Letter to the Editor
Hypothesis for the Neurophysiology of Dreaming

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During wakefulness, the cerebral cortex, which is responsible for generating mental activities, is activated by brain stem ascending influences. This is evidenced by classic electrophysiological field and unitary activities, gamma range activity and cortical blood flow. However, aminergic ascending neurons exert mainly diffuse inhibitory influences. These two kinds of influences together support reflective and rational psychological activities. During slow wave sleep, both kinds of ascending influences decrease and the mental content comprises low-intensity thought-like activities, similar to the waking mode of functioning. During rapid eye movement sleep, the principal dreaming stage, the cortex is activated but significantly disinhibited since all aminergic neurons are silent except the dopaminergic ones. We hypothesize that, in addition to this unusual state, the persistent release of dopamine associated with the specific silence of noradrenergic neurons could explain the characteristics of dream mental activity which are somewhat similar to psychotic symptoms.

CURRENT CLAIM: The psychotic-like mental activity of dreaming could be explained by the fact that during REM sleep, the cortex is activated but is mostly disinhibited and that, in addition, the persistent release of dopamine is associated with the absence of noradrenaline.

For thousands of years, dreams have fascinated mankind: "An uninterpreted dream is an unread letter" (Talmud in Fromm, 1953). In a similar perspective, Freud (in Freud, 1975) made dream interpretation the cornerstone of his theory of the unconscious. Moreover, analogies between dreaming and madness were emphasized by several philosophers: "the madman is a waking dreamer" (Kant in Freud, 1975), "dreams are brief madness and madness a long dream" (Schopenhauer in Freud, 1975). We intend to determine the neurophysiological background of the mental activity of sleep by comparing it with wakefulness psychological functioning. This analysis will focus on the most recent phylogenetic brain level implicated in consciousness, i.e., the cerebral cortex.

During active wakefulness, cortical electrophysiological field activity (electroencephalogram) is rapid and low voltage. Many researchers have long shown that it corresponds to an activated state (Moruzzi and Magoun, 1949), also identified by unitary cell activity (Evarts, 1962) which shows a high level of firing. The synchronized gamma range activity centered on 40 Hz which occurs during attentive wakefulness in cats (Bouyer et al., 1981) and humans (Ribary et al., 1991) and which decreases in Alzheimer's disease (Ribary et al., 1991), recently strengthened this finding. Finally, the cerebral blood flow level and glucose utilization provide a final confirmation that the cortex is activated during waking (Maquet et al., 1996; Braun et al., 1998). From the neurochemical standpoint, acetylcholine, predominantly issued from the basal forebrain (Kurosawa et al., 1989) as well as the Meynert nucleus in humans, favors cortical low voltage activity (Kinai and Szerb, 1965). All of these activating processes are sustained by brain stem ascending influences (Moruzzi and Magoun, 1949; Steriade and McCarley, 1990). They are crucial. Indeed, their disappearance induces coma.

During wakefulness, inhibitory influences are also exerted on the cortex by subcortical ascending neurons. There are aminergic terminals of brain stem and hypothalamic neurons which fire during waking. Now, dopamine, noradrenaline, serotonin (Krnjevic and Phillis, 1963; Reader et al., 1979) and histamine (Sastry and Phillis, 1976; Haas and Wolf, 1977) mostly inhibit cortical principal cells either directly, or by depolarizing cortical inhibitory interneurons. These influences are most often induced by neurotransmitter diffuse release at varicosities (axon terminal enlargements). It is worth mentioning that, as early as 1966, Demetrescu et al. (1966), in a study of thalamocortical responsiveness, described the coexistence of cortical activating and inhibitory influences during waking.

The mental content functioning of wakefulness is well known. It is reflective and rational. It controls and integrates sensory information. The two kinds of influences contribute to the waking teleological adapted state. The activating influences allow cortex functioning, just as petrol propels an auto engine, and the inhibitory influences in some way control this activation, and consequently “normalize” mental functioning. Indeed, the decrease of nonadrenergic and/or serotonergic inhibitory influences induces depression psychological disturbances.

The hypnagogic hallucinations that occur on falling asleep

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were extensively studied by Maury (1861). They are characterized by "floating sensations, flashing lights, lantern slide phenomena, fleeting progressions of thoughts and images" (Foulkes, 1962). However, from Stage 2, cortical spindles and slow waves progressively appear, cortical neuron firing decreases in animals and tends to occur by bursts accompanying the slow waves. Gamma range activity decreases (Llinas and Ribary, 1993), as do the thalamocortical responsiveness (Demetrescu et al., 1966), and cortical blood flow (Maquet et al., 1997; Hofle et al., 1997), except for an increase in the visual and less markedly in the secondary auditory cortex (Hofle et al., 1997). The rather general cortical decrease in activation is accompanied, on the neurochemical side, by a decrease in acetylcholine release (Celesia and Jasper, 1966). The inhibitory influences are also depressed. The firing of the noradrenergic (Aston-Jones and Bloom, 1981) and serotoninergic (McGinty and Harper, 1976; Rasmussen et al., 1984) neurons decreases while the histaminergic neurons become silent (Vanni-Mercier et al., 1984). Only the dopaminergic neurons continue to fire as shown in rats (Miller et al., 1983) and cats (Trulson and Preussler, 1984). It can be concluded that during slow wave sleep activating and inhibitory influences acting at cortical levels decrease together in the same way.

Foulkes (1962) showed that, psychologically, the brain is not silent during slow wave sleep. He determined that the mental content is different from hypnagogic and hypnopompic (pre-arousing) hallucinations, and that it is "less often visual and had a higher degree of correspondence with reality". This "thought-like" activity somewhat corresponds to Freud's (1900) "secondary process" which sustains waking psychological controlled activity. Foulkes (1962), as recently confirmed (Bosinelli, 1995), also found dream contents during slow wave sleep, which could correspond with the activation of the visual and secondary auditory cortex. However, recent experimental findings show that dreaming only occurs on REM sleep psychological background (Takeuchi et al., 1999; Neilsen, 2000).

Rapid eye movement sleep (REM sleep), also called paradoxical sleep, which usually appears following slow wave sleep, is the main dreaming stage. It is characterized by low voltage cortical activity in animals (Dement, 1958; Jouvet et al., 1959) and humans (Loomis et al., 1937; Aserinsky and Kleitman, 1953), which most often does not differ from that of wakefulness. Neuron firing is as high as during waking (Evarts, 1962) and gamma range activity occurs (Llinas and Ribary, 1993; Paré and Llinas, 1995). Moreover, the cortical blood flow is higher than during slow wave sleep. Sometimes it is even higher than during waking, particularly in the integrative visual cortex and limbic areas (Maquet et al., 1996; Braun et al., 1998). A decrease in activation was described in the dorsolateral prefrontal cortex as compared to waking (Maquet et al., 1996; Braun et al., 1998); however, during the eye movements, two teams found an increase of activation (Hong et al., 1995; Nofzinger et al., 1997). Finally, acetylcholine release is even slightly higher than during waking (Celesia and Jasper, 1966). Thus, during REM sleep, the cortex is globally activated, as during wakefulness.

One difference with wakefulness is that, although gamma range activity can be present, there is no reset by peripheral stimulation. This is also the case during slow wave sleep (Llinas and Ribary, 1993). Moreover, the late components of the sensory evoked potentials (which partly correspond to what are nowadays called event-related potentials and reflect cortical processing and integration of sensory information) are suppressed (Williams et al., 1964). These two facts suggested to Llinas and Ribary (1993) that "the dreaming condition (is) a state of hyperattentiveness in which sensory input cannot address the machinery that generates conscious experience." It is worth mentioning that, unlike the associative visual cortex which is activated, the primary visual cortex is deactivated during REM sleep (Braun et al., 1998).

The main difference lies in the silence of noradrenergic (Aston-Jones and Bloom, 1981), serotoninergic (McGinty and Harper, 1976; Rasmussen et al., 1984), and histaminergic (Vanni-Mercier et al., 1984) neurons. The only aminergic neurons, which continue to fire, are the dopaminergic ones. Consequently, the cortex is significantly disinhibited during REM sleep. The coexistence of cortical activation and disinhibition processes, which had already been shown by Demetrescu et al. (1966), led us at that time to draw up psychophysiological hypotheses about the neurophysiological background of dreaming (Gottesmann, 1967, 1971). What conclusions can be highlighted today?

During REM sleep, as during wakefulness, the cortex is activated and is thus able to function. However, during waking, powerful diffuse inhibitory influences apparently modulate and control cortical functioning. During REM sleep, these inhibitory influences, and consequently the probable control they exert, are significantly decreased and could explain the bizarre mental functioning of this sleep stage. The "manifest content" (Freud, 1900) of dreams which, according to Freud, is the disguised representation of previous "latent content" (which cannot obtain access to consciousness since it would create disturbing anguish), is most often illogical and comprises irrational event associations. The possible dorsolateral prefrontal cortex deactivation (Hobson et al., 1998) but more likely the silence of aminergic neurons except dopaminergic ones, could account for such an unusual mode of functioning. The frequently observed rapid sequences of mental content could also result from a disinhibition process. The instantaneous dream of Maury (1861) provides a classic example. Maury had a long dream in which he was arrested, sentenced to death under the revolutionary terror regime and later driven off to Revolution Square, where he mounted the scaffold, etc. He awoke as the guillotine blade descended. In fact, the bedpost fell at the same moment on his cervical vertebrae. Although this dream is debatable because it had occurred 40 years before the narration and Maury was unwell at the time, the decrease in cortical control could explain the rapid succession of fantasies.

As already mentioned, the relationship between dreaming and psychotic mental functioning has long been emphasized. Hobson et al. (1998), found that dreaming in REM sleep is characterized by "sensorimotor hallucinations, bizarre imagery...diminished self-reflective awareness, orientational instability...intensification of emotion, instinctual behaviors," symptoms often encountered in schizophrenia. The possible deactivation of the dorsolateral prefrontal cortex, when confirmed, could be of importance. Following Jackson's theory, deactivation of this most recent phylogenetic brain area could create a deficit in psychological functioning by suppression of its specific potentialities (negative consequences) and could suppress control exerted on even
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explaining the rich distorted mental activity characteristic of dreams. It is of interest to recall that the prefrontal cortex blood flow is not increased during cognitive activity in impaired schizophrenic patients (Berman et al., 1993).

There is another hypothesis. The leading French psychiatrist H. Ey (1967) stated, "It is obvious, it cannot be but obvious that dream and madness spring from the same sources." Indeed, all neurophysiological data show that the influences generating mental functioning are not induced, but sustained by the brain stem, i.e., rather old phylogenetic structures. Once again, the ascending facilitatory influences allow cortical functioning while the inhibitory ones seem to control these activating processes. The major decrease in the inhibitory ascending influences could explain the unusual modalities of mental activities during REM sleep. It is our belief that, in addition to this cortical unusual state, the persistence of dopaminergic influences could play a crucial role in the often psychiatric-like mode of psychological functioning. Indeed, it is known that aside from the nightmares induced by dopamine agonists (Thompson and Pierce, 1999), an excess of dopamine release (Pehuk, 1999) leads to psychotic disorders (Buffenstein et al., 1999). Moreover, neuroleptics used to alleviate schizophrenia reduce dopamine influence at cortical and limbic levels by acting on pre and/or postsynaptic receptors (Kinon and Lieberman, 1996). Finally, new atypical neuroleptics increase noradrenaline release at cortical levels (Nutt et al., 1997). Consequently, in this activated and disinhibited cortical state of REM sleep, the specific release of dopamine and the silence of noradrenergic neurons could lead to fantasies and the generally irrational mental activities of dreaming, somewhat similar to those of psychotic diseases.

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