elevated number of alpha-2 receptors in the locus coeruleus. Brain Res. 500, 209–214.

Fulton, M.K., Armitage, R., Rush, A.J., 2000. Sleep electroencephalographic coherence abnormalities in individuals at high risk for depression: a pilot study. Biol. Psychiat. 47, 618–625.

Fuxe, K., 1965. Evidence for the existence of monoamine neurons in the central nervous system. IV. Distribution of monoamine nerve terminals in the central nervous system. Acta Physiol. Scand. 247 (Suppl.), 37–85.

Fuxe, K., Hamberger, B., Hökfelt, T., 1968. Distribution of noradrenaline nerve terminals in cortical areas if the rat. Brain Res. 8, 125–131.

Gaillard, J.M., Martinoli, R., Kafi, S., 1977. Automatic analysis of states of vigilance in the rat. In: Sleep 1976, Karger, Basel, pp. 455–457.

Gandolfo, G., Arnaud, C., Gottesmann, C., 1980. Transmission in the ventrobasal complex of rat during the sleep–waking cycle. Brain Res. Bull. 5, 921–927.

Gastaut, H., Duron, B., Papy, J.J., Tassinari, C.A., Waltregny, A., 1966. Etude polygraphique comparative du cycle nycthémérique chez les narcoleptiques, les Pickwickiens, les obèses et les insuffisants respiratoires. Rev. Neurol. 115, 456–462.

George, R., Haslett, W.L., Jenden, D.J., 1964. A cholinergic mechanism in the brainstem reticular formation: induction of paradoxical sleep. Int. J. Neuropharmacol. 3, 541–552.

Ghelarducci, B., Pisa, M., Pompeiano, M., 1970. Transformation of somatic afferent volleys across the prethalamic and thalamic components of the lemniscal sytem during the rapid eye movements of sleep. Electroenceph Clin. Neurophysiol. 29, 348–357.

Giles, D.E., Biggs, M.M., Rush, A.J., Roffwarg, H., 1988a. Risk factors in families of unipolar depression. I. Psychiatric illness and reduced REM latency. J. Affect Disord. 14, 51–59.

Giles, D.E., Jarret, R.B., Roffwarg, H., Rush, A.J., 1988b. Reduced eye movement latency. A predictor of recurrence in depression. Neuropsychopharmacology 1, 33–39.

Giles, D.E., Jarret, R.B., Rush, A.J., Biggs, M.M., Roffwarg, H., 1993. Prospective assessment of electroencephalographic sleep in remitted major depression. Psychiat. Res. 46, 269–284.

Giles, D.E., Kupfer, D.J., Rush, A.J., Roffwarg, H., 1998. Controlled comparison of electrophysiological sleep in families of probands with unipolar depression. Am. J. Psychiat. 155, 192–199.

Gillin, J.C., Sohn, J.W., Stahl, S.M., Lardon, M., Kelsoe, J., Rapaport, M.H., Ruiz, C., Golshan, S., 1996. Ipsapirone, a 5-HT1A agonist, suppresses REM sleep equally in unmedicated depressed patients and normal controls. Neuropsychopharmacology 15, 109–115.

Gillin, J.C., Wyatt, R.J., Fram, D., Snyder, F., 1978. The relationship between changes in REM sleep and clinical improvement in depressed patients with amitriptyline. Psychopharmacology 59, 267–272.

Glin, L., Arnaud, C., Berracochéa, D., Galey, D., Jaffard, R., Gottesmann, C., 1991. The intermediate stage of sleep in mice. Physiol. Behav. 50, 951–953.

Goetz, R.R., Wolk, S.I., Coplan, J.D., Ryan, N.D., Weissman, M.M., 2001. Premorbid polysomnographic signs in depressed adolescents: a reanalysis of vEEG sleep after longitudinal follow-up in adulthood. Biol. Psychiat. 2001, 930–942.

Goldman, M., Tandon, R., DeQuardo, J.R., Taylor, S.F., Goodson, J., McGrath, M., 1996. Biological predictors of 1-year outcome in schizophrenia in males and females. Schizophr. Res. 21, 65–73.

Goldsteinas, L., Guennoc, A., Vidal, J.C., 1966. Nouvelles données cliniques sur le vécu des "phases intermédiaires" du sommeil. Rev. Neurol. 115, 507–511.

Goldsteinas, L., Lairy, G.C., 1965. Etude du sommeil de nuit dans certains cas de confusion mentale. Rev. Neurol. 113, 284–290.

Gonon, F.G., 1988. Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry. Neuroscience 24, 19–28.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiat. 160, 636–645.

Gottesman, I.I., Shields, J., 1967. A polygenic theory of schizophrenia. Proc. Natl. Acad. Sci. USA 58, 199–205.

Gottesman, I.I., Shields, J., 1973. Genetic theorizing and schizophrenia. Br. J. Psychiat. 122, 15–36.

Gottesmann, C., 1964. Données sur l'activité corticale au cours du sommeil profond chez le rat. C.R. Soc. Biol. 158, 1829–1834.

Gottesmann, C., 1966. Identification d'une activité électrophysiologique phasique indépendante de la phase paradoxale du sommeil chez le rat. C.R. Soc. Biol. 160, 528–534.

Gottesmann, C., 1967a. Données récentes sur les activités électrophysiologiques phasiques. Psychol. Franç. 12, 1–14.

Gottesmann, C., 1967b. Recherche sur la psychophysiologie du sommeil chez le rat. Presses du Palais Royal, Paris.

Gottesmann, C., 1969. Etude sur les activités électrophysiologiques phasiques chez le rat. Physiol. Behav. 4, 495–504.
Gottesmann, C., 1970. La psychophysiologie du sommeil. Bull. Psychol. 24, 520–528.
Gottesmann, C., 1971. Psychophysiologie du sommeil. Ann. Psychol. 71, 451–488.
Gottesmann, C., 1996. The transition from slow wave sleep to paradoxical sleep: evolving facts and concepts of the neurophysiological processes underlying the intermediate stage of sleep. Neurosci. Biobehav. Rev. 20, 367–387.
Gottesmann, C., 1997. Introduction to the neurophysiological study of sleep: central regulation of skeletal and ocular activities. Arch. Ital. Biol. 135, 279–314.
Gottesmann, C., 1999. Neurophysiological support of consciousness during waking and sleep. Prog. Neurobiol. 59, 469–508.
Gottesmann, C., 2001. The golden age of rapid eye movement sleep discoveries. I. Lucretius-1964. Prog. Neurobiol. 65, 211–287.
Gottesmann, C., 2005a. Dreaming and schizophrenia. A common neurobiological background. Sleep Biol. Rhyt. 3, 64–74.
Gottesmann, C., 2005b. The golden age of rapid eye movement sleep discoveries: 1965–1966. Nova Science Publishers Inc., New York.
Gottesmann, C., 2006a. The dreaming sleep stage: a new neurobiological model of schizophrenia? Neuroscience 140, 1105–1115.
Gottesmann, C., 2006b. Neurobiological disturbances during the dreaming-sleep stage can explain dream bizarreness without recourse to censorship. Neuro-Psychoanalysis 8, 27–32.
Gottesmann, C., Gandolfo, G., Zernicki, B., 1984. Intermediate stage of sleep in the cat. J. Physiol. Paris 79, 359–372.
Gottesmann, C., User, P., Gioanni, H., 1980. Sleep: a physiological cerveau isolé stage? Waking Sleep 4, 111–117.
Gould, T.D., Gottesman, I.I., 2006. Psychiatric endophenotypes and the development of valid animal models. Genes Brain Behavior. 5, 113–119.
Grace, A.A., 1991. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41, 1–24.
Grace, A.A., 2000. Gating information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res. Rev. 31, 330–341.
Green, W.J., Stajduhar, P.P., 1966. The effect of ECT on the sleep–dream cycle in a psychotic depression. J. Nerv. Ment. Dis. 143, 123–134.
Gresham, S.C., Agnew, H.W.J., Williams, R.L., 1965. The sleep of depressed patients. An EEG and eye movement study. Arch. Gen. Psychiat. 13, 503–507.
Griffin, J., Tyrrell, I., 2003. Human givens: a new approach to emotional health and clear thinking. HG Publishing, New York.
Grubar, J.C., 1983. Sleep in mental deficiency. Rev. EEG Neurophysiol. 13, 107–114.
Hartmann, E., Verdone, P., Snyder, F., 1966. Longitudinal studies and dreaming patterns in psychiatric patients. J. Nerv. Ment. Dis. 142, 117–126.
Hasler, G., Drevets, W.D., Gould, T.D., Gottesman, I.I., Manji, H.M., 2006. Toward constructing an endophenotype strategy for bipolar disorders. Biol. Psychiat. 60, 93–105.
Hasler, G., Drevets, W.C., Manji, H.M., Charmey, D.S., 2004. Discovering endophenotypes for major depression. Neuropharmacology 57, 1765–1781.
Hawkins, D.R., Puryear, H.B., Wallace, C.D., Deal, W.B., Thomas, E.S., 1962. Basal skin resistance during sleep and dreaming. Science 136, 321–322.
Hennevin, E., Hars, B., Maho, C., Bloch, V., 1995. Processing of learned information in paradoxical sleep: relevance for memory. Behav. Brain Res. 69, 125–135.
Heresco-Levy, U., 2000. *N*-methyl-D-aspartate (NMDA) receptor-based treatment approaches in schizophrenia: the first decade. Int. J. Neuropharmacol. 3, 243–258.
Hernandez-Peon, R., Chavez-Ibarra, G., Morgane, P.J., Timo-Iaria, I., 1963. Limbic cholinergic pathways involved in sleep and emotional behavior. Exp. Neurol. 8, 93–111.
Hishikawa, Y., Kaneko, Z., 1965. Electroencephalographic study of narcolepsy. Electroenceph Clin. Neurophysiol. 18, 249–259.
Hobson, J.A., 1964. L'activité électrique phasique du cortex et du thalamus au cours du sommeil désynchronisé chez le Chat. C.R. Soc. Biol. 158, 2131–2135.
Hobson, J.A., McCarley, R.W., Wyzinski, P.W., 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189, 55–58.
Huang, M., Li, Z., Ichikawa, J., Dai, J., Meltzer, H.Y., 2006. Effects of divalproex and atypical antipsychotic drugs on dopamine and acetylcholine efflux in rat hippocampus and prefrontal cortex. Brain Res. 1099, 44–55.
Ising, M., Kunzel, H.E., Binder, E.B., Nickel, T., Modell, S., Holsboer, F., 2005. The combined dexamethasone/CRH test as a potential surrogate marker of depression. Prog. Neuropsychopharmacol. Biol. Psychiat. 29, 1085–1093.
Iwama, K., Kawamoto, T., Sakkakura, H., Kasamatsu, T., 1966. Responsiveness of cat lateral geniculate at pre- and postsynaptic levels during natural sleep. Physiol. Behav. 1, 45–53.
Jackson, M.E., Frost, A.S., Moghaddam, B., 2001. Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in nucleus accumbens. J. Neurochem. 78, 920–923.
Jakovljevic, M., Sagud, M., Mihaljevic-Peles, A., 2003. Olanzapine in the treatment-resistant, combat-related PTSD—a series of case reports. Acta Psychiat. Scand. 107, 394–396.
Jasper, H.H., Tessier, J., 1971. Acetylcholine liberation from cerebral cortex during paradoxical (REM sleep). Science 172, 601–602.
Johnson, L.C., Lubin, A., 1966. Spontaneous electrodermal activity during waking and sleeping. Psychophysiology 3, 8–17.
Jones, B.E., 1991. Paradoxical sleep and its chemical/structural substrates in the brain. Neuroscience 40, 637–656.
Jones, B.E., 2004. Paradoxical sleep promoting and permitting neural networks. Arch. Ital. Biol. 142, 379–396.
Jouvet, M., 1975. Cholinergic mechanisms and sleep. In: Waser, P.G. (Ed.), Cholinergic Mechanisms. Raven Press, New York, pp. 455–476.
Jouvet, M., 1992. Le sommeil et le rêve. Jacob, Paris, 220.
Jouvet, M., Michel, F., 1959. Corrélations électromyographiques du sommeil chez le Chat décortiqué et mésencéphalique chronique. C.R. Soc. Biol. 153, 422–425.
Jouvet, M., Michel, F., 1960a. Déclenchement de la "phase paradoxale" du sommeil par stimulation du tronc cérébral chez le Chat intact et mésencéphalique chronique. C.R. Soc. Biol. 154, 636–641.
Jouvet, M., Michel, F., 1960b. Nouvelles recherches sur les structures responsables de la phase paradoxale du sommeil. J. Physiol. Paris 52, 130–131.
Jouvet, M., Michel, F., Courjon, J., 1959. Sur un stade d'activité électrique rapide au cours du sommeil physiologique. C.R. Soc. Biol. 153, 1024–1028.
Keck, M.E., Ohl, F., Holsboer, F., Muller, M.B., 2005. Listening to mutant mice: a spotlight on the role of CRF/CRF receptor systems in affective disorders. Neurosci. Biobehav. Rev. 29, 867–889.
Kelly, P.H., 1998. Defective inhibition of dream event memory formation: a hypothesized mechanism in the onset and progression of symptoms of schizophrenia. Brain Res. Bull. 46, 189–197.
Kilduff, T.S., Bowersox, S.S., Katin, K.I., Baker, T.L., Ciaranello, R.D., Dement, W.C., 1986. Muscarinic cholinergic receptors and the canine model of narcolepsy. Sleep 9, 102–106.
Kisley, M.A., Olincy, A., Robbins, E., Polk, S.D., Adler, L.E., Waldo, M.C., Freedman, R., 2003. Sensory gating impairement associated with schizophrenia persists into REM sleep. Psychophysiology 40, 29–38.
Kiyono, S., Iwama, K., 1965. Phasic activity of cat's cerebral cortex during paradoxical sleep. Med. J. Osa. Univ. 16, 149–159.
Klein, M., Michel, F., Jouvet, M., 1964. Etude polygraphique du sommeil chez les oiseaux. C.R. Soc. Biol. 158, 99–103.
Krnjevic, K., Phillis, J.W., 1963. Actions of certain amines on cerebral cortex neurons. Br. J. Pharmacol. 20, 471–490.
Kuhn, R., 1958–59. The treatment of depressive states with G 22355 (imipramine hydrochloride). Am. J. Psychiat. 115, 459–464.
Laborit, H., Huguenard, P., 1951. L'hibernation artificielle par moyens pharmacodynamiques et physiques. Pres. Med. 59, 1329.
Lairy, G.C., Barros-ferreira, M., Goldsteinas, L., 1968. Données récentes sur la physiologie et la physiopathologie de l'activité onirique. In: Gastaut, H., Berti Ceroni, E.L.G., Coccagna, G. (Eds.), The Abnormalities of Sleep in Man. Aulo Gaggi, Bologna, pp. 275–283.

Lancel, M., Grönlein, T.A.M., Faulhaber, J., 1996. Role of GABAa receptors in sleep regulation. Differential effects of muscimol and midazolam on sleep in rats. Neuropsychopharmacology 15, 63–74.

Lapiz, M.D.S., Morilak, D.A., 2005. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as mesured by attentional set shifting capability. Neuroscience 137, 1039–1049.

Larson, J.D., Foulkes, D., 1969. Electromyogram suppression during sleep, dream recall and orientation time. Psychophysiology 5, 548–555.

Lauer, C.J., Krieg, J.C., Rieman, D., Zulley, J., Berger, M., 1990. A polysomnographic study in young psychiatric inpatients: majore depression, anorexia nervosa, bulimia nervosa. J. Affect Disord. 18, 235–245.

Lauer, C.J., Rieman, D., Wiegand, M., Berger, M., 1991. From early to late adulthood. Changes in EEG sleep of depressed patients and healthy volunteers. Biol. Psychiat. 29, 979–993.

Lauer, C.J., Schreiber, W., Holsboer, F., Krieg, J.C., 1995. In quest of identifying vulnerability markers for psychiatric disorders by all-night polysomnography. Arch. Gen. Psychiat. 52, 145–153.

Lauer, C.J., Schreiber, W., Pollmacher, T., Holsboer, F., Krieg, J.C., 1997. Sleep in schizophrenia: a polysomnographic study on drug-naive patients. Neuropsychopharmacology 16, 51–60.

Lauriat, T.L., Dracheva, S., Chin, B., Schmeidler, J., McInnes, L.A., Haroutunian, V., 2005. Quantitative analysis of glutamate transporter mRNA expression in prefrontal and primary visual cortex in normal and schizophrenic brain. Neuroscience 137, 843–851.

Léna, I., Parrot, S., Deschaux, O., Muffat, S., Sauvinet, V., Renaud, B., Suaud-Chagny, M.F., Gottesmann, C., 2005. Variations in the extracellular levels of dopamine, noradrenaline, glutamate and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J. Neurosci. Res. 81, 891–899.

Linner, L., Wiker, C., Wadenberg, M.L., Schalling, M., Svensson, T.H., 2002. Noradrenaline reuptake inhibition enhances the antipsychotic-like effect of raclopride and potentiates D2-blockade-induced dopamine release in the medial prefrontal cortex of the rat. Neuropsychpharmacology 27, 691–698.

Llinas, R., Ribary, U., 1993. Coherent 40 Hz oscillation characterizes dream state in humans. Proc. Natl. Acad. Sci. USA 90, 2078–2081.

Loomer, H.P., Saunders, J.C., Kline, N.S., 1957. A clinical and pharmacodynamic evaluation of iproniazid as a psychic energizer. In: Affects, D.A. (Ed.), Proceedings of the Psychiatric Research reports, New York. Am. Psychiat. Assoc., 8, pp. 129–141.

MacKay, A.V., Iversen, L.L., Rossor, M., Spokes, E., Bird, E., Arregui, A., Snyder, S., 1982. Increased brain dopamine and dopamine receptors in schizophrenia. Arch. Gen. Psychiat. 39, 991–997.

Madsen, P.L., Holm, S., Vorstrup, S., Friberg, L., Lassen, N.A., Wildschiodtz, G., 1991. Human regional cerebral blood flow during rapid-eye-movement sleep. J. Cerbr. Blood Flow Met. 11, 502–507.

Mallick, B.N., Majumdar, S., Faisal, M., Yadav, V., Madan, V., Pal, D., 2002. Role of norepinephrine in the regulation of rapid eye movement sleep. J. Biosci. 27, 539–551.

Mallick, B.N., Singh, S., Pal, D., 2005. Role of alpha and beta adrenoceptors in locus coeruleus stimulation-induced reduction in rapid eye movement sleep in freely moving rats. Behav. Brain Res. 158, 9–21.

Maloney, K.J., Cape, E.G., Gotman, J., Jones, B.E., 1997. High-frequency-electroencephalogram activity in association with sleep–wake states and spontaneous behaviors in the rat. Neuroscience 76, 541–555.

Maloney, K.J., Mainville, L., Jones, B.E., 2002. c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum oafter paradoxical sleep deprivation and recovery. Eur. J. Neurosci. 15, 774–778.

Mansour, H.A., Wood, J., Logue, T., Chowdari, K.V., Dayal, M., Kupfer, D.J., Monk, T.H., Devlin, B., Nimgaonkar, V.L., 2006. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. Genes Brain Behav..

Manunta, Y., Edeline, J.M., 1999. Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow wave sleep. Eur. J. Neurosci. 11, 2134–2150.

Maquet, P., 2000. Functional neuroimaging of normal sleep by positon emission tomography. J. Sleep Res. 9, 207–231.

Maquet, P., Franck, G., 1997. REM sleep and amygdala. Mol. Psychiat. 2, 195–196.

Maquet, P., Peters, J.M., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., Franck, G., 1996. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383, 163–166.

Marrosu, F., Portas, C., Mascia, M.F., Casu, M.A., Fa, M., Giagheddu, M., Imperato, A., gessa, G.L., 1995. Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep–wake cycle in freely moving cats. Brain Res. 671, 329–332.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., Tononi, G., 2005. Breakdown of cortical effective connectivity during sleep. Science 309, 2228–2232.

McCarley, R.W., Hobson, J.A., 1971a. Single neuron activity in desynchronized sleep. Science 167, 901–903.

McCarley, R.W., Hobson, J.A., 1971b. Single neuron activity in giganto cellular tegmental field: selectivity of discharge in desynchronized sleep. Science 174, 1250–1252.

McCarley, R.W., Winkelman, J.W., Duffy, F.H., 1983. Human cerebral potentials associated with REM sleep rapid eye movements: links to PGO waves and waking potentials. Brain Res. 274, 359–364.

McCormick, D.A., 1992. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. Prog. Neurobiol. 39, 337–388.

McGinty, D.J., Harper, R.M., 1976. Dorsal raphe neurons: depression of firing during sleep in cats. Brain Res. 101, 569–575.

McGinty, D.J., Harper, R.M., Fairbanks, M.K., 1974. Neuronal unit activity and the control of sleep states. In: Weitzman, E.D. (Ed.), Advances in Sleep Research, vol. 1. Spectrum, New York, pp. 173–216.

Meyer-Lindenberg, A., Olsen, R.K., Kohn, P.D., Brown, T., Egan, M.F., Weinberber, D.R., Berman, K.F., 2005. Regionally specific disturbance of dorsolateral prefrontal-hippocampal function connectivity in schizophrenia. Arch. Gen. Psychiat. 62, 379–386.

Meyer-Lindenberg, A., Poline, J.B., Kohn, P.D., Holt, J.L., Egan, M.F., Weinberger, D.R., Berman, K.F., 2001. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am. J. Psychiat. 158, 1809–1817.

Meyer-Lindenberg, A., Weinberger, D.R., 2006. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat. Rev. Neurosci. 7, 818–827.

Michel, F., Jeannerod, M., Mouret, J., Rechtschaffen, A., Jouvet, M., 1964. Sur les mécanismes de l'activité de pointes au niveau du système visuel au cours de la phase paradoxale du sommeil. C.R. Soc. Biol. 158, 103–106.

Mikiten, T.M., Niebyl, P.H., Hendley, C.D., 1961. EEG desynchronization during behavioral sleep associated with spike discharges from the thalamus of the cat. Fed. Proc. 20, 327.

Miller, J.D., Farber, J., Gatz, P., Roffwarg, H., German, D., 1983. Activity of mesencephalic dopamine and non-dopamine neurons across stages of sleep and waking in the rat. Brain Res. 273, 133–141.

Miyauchi, S., Takino, R., Fukuda, H., Torii, S., 1987. Electrophysiological evidence for dreaming: human cerebral potentials associated with rapid eye movements during REM sleep. Electroenceph Clin. Neurophysiol. 66, 383–390.

Mizuno, S., Kameda, A., Inagaki, T., Horiguchi, J., 2004. Effects of donepezil on Alzheimer's disease: the relationship between cognitive function and rapid eye movement sleep. Psychiat. Clin. Neurosci. 58, 660–665.

Modell, S., Ising, M., Holsboer, F., Lauer, C.J., 2005. The Munich vulnerability study on affective disorders: premorbid polysomnographic profile of affected high-risk probands. Biol. Psychiat. 58, 694–699.

Moises, H.W., Zoega, T., Gottesman, I.I., 2002. The glial growth factors deficiency and synaptic destabilization hypothesis of schizophrenia. BMC Psychiat. 2, 8.

Moraes, W.D., Povares, D.R., Guilleminault, C., Ramos, L.R., Bertolucci, P.H., Tifik, S., 2006. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep 29, 199–205.

Moroz, G., Foutz, A.S., Gottesmann, C., 1977. Paradoxical sleep and pontine activation in the rat. In: Koella, W.P., Levin, P. (Eds.), Sleep 1976. pp. 186–188.

Murck, H., Held, K., Ziegenbein, M., Kunzel, H.E., Holsboer, F., Steiger, A., 2004. Intravenous adminstration of the neuropetid galanin has fast antidepressant efficacy and affects the sleep EEG. Psychoneuroendocrinology 29, 1205–1211.

Muzio, J.N., Roffwarg, H.P., Kaufman, E., 1966. Alterations in the nocturnal sleep cycle resulting from LSD. Electroenceph Clin. Neurophysiol. 21, 313–324.

Nagamoto, H.T., Adler, L.E., McRae, K.A., Huettl, P., Cawthra, E., Gerhardt, G., Hea, R., Griffith, J., 1999. Auditory P50 in schizophrenics on clozapine: improved gating parallels clinical improvement and changes in plasma 3-methoxy-4-hydroxyphenylglycol. Neuropsychobiology 39, 10–17.

Nelson, C.N., Hoffer, B.J., Chu, N.S., Bloom, F.E., 1973. Cytochemical and pharmacological studies on polysensory neurons in the primate frontal cortex. Brain Res. 62, 115–133.

Nicol, S.C., Andersen, N.A., Phillis, N.H., Berger, R.J., 2000. The echidna manifests typical characteristics of rapid eye movement sleep. Neurosci. Lett. 283, 49–52.

Nielsen, T., 2000. cognition in REM and NREM sleep: a review and possible reconciliation of two models of sleep mentation. Behav. Brain Sci. 23, 851–866.

Nievergelt, C., Kripke, D.F., Barrett, T.B., Burg, E., Remick, R.A., Sadovnick, A.D., McElroy, S.L., Keck, P.E.J., Schork, N.J., Kelsoe, J.R., 2006. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am. J. Med. Gen. Neuropsychiat. Gen. 141B, 234–241.

Nissen, C., Feige, B., Nofzinger, E.A., Rieman, D.,M.B., Voderholzer, U., 2005. Transient narcolepsy–cataplexy syndrome after discontinuation of the antidepressant venlafaxine. J. Sleep Res. 14, 207–208.

Nofzinger, E.A., Mintun, M.A., Wiseman, M.B., Kupfer, J., 1997. Forebrain activation during REM sleep: an FDG PET study. Brain Res. 770, 192–201.

Numberger, J.L.J., Berretini, W., Mendelson, W.B., Sacks, D., Gershon, E.S., 1989. Mesuring cholinergic sensitivity: arecoline effects in bipolar patients. Biol. Psychiat. 25, 610–617.

Numberger, J.L.J., Sitaram, N., Gershon, E.S., Gillin, J.C., 1983. A twin study of cholinergic REM induction. Biol. Psychiat. 18, 1161–1165.

Olincy, A., Harris, J.G., Johnson, L.L., Pender, V., Kongs, S., Allensworth, D., Ellis, J., Zerbe, G.O., Leonard, S., Stevens, K.E., Stevens, J.O., Martin, L., Adler, L.E., Soti, F., Kem, W.R., Freedman, R., 2006. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch. Gen. Psychiat. 63, 630–638.

Onoe, H., Sakai, K., 1995. Kainate receptors: a novel mechanism in paradoxical (REM) sleep generation. Neuroreport 6, 353–356.

Ookawa, T., Gotoh, J., 1964. Electroencephalographic study of chickens: periodic recurrence of low voltage and fast waves during behavioral sleep. Poult. Sci. 43, 1603–1604.

Ookawa, T., Gotoh, J., 1965. Electroencephalogram of the chicken recorded from the skull under various conditions. J. Comp. Neurol. 124, 1–14.

Overeem, S., Scammell, T.E., Lammers, G.J., 2002. Hypocretin/orexin and sleep: implications for the pathophysiology and diagnosis of narcolepsy. Curr. Opin. Neurol. 15, 739–745.

Overstreet, D.H., 1993. The Flinders sensitive line rats: a genetic model of depression. Neurosci. Biobehav. Rev. 17, 51–68.

Parsons, L.M., Sergent, J., Hodges, D.A., Fox, P.T., 2005. The brain basis of piano performance. Neuropsychologia 43, 199–215.

Peled, A., Geva, A.B., Kremen, W.S., Blankfeld, H.M., Esfandiarfard, R., Nordahl, T.E., 2000. Functional connectivity and working memory in schizophrenia: an EEG study. Int. J. Neurosci. 106, 47–61.

Perez-Garci, E., del Rio-Portilla, Y., Guevara, M.A., Arce, C., Corsi-cabrera, M., 2001. Paradoxical sleep is characterized by uncoupled gamma activity between frontal and perceptual cortical regions. Sleep 24, 118–126.

Perry, E., Walker, M., Grace, J., Perry, R., 1999. Acetylcholine in mind: a neurotransmitter of consciousness? Trends Neurosci. 22, 273–280.

Popa, D., El Yacoubi, M., Vaugeois, J.M., Hamon, M., Adrien, J., 2005. Homeostatic regulation of sleep in a genetic model of depression in the mouse: effects of muscarinic and 5-HT1A receptor activation. Neuropsychopharmacology 31, 1637–1646.

Portas, C.M., Thakkar, M., Rainnie, D., McCarley, R.W., 1996. Microdialysis perfusion of 8-hydroxy-2-′di-*n*-propylamine)tetralin (8-OH-dPAT) in the dorsal raphe nucleus decreases serotonin release and increases rapid eye movement sleep in the freely moving cat. J. Neurosci. 16, 2820–2828.

Pralong, E., Magistretti, P., Stoop, R., 2002. Cellular perspectives on the glutamate-monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. Prog. Neurobiol. 67, 173–202.

Raedler, T., Knable, M., Jones, D., Urbina, R., Gorey, J., Lee, K., Egan, M., Coppola, R., Weinberger, D., 2003. In vivo determination of muscarinic acetylcholine receptor availability in schizophrenia. Am. J. Psychiat. 160, 118–127.

Raisman, R., Briley, M., Langer, S.Z., 1979. Specific tricyclic antidepressant binding sites in rat brain. Nature 281, 140–150.

Rao, U., Dahl, R.E., Ryan, N.D., Birmaher, B., Williamson, D.E., Giles, D.E., Rao, R., Kaufman, J., Nelson, B., 1996. The relationship between longitudinal clinical course and sleep and cortisol changes in adolsecent depression. Biol. Psychiat. 40, 474–484.

Rasmussen, K., Heym, J., Jacobs, B.L., 1984. Activity of serotonin-containing neurons in nucleus centralis superior of freely moving cats. Exp. Neurol. 83, 302–317.

Reader, T.A., Ferron, A., Descarries, L., Jasper, H.H., 1979. Modulatory role for biogenic amines in the cerebral cortex. Microiontopheric studies. Brain Res. 160, 219–229.

Rechtschaffen, A., Wolpert, E.A., Dement, W.C., Mitchell, S.A., Fisher, C., 1963. Nocturnal sleep in narcoleptics. Electroenceph Clin. Neurophysiol. 15, 599–609.

Reeves, M., Lindholm, D.E., Myles, P.S., Fletcher, H., Hunt, J.O., 2001. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blind, randomized trial. Anesth. Analg. 93, 116–120.

Ribary, U., Ionnides, A.A., Singh, K.D., Hasson, R., Bolton, J., Lado, F., Mogilner, A., Llinas, R., 1991. Magnetic field tomography of coherent thalamocortical 40 Hz oscillations in humans. Proc. Natl. Acad. Sci. USA 88, 11037–11041.

Risch, S.C., Kalin, N.H., Janowsky, D.S., 1981. Cholinergic challenges in affective illness: behavioral and neuroendocrine correlates. Psychopharmacologia 1, 186–192.

Rush, A.J., Erman, M.K., Giles, D.E., Schlesser, M.A., Carpenter, G., Vasavada, N., Roffwarg, H.P., 1986. Polysomnographic findings in recently drug-free and clinical remitted depressed patients. Arch. Gen. Psychiat. 43, 878–884.

Sakai, K., Crochet, S., 2003. A neural mechanism of sleep and wakefulness. Sleep Biol. Rhyt. 1, 29–42.

Salomon, R., Ripley, B., Kennedy, J.S., Johnson, B., Schmidt, D., Zweitzer, J.M., Nishino, S., Mignot, F., 2003. Diurnal variations of CSF hypocretin-1 levels in control and depressed patients. Biol. Psychiat. 54, 96–104.

Sarter, M., Bruno, J.P., 2000. Cortical cholinergic inputs mediating arousal, attentional processing and dreaming: differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents. Neuroscience 95, 933–952.

Satoh, T., 1971. Direct cortical response and PGO spike during paradoxical sleep of the cat. Brain Res. 28, 576–578.

Siegel, J.M., Manger, P.R., Nienhuis, R., Fahringer, H.M., Pettigrew, J.D., 1996. The echidna Tachyglossus aculeatus combines REM and non-REM aspects in single sleep state: implications for the evolution of sleep. J. Neurosci. 16, 3500–3506.

Siegel, J.M., Manger, P.R., Nienhuis, R., Fahringer, S.T., Pettigrew, J.D., 1999. Sleep in the platypus. Neuroscience 91, 391–400.

Siegel, C., Waldo, M., Mizner, G., Adler, L.E., Freedman, R., 1984. Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. Arch. Gen. Psychiat. 41, 607–612.

Silver, H., Barash, I., Aharon, N., Kaplan, A., Poyurovsky, M., 2000. Fluvoxamine augmentation of antipsychotics improves negative symptoms in psychotic chronic schizophrenic patients: a placebo-controlled study. Int. Clin. Psychopharmacol. 15, 257–261.

Sitaram, N., Gillin, J.C., 1980. Development and use of pharmacological probes of the CNS in man: evidence of cholinergic abnormality in primary affective illness. Biol. Psychiat. 15, 925–955.

Sitaram, N., Moore, A.M., Gillin, J.C., 1978a. The effect of physostigmine on normal human sleep and dreaming. Arch. Gen. Psychiat. 35, 1229–1243.

Sitaram, N., Moore, A.M., Gillin, J.C., 1978b. Induction and restting of REM sleep rhythm in normal man by arecholine: blckade by scopolamine. Sleep 1, 83–90.

Sitaram, N., Numberger, J.L.J., Gershon, E.S., Gillin, J.C., 1980. Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. Science 208, 200–202.

Sitaram, N., Numberger, J.L.J., Gershon, E.S., Gillin, J.C., 1982. Cholinergic regulation of mood and REM sleep potential model and marker of vulnerability to affective disorder. Am. J. Psychiat. 139, 571–576.

Smith, C., 1995. Sleep states and memory processes. Behav. Brain Res. 69, 137–145.

Solms, M., 2000. Dreaming and REM sleep are controlled by different brain mechanisms. Behav. Brain Sci. 23, 843–850.

Stanton, T., Bodden-Watson, C., Cusack, B., Richelson, E., 1993. Antagonism of the five cloned human muscarinic cholinergic receptors expressed in CHO-K1 cells by antidepressants and histaminics. Biochem. Pharmacol. 45, 2352–2354.

Stassen, H.H., Coppola, R., Gottesman, I.I., Torrey, E.F., Kuny, S., Rickler, K.C., Hell, D., 1999. EEG differences in monozygotic twins discordant and concordant for schizophrenia. Psychophysiology 36, 109–117.

Steriade, M., 1970. Ascending control of thalamic and cortical responsiveness. Int. Rev. Neurobiol. 12, 87–144.

Steriade, M., Paré, D., Bouhassira, D., Deschènes, M., Oakson, G., 1989. Phasic activation of lateral geniculate and perigeniculate thalamic neurons during sleep with ponto-geniculate-occipital waves. J. Neurosci. 9, 2215–2229.

Suzuki, J., 1966. Narcoleptic syndrome and paradoxical sleep. Fol. Psychiat. Neurol. 20, 123–149.

Tafti, M., Chollet, D., Valatx, J.L., Franken, P., 1999. Quantitative trait loci approach to the genetics of sleep in recombinant inbred mice. J. Sleep Res. 8 (Suppl. 1), 37–43.

Takahata, R., Moghaddam, B., 2000. Target-specific glutamatergic regulation of dopamine neurons in the ventral tegmental area. J. Neurochem. 75, 1775–1778.

Takeuchi, T., Miyasita, A., Inugami, M., Yamamoto, Y., 2001. Intrinsic dreams are not produced without REM sleep mechanims: evidence through elicitation of sleep onset periods. J. Sleep Res. 10, 43–52.

Takeuchi, T., Ogilvie, R.D., Ferrelli, A.V., Murphy, T., Yamamoto, Y., Inugami, M., 1999. Dreams are not produced without REM sleep mechanisms. Sleep Res. Online 2 (Suppl. 1), 279.

Terao, A., Wisor, J.P., Peyron, C., Apte-Deshpande, A., Wurts, S.W., Edgar, D.M., Kilduff, T.S., 2006. Gene expression in the rat brain during sleep deprivation and recovery sleep: an Affymetrix GeneChip study. Neuroscience 137, 593–605.

Thannickal, T.C., Moore, R.Y., Nienhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Cornford, M., Siegel, J.M., 2000. Reduced number of hypocretin neurons in human narcolepsy. Neuron 27, 464–474.

Thomas, D.R., Melotto, S., Massagrande, M., Gribble, A.D., Jeffrey, P., Stevens, A.J., Deeks, N.J., Eddershaw, P.J., TFenwick, S.H., Riley, G., Stean, T., Scott, C.M., Hill, M.J., Middlemiss, D.N., Hagan, J.J., Price, G.W., Forbes, I.T., 2003. SB-656104-A, a novel selective 5-HT7 receptor antagonist, modulates REM sleep in rats. Br. J. Pharmacol. 139, 705–714.

Thompson, D.F., Pierce, D.R., 1999. Drug-indiced nightmares. Ann. Pharmacother. 33, 93–98.

Tokizane, T., 1964. Hypothalamic control of cortical activity and some observations during different stages of sleep. Electroenceph Clin. Neurophysiol. 17, 450.

Toyoda, J., 1964. The effects of chlorpromazine and imipramine on the human nocturnal sleep electroencephalogram. Folia Psychiat. Neurol. 18, 198–221.

Tradarti, V., 1966. Sleep in the pigeon. Arch. Ital. Biol. 104, 516–521.

Trulson, M.E., Preussler, D.W., 1984. Dopamine-containing ventral tegmental area neurons in freely moving cats: activity during the sleep–waking cycle and effects of stress. Exp. Neurol. 83, 367–377.

Van Hes, R., Smid, P., Stroomer, C.N., Tipker, K., Tulp, M.T., Van der Heyden, J.A., McCreary, A.C., Hesselink, M.B., Kruse, C.G., 2003. SL V310, a novel, potential antipsychotic, combining potent dopamine d2 receptor antagonism with serotonin reuptake inhibition. Bioorg. Med. Chem. Lett. 13, 405–408.

Vasquez, J., Baghdoyan, H.A., 2001. Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. Am. J. Physiol. 280, R598–R601.

Vertes, R.P., 1977. Selective firing of rat pontine gigantocellular neurons during movement and REM sleep. Brain Res. 128, 146–152.

Vincent, J.D., Favarel-Garrigues, B., Faure, J., Julien, J., 1966. Sur un cas de narcolepsie avec des phénomènes végétatifs paroxystiques: étude diurne et nocturne. Rev. Neurol. 115, 464–468.

Vogel, G., 1983. Evidence for REM sleep deprivation as the mechanism of action of antidepressant drugs. Neuro-Psychopharmacol. Biol. Psychiat. 7, 343–349.

Vogel, G., Feng, P., Kinney, G.G., 2000. Ontogeny of REM sleep in rats. Possible implications for endogenous depression. Physiol. Behav. 68, 453–461.

Vogel, G., Foulkes, D., Trosman, H., 1966. Ego functions and dreaming during sleep onset. Arch. Gen. Psychiat. 14, 238–248.

Vogel, G.W., Thompson, F.C.J., Thurmon, A., Rivers, B., 1973. The effect of REM deprivation on depression. Psychosomatics 14, 104–107.

Wall, P.D., 1958. Excitability changes in afferent fiber terminaisons and their relation to slow potential. J. Physiol London 142, 1–21.

Wehr, T.A., Wirz-Justice, A., Goodwin, F.K., Duncan, W., Gillin, J.C., 1979. Phase advance of the circadian sleep–wake cycle as an antidepressant. Science 206, 710–713.

Weinberger, D.R., Berman, K.F., Zec, R.F., 1986. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. 1. Regional cerebral blood flow evidence. Arch. Gen. Psychiat. 43, 114–124.

Weiss, T., Adey, W.R., 1965. Excitability changes during paradoxical sleep in the rat. Experentia 21, 1–4.

Yavari, P., Vogel, G.W., Neill, D.B., 1993. Decreased raphe unit activity in a rat model of endogenous depression. Brain Res. 611, 31–36.

Young, C.E., Beach, T.G., Falkai, P., Honer, W.G., 1998. SNAP-25 deficit and hippocampal connectivity in schizophrenia. Cer. Cort. 8, 261–268.

Zarcone, V.P., Azumi, K., Dement, W., Gulevich, G., Kraemer, H., Pivik, T., 1975. REM phase deprivation and schizophrenia II. Arch. Gen. Psychiat. 32, 1431436.

Zarcone, V.P., Gulevich, G., Pivik, T., Azumi, K., Dement, W., 1969. REM deprivaztion and schizophrenia. Biol. Psychiat. 1, 179–184.

Zhang, B., Veasey, S., Wood, M.A., Leng, L.Z., Kaminski, C., Leight, S., Abel, T., Lee, V.M., Trojanowski, J., 2005. Impaired rapid eye movementsleep in the Tg2576 APP murine model of Alzheimer's disease with injury to pedunculopontine cholinergic neurons. Am. J. Pathol. 167, 1361–1369.

Zubenko, G.S., Maher, B., Hughes, H.B., Zubenko, W.N., Stiffler, J.F., Kaplan, B.B., Marazita, M.L., 2003. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am. J. Genet. B Neuropsychiat. Genet. 123, 1–18.