The dreaming sleep stage: a new neurobiological model of schizophrenia?

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Abstract—The rapid eye movement dreaming sleep stage and schizophrenia are both characterized by common intracerebral disconnections, disturbed responsiveness and sensory deafferentation processes. Moreover, in both states, there is dorsolateral prefrontal deactivation as shown by the decrease of blood flow. Finally, identical pharmacological and neurochemical variations are observed for acetylcholine, dopamine, noradrenaline, serotonin and glutamate concentrations. Consequently, rapid eye movement sleep could become a useful new neurobiological model of this mental disease since more functional than current rat models using stimulation, lesion or drugs. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: paradoxical sleep, hallucinations, delusions, neurotransmitters.

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Schizophrenia is a mental disease mainly characterized by hallucinations, delusions, bizarre thought processes and a decrease in reflectiveness. Dreaming shows psychological characteristics such as “sensory hallucinations, bizarre imagery . . . diminished reflective awareness, orientational instability . . . intensification of emotion and instinctual behaviors” (Hobson et al., 1998) which resemble schizophrenic symptoms. For a number of decades there appeared series of experimental data which progressively enriched the analogy between both states as already described by philosophers such as Kant (Freud, 1967) “the madman is a waking dreamer,” Schopenhauer “dreams are short madness and madness a long dream,” neurophysiopathologists like Hughlings Jackson (in Nahum, 1965) “Find out about dreams and you will find out about insanity,” or more recently neuropsychiatrists like Henri Ey (Ey, 1967) who stated: “It is obvious, it cannot be but obvious that the dream and madness spurt from the same source.”

We would like to follow the evolution of our knowledge in this field by showing the neurobiological background of dreaming during successive decades and by stressing the physiological similarities with schizophrenia. The psychological resemblances aside (during dreaming visual hallucinations are present in nearly all dreams, and auditory elements occur in about 40–60% of dreams (Maquet et al., 2004), while in schizophrenia the most frequent hallucinations are auditory, although the composer Robert Schumann indeed heard an insistent “A” note and the painter Vincent Van Gogh saw vertiginous skies), what are these shared data supplied by electrophysiology, blood flow, pharmacology and finally neurochemistry?

RESULTS

It has first to be emphasized that most dreams occur during rapid eye movement (REM) sleep. When they are infrequently detected during other sleep stages (Foulkes, 1962), some criteria of REM sleep are generally present (Werth et al., 2002). Today, several studies have shown that dreaming cannot appear without the neurobiological support of REM sleep (Takeuchi et al., 1999; Nielsen, 2000; Takeuchi et al., 2001) even if some of its criteria are “covert” (Nielsen, 2000).

Electrophysiology

Two powerful premonitory results appeared in 1964 and 1966. First, Evarts (1964), in the monkey, recorded cortical pyramidal neurons. He observed regular high rate neuron firing during waking, lower frequency and more irregular spike discharges during slow wave sleep and high frequency firing bursts alternating with long silences during REM sleep (Fig. 1, top). The author postulated that the regular firing during waking was consecutive to cortical control processes involving inhibitory mechanisms which disappear during REM sleep (in fact, recent results show that the silent periods between the spike bursts are related to active inhibition processes in contrast to disinhibition ones which occur during slow wave sleep (Steriade et al., 2001; Timofeev et al., 2001)). Two years later, working on cats, Demetrescu et al. (1966) used a complex paradigm of four consecutive pulse stimulations in the lateral geniculate nucleus. The second and fourth pulse were delivered at short latency (about 7–10 ms) while the third occurred about 40–50 ms after the second pulse. By studying the recovery cycle of evoked potentials (today we would talk of prepulse inhibition), the authors were led to show both activating and inhibitory influences acting at cortical level (Fig. 1, bottom). Of high intensity during active waking, both kinds of influences decreased during quiet waking, still more during slow wave sleep, to become minimal prior to REM sleep. During this dreaming sleep stage, there was...
reappearance of activating influences while the inhibitory processes were at their lowest level. Already at the time, the present author stressed that the opposition of waking with an activated and controlled cortex and an activated but disinhibited brain during REM sleep could explain the irrational mentation encountered during dreaming (Gottesmann, 1967, 1970, 1971).

The next step was performed by the teams of McGinty and Hobson in 1974 and 1975, respectively. The first authors (McGinty et al., 1974; McGinty and Harper, 1976) recorded the serotonergic neurons of the mesencephalic dorsal raphe nucleus and showed that the highest firing rate, although of low frequency, occurs during waking, with a decrease during slow wave sleep and a silence during REM sleep (Fig. 2, bottom). Hobson et al. (1975) found a similar result with the noradrenergic neurons of the pontine locus coeruleus nucleus. These two kinds of neurons send axon terminals to the forebrain, particularly to all cortex areas (Dahlstrom and Fuxe, 1964; Fuxe et al., 1968).

These two results combined for the first time cellular electrophysiological and neurochemical data with sleep–waking processes (Aston-Jones and Bloom, 1981a). Interest-

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**Fig. 1.** Top. Pyramidal neuron discharges during sleep-waking cycle (Evarts, 1964). The activated neurons fire regularly during waking and very irregularly, in strong bursts of spikes, during REM sleep. Sleep: slow wave sleep; S-LVF: REM sleep. Reprinted from the *Journal of Neurophysiology*. Bottom. Cortical acting, facilitating and inhibitory influences (Demetrescu et al., 1966). While during waking both kinds of influences are strong and simultaneously decrease during slow wave sleep, there is pronounced disinhibition associated with cortical activation during REM sleep. See text. Reprinted from *Electroencephalography and Clinical Neurophysiology*. 
ingly, it had been already described that both neuromodulators exercise inhibitory influences on the cortex (Krnjevic and Phillis, 1963; Frederickson et al., 1971; Nelson et al., 1973; Foote et al., 1975; Reader et al., 1979) a finding which has recently been confirmed (Araneda and Andrade, 1991; Manunta and Edeline, 1999). However, these two neuromodulators, which either directly inhibit cortical neurons by blocking Ca\(^{2+}\)/H\(^{+}\) channels or opening K\(^{+}\)/H\(^{+}\) ones, or activate cortical inhibitory interneurons, increase the signal-to-noise ratio of neuron functioning (Foote et al., 1975; Aston-Jones and Bloom, 1981b; McCormick, 1992) and noradrenaline, at least, induces regular firing of cortical neurons (Wang and McCormick, 1993) as is the case during waking (Evarts, 1964). Thus, both increase neuron functioning efficiency, and the silence of their generating neurons during REM sleep should induce a cortical general disinhibition and a decrease or loss of brain function control. It has to be mentioned that the noradrenergic neurons (at least) begin to fire again several seconds prior to awakening (Fig. 2, top, in the insert). Consequently, the brain is in the neurochemical state of waking when arousal occurs. This could explain the usual immediate or rapid forgetting of dreams which are generally unrecorded in the waking memory processes. Freud makes a comparison with the “mystic writing-pad” game (Freud, 1925). When this physiological “censorship-like” process totally fails, this could favor the advent of the schizophrenic hallucinatory state (Kelly, 1998).

Two similar findings concerned dopaminergic neurons recorded in the mesencephalic ventral tegmental (A\(_{10}\)) area which sends axon terminals via two different tracks to the limbic system and the prefrontal cortex. They were first...
recorded in the rat by Miller et al. (1983) who showed that the neurons fire statistically at the same slow frequency, a characteristic of all monoaminergic neurons, during waking slow wave sleep and REM sleep (Fig. 3, top). Trulson and Preussler (1984) recorded the same neurons in the cat and also found no significant difference during sleep–waking stages (Fig. 3 center). Dopamine also mainly inhibits cortical neurons (Krnjevic and Phillis, 1963; Pirot et al., 1992; Grobin and Deutch, 1998; Abi-Dargham and Moore, 2003) and increases the signal-to-noise ratio in neuron functioning (Luciana et al., 1998). Interestingly, Miller et al. (1983), in one short sentence, wrote that the firing was more

![Image of neuronal firing patterns](image-url)
Fig. 4. Top. The cortical gamma rhythm is recorded in humans during waking and REM sleep (Llinas and Ribary, 1993). Reprinted from Proceedings of the National Academy of Sciences USA. Bottom. The cortical gamma rhythm becomes uncoupled during REM sleep (Perez-Garci et al., 2001). It is an indication of some disconnection between areas. The stars show statistical differences between waking and REM sleep frequencies. W, waking; PS, REM sleep. See text. Reprinted from Sleep.
irregular during REM sleep than during slow wave sleep. This could mean that there were some bursts (this research has not been replicated so far). However, this observation is crucial. Indeed, recent results show that when the dopaminergic neurons fire in bursts there is greater release of this neuromodulator (Chergui et al., 1994) (Fig. 3, bottom). This was the first indication of a possible neurochemical relation between an increase of dopamine functioning and dreaming sleep stage as had been shown for schizophrenia in the nucleus accumbens in the preceding years (MacKay et al., 1982). This fact has been highlighted for schizophrenia more recently (Grace, 1991).

The next finding was the identification of the EEG gamma rhythm. First described in the cat during waking (Bouyer et al., 1981), then in humans (Ribary et al., 1991), the gamma rhythm was further identified during REM sleep in humans (Llinas and Ribary, 1993) (Fig. 4, top) and animals (Franken et al., 1994; Maloney et al., 1997). However, interesting differences progressively appeared between waking and REM sleep. First, there is no reset of this rhythm during REM sleep (Llinas and Ribary, 1993) which could suggest, partly at least, a disconnection from the periphery. Second, while this activity is synchronized over the cortical areas during waking, it becomes uncou-

![Fig. 5. A prepulse inhibition is observed in the normal subject during waking (as shown by the decreased amplitude of the second (test) evoked potential) (top), contrary to schizophrenic patients (center). Bottom. During REM sleep there is a similar lack of prepulse inhibition in the normal subject (Kisley et al., 2003). Circle, schizophrenic patients; square, normal subjects. See text. Reprinted from Psychophysiology.](image-url)
plied during REM sleep, particularly between the perceptual areas and the frontal and prefrontal cortex (Perez-Garcì et al., 2001) (Fig. 4, bottom). This now rather classical argument of breakdown of cortical connectivity during REM sleep (absence of crosstalk) is strongly supported by new results showing, in addition to cortical uncoupled areas, the suppression of gamma rhythm coherence between the cortex and hippocampus (Cantero et al., 2004; Massimini et al., 2005). This has to be compared with one of the most common features of schizophrenia, the disconnection between central structures which has been identified by similar approaches (Young et al., 1998; Peled et al., 2000; Meyer-Lindenberg et al., 2001).

Another similarity related to central responsiveness between REM sleep and schizophrenia has recently been described. When two sensory stimulations are delivered at short intervals to normal subjects, the negative component (N100) of the evoked potential (occurring at 500 ms latency) is considerably reduced in the second response (Kisley et al., 2003) (Fig. 5 top recording). This is what is called the prepulse inhibition. In contrast, in the schizophrenic patient, there is no inhibition (Fig. 5 lower recording). However, during REM sleep, there is also no inhibition of the second potential in the normal subject. Consequently, the same lack of central inhibitory processes is observed in the normal subject during the dreaming sleep stage and in the schizophrenic subject during waking and REM sleep (Fig. 5, bottom). A recent result reinforces these disturbances of responsiveness. Indeed, on emerging from REM sleep dreaming there is a confusion between self- and external-stimulation as in the case in schizophrenia (Blagrove et al., in press).

Tomography

The study of cerebral blood flow by the tomographic approach has also provided important information. Although the majority of brain structures are activated during REM sleep, several structures in the limbic system are even more activated than during waking. In contrast, the dorsolateral prefrontal cortex is deactivated during REM sleep (Maquet et al., 1996; Braun et al., 1997; Maquet, 2000) and one of the characteristics of schizophrenia is the deactivation of the same prefrontal area (Weinberger et al., 1986). In addition, while the extrastriate visual associative areas are activated, the primary striate occipital cortex is less activated (Braun et al., 1998). This is an indication of some disconnection from the periphery, which was already suggested by the absence of reset of the gamma rhythm (Linas and Ribary, 1993). This disconnection from the sensory input is reinforced at subcortical level. Indeed, while the postsynaptic responsiveness in the thalamic relay nuclei is high during REM sleep (Albe-Fessard et al., 1964; Favale et al., 1965; Rossi et al., 1965; Steriade, 1970; Gandolfo et al., 1980) there seems to be a kind of presynaptic-like inhibition (Wall, 1958) during the eye movement bursts—during which dreams are particularly active—as shown by the increase in amplitude of the antidromic stimulation of lemniscus medialis induced by ventrobasal thalamic stimulation (Iwama et al., 1966; Dagnino et al., 1969; Ghelarducci et al., 1970; Steriade, 1970; Gandolfo et al., 1980). Indeed, this sensory disconnection during the hallucinatory activity of the dreaming sleep stage has to be compared with the current hypothesis whereby a decrease in sensory constraints could be responsible for the hallucinatory activity of schizophrenia (Behrendt and Young, 2005).

Neurochemistry and pharmacology

Among the activating influences acting in the cortex, acetylcholine is of major importance for mentation, although this transmitter also has inhibitory influences at cortical level (Muzur et al., 2002). Indeed, mental disturbances result when its central concentration decreases (Perry et al., 1999; Sarter and Bruno, 2000). It has been shown in cats that acetylcholine reaches a high cortical level during REM sleep as well as during waking. However, the concentration during the dreaming sleep stage is lower than during active waking, i.e. at the level of quiet waking (Marrosu et al., 1995), despite being at its highest level in the subcortical basalis (Meynert) nucleus (Vasquez and Bagdoyan, 2001) which projects axon terminals to the whole cortex (Fig. 6). One of the significant hypotheses related to schizophrenic hallucinations is also a decrease of acetylcholine functioning (Collerton et al., 2005).

The monoaminergic pharmacological approach also links the dreaming sleep stage and schizophrenia. Today, there are two main neurochemical theories which are advanced to explain schizophrenic symptoms. An excess of dopamine functional power in nucleus accumbens is thought to be responsible for the positive symptoms of schizophrenia (hallucinations, delusions, bizarre thought processes) (MacKay et al., 1982), while a dopamine deficit in the prefrontal cortex is believed to induce the negative symptoms of schizophrenia (among them the decrease or loss of reflectiveness) (Abi-Dargham and Moore, 2003). Both kinds of symptoms are observed during dreaming which decreases under neuroleptics, particularly nightmares (Solms, 2000; Jakovljevic et al., 2003). Perhaps even more importantly, glutamate is also involved in schizophrenia, particularly through a decrease in nucleus accumbens. The hypothesis linking the dreaming sleep stage and schizophrenia is supported by the fact that dopaminergic agonists (in some cases in the treatment of Parkinson’s disease) as well as glutamate antagonists induce not only psychotic symptoms but also vivid dreaming (Larsen and Tandberg, 2001; Reeves et al., 2001).

Consequently, we undertook in rats the study of dopamine, noradrenaline and glutamate release in the medial prefrontal cortex and nucleus accumbens during sleep–waking stage (Léna et al., 2005) (Fig. 6). It has to be mentioned that Feenstra et al. (2000) already compared in rats the release of these two neuromodulators during day and night in the two structures. They found a shared significant increase of efflux in the prefrontal cortex during the dark period, while there was a dopamine non-significant increase in nucleus accumbens. Our results showed that the release of dopamine was maximal during REM sleep in nucleus accumbens while it was significantly decreased when compared with wak-
ing in the prefrontal cortex. Although the difference with waking was not significant in the nucleus accumbens, the tendency is the same as postulated for schizophrenia. The maximal release in nucleus accumbens, which also occurs in humans, could favor the hallucinatory activity of dreaming, the delusions and bizarre thought processes, while the decrease in the prefrontal cortex could lead dopamine to be outside the narrow limits of its optimal functional level (Abi-Dargham and Moore, 2003) and explain the decrease or loss of reflectiveness, a characteristic of dreaming as well as of schizophrenia. Glutamate was unchanged at prefrontal level. This result is important since in schizophrenic patients there is also no change of glutamate transporter mRNA expression in the prefrontal and primary visual cortex (Lauriat et al., 2005). In contrast, and significantly, glutamate was at its lowest concentration in nucleus accumbens during REM sleep when compared with waking. This result is in accord with the conclusions of Grace (2000) who stated that in schizophrenia a decrease of glutamate input from the ventral hippocampus would prevent the prefrontal issued glutamate release from functioning. Consequently, the influences of the amygdala, which controls the emotional processes, would become predominant. It is important to add that the amygdala is also particularly activated during the dreaming sleep stage (Maquet and Franck, 1997). Hence, dopamine and glutamate extracellular concentrations in nucleus accumbens vary in the same way as in schizophrenia. Significantly, noradrenaline was at its lowest level during REM sleep in the prefrontal cortex as well as in nucleus accumbens. It is of interest that, although the corresponding neurons are silent, there is maintenance of a given level of noradrenaline. This is certainly consecutive to the fact that noradrenaline, like other monoamines, is released diffusely at varicosity level (Descarries et al., 1977) without active reuptake and enzyme destruction, both synaptic processes rapidly eliminating transmitters. Moreover, the massive decrease of noradrenaline during REM sleep and the silence of serotonergic neurons have to be emphasized, since there is a deficit of both neuromodulators in schizophrenia (Friedman et al., 1999; Silver et al., 2000; Linner et al., 2002; Van Hes et al., 2003), and more generally a similar glutamate-monoamines imbalance in REM sleep and in schizophrenia (Pralong et al., 2002).

Finally, a possible involvement of the newly discovered neuropeptide hypocretin/orexin needs to be evaluated. Indeed, its decreased synthesis in the hypothalamus induces narcoleptic symptoms (Nishino et al., 2000) of which, particularly hypnagogic hallucinations, point to a severe schizoaffective disorder (Douglass, 2003). However, the role of hypocretin/orexin in schizophrenia is still open to discussion since, although there is a positive correlation between cerebrospinal fluid level and characteristic sleep disturbances of schizophrenia (Nishino et al., 2002), its infusion in the ventral tegmental area induces an increase of dopamine release in the prefrontal cortex (which could indicate an improvement in the negative symptoms of schizophrenia, particularly the loss of reflectiveness), while its release in nucleus accumbens is not modified (Vittoz and Berridge, 2005).
The psychological, electrophysiological, blood flow, pharmacological and neurochemical processes of the dreaming sleep stage are very similar to the characteristics observed in schizophrenia (Gottesmann, 1999, 2000, 2002, 2004). The dorsolateral prefrontal cortex, possibly consecutive to the marked noradrenergic and/or serotonergic deficit during REM sleep, could account for these shared features. Indeed, this structure is known to modulate dopamine release in both the prefrontal cortex and nucleus accumbens (Brake et al., 2000; Jackson et al., 2001). This cortical deactivation also cooperates to induce the glutamate deficit in nucleus accumbens (Grace, 2000). These data are in agreement with the hypothesis of Hughlings Jackson (1932), at the beginning of last century, which stated that in the progressive phylogenetic development of the brain, the appearance of a new structure allows more elaborate cerebral performances and the additional control of older subcortical structures. Consequently, the dorsolateral prefrontal deactivation observed both during REM sleep and in schizophrenia seems to suppress or decrease its own functions, including the loss or decrease of reactivity, and at the same time disinhibits older subcortical structures and corresponding functions, with the exaggeration of accumbens’ and amygdala nuclei’s own processes: in our case, the appearance of hallucinations, delusions, bizarre thought processes, and affective disturbances. Because of all their shared characteristics, it seems that the REM sleep stage could become a new useful neurobiological model for schizophrenia. This would be particularly beneficial in fundamental and clinical research, since it is a behavioral stage requiring no experimental intervention contrary to models using lesions, stimulations or pharmacological compounds. Today, although schizophrenia is a long-established polygenic disease (Gottesman and Shields, 1967), REM sleep is a surprising sum of schizophrenia (endophenotypes) (Gottesman and Shields, 1973; Gottesman and Gould, 2003), and also probably of other mental diseases (C. Gottesman and I. I. Gottesman, in preparation).

Acknowledgment—I gratefully thank Marc Rodi for the iconography and Professor George Morgan for improving the English of the manuscript.

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