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Review Article

The neurochemistry of waking and sleeping mental activity: The disinhibition-dopamine hypothesis

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Abstract This paper describes a hypothesis related to the neurochemical background of sleep-waking mental activity which, although associated with subcortical structures, is principally generated in the cerebral cortex. Acetylcholine, which mainly activates cortical neurons, is released at the maximal rate during waking and rapid eye movement (REM) sleep dreaming stage. Its importance in mental functioning is well-known. However, brainstem-generated monoamines, which mainly inhibit cortical neurons, are released during waking. Both kinds of influences contribute to the organized mentation of waking. During slow wave sleep, these two types of influence decrease in intensity but maintain a sufficiently high level to allow mental activity involving fairly abstract pseudo-thoughts, a mode of activity modelled on the diurnal pattern of which it is a poor reply. During REM sleep, the monoaminergic neurons become silent except for the dopaminergic ones. This results in a large disinhibition and the maintained dopamine influence may be involved in the familiar psychotic-like mental activity of dreaming. Indeed, in this original activation–disinhibition state, the increase of dopamine influence at the prefrontal cortex level could explain the almost total absence of negative symptoms of schizophrenia during dreaming, while an increase in the nucleus accumbens is possibly responsible for hallucinations and delusions, which are regular features of mentation during this sleep stage.

Key words acetylcholine, dopamine, dreaming, norepinephrine, schizophrenia, serotonin, sleep.

Investigations into the psychic phenomena occurring during the waking and sleep states were for many years conducted exclusively by the humanities. Then, psychopharmacology for clinical practice and neuropharmacology for fundamental research outlined the first principles behind the mechanisms underpinning normal and pathological brain functioning, thus opening up a broad field of investigation for the understanding and treatment of mental diseases.

However, despite the advances, there remained many areas in which only a more intimate knowledge of the neurotransmitters involved in the development of mental activity will enable us to elucidate. The interest shown by the neurosciences in the neurochemical bases of consciousness should make a decisive contribution to understanding the complex phenomenon of mentation in both the healthy subject and the mentally ill subject. Waking and sleep behavior provide an excellent experimental model to achieve this goal. Indeed, the waking state with its structured and rational mental activity can be contrasted with dreaming, which is whimsical, disorderly and, in many respects, closely resembles the symptoms of schizophrenia. Several authors have underlined this similarity. As Freud[1] observed (p. 90), the German philosopher Kant stated that 'The madman is a waking dreamer', while another German philosopher Schopenhauer wrote that 'Dreams are brief madness and madness a long dream'. Finally, Maury[2] in a well-known book on sleep, stated that 'Dreaming is a kind of delusion' (p. 26).

The basic mechanisms governing waking and sleeping emanate from the subcortical structures. In contrast, the neurochemical phenomena involved in psychogenesis are controlled mainly by the cerebral cortex, the linchpin of the central nervous system,

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with the backing of subcortical adjacent structures.[3,4] Consequently, it is on the cerebral cortex that research into mental activity during the waking–sleeping cycle is principally focused. However, since the nucleus accumbens is involved in the mental troubles of schizophrenia and acts in coordination with the cortex, its functioning will be also examined.

The waking–sleeping cycle involves three main phases beginning with the waking state and ending with rapid eye movement (REM) sleep and transiting through slow wave sleep.

WAKING PROCESSES

The waking state is the outcome of the combined action of both antagonistic and complementary activating and inhibiting processes.

From Moruzzi and Magoun[5] we know that the fast, low voltage global cortical electrophysiological activity (electroencephalogram (EEG)) that is recorded during wakefulness, corresponds to strong activation of the cortical neurons as shown by the multiplication of the action potentials.[6–8] The gamma synchronized rhythm centered on 40 c/s also points to this activation. This rhythm, which has been identified during the attentive waking state in cats[9] and in humans,[10] deteriorates in Alzheimer's disease and could constitute a criterion of mental integrity.[10] Blood flow and the consumption of glucose at the cortical level, as evidenced by positron emission tomography,[11–13] also participate in the dynamics of the waking state.

Acetylcholine, a neurotransmitter produced by the basal subcortical nucleus (Meynert's nucleus in humans) is the principal driving force behind these cortical activating processes,[14,15] which all originate in the brainstem,[5] and particularly in the pedunculopontine and dorsolateral tegmental nuclei.[16] Indeed, acetylcholine acting at the cortical level has predominant excitatory influences on muscarinic receptors. It decreases K^+ currents and blocks both an early Ca^{2+}-dependent component of the slow hyperpolarization that follows the action potential as well as a late component that is Ca^{2+}-independent and appears to be mediated by a NA^+-dependent K^+ current. Moreover, acetylcholine blocks the M current, a non-activating current, which is minimally active at resting potentials and turns on slowly with depolarization (it acts as a brake on repetitive firing).[17] These activating processes are vital because their absence induces coma.

However, inhibiting influences also act upon the cortex during waking via the monoaminergic axonal endings of neurons which are located in the brainstem and the posterior hypothalamus. Norepinephrine, serotonin and histamine inhibit many cortical neurons when they are infused by microiontophoresis. They act on the principal cells either directly or by activating inhibitory interneurons. Indeed, classical and recent studies have shown that norepinephrine first diminishes the cortical firing rate[18–24] but at the same time increases the signal-to-noise ratio.[22,25] These inhibitory influences seem to be mediated by α_2 receptors situated at postsynaptic level which block Ca^{2+} channels or open K^+ channels. In contrast, recent data show that β_1 receptors are positively coupled to adenylate cyclase and α_1 receptor activation results in a decrease in resting K^+ conductance.[17] Moreover, norepinephrine modifies the activity of corticocollicular and corticopontine neurons from bursting to tonic firing[26] as during waking activity, but early on Evarts[8] said that this kind of regular tonic firing involves inhibitory control processes because the firing becomes irregular during sleep. In the same way, other classical studies have also shown that serotonin influences cortical inhibition.[20–23] More recent data confirm that serotonin, via 5-HT_{1A} receptors, inhibits cortical neurons by increasing K^+ conductance. However, in some cases it induces a depolarization of cortical neurons by 5-HT_2 receptors.[27] Nevertheless, this activation seems to act partly on GABAergic interneurons, which results in a hyperpolarization of pyramidal neurons.[28] In fact, Araneda and Andrade[29] described the 'very high prevalence' hyperpolarization of rat prefrontal pyramidal neurons by serotonin. They hypothesized that the 5-HT_{1A} and 5-HT_2 receptors might be situated on the same pyramidal neurons, and that they might be impinged upon by different serotoninergic terminals (dorsal and median raphe nuclei). As postulated by McCormick,[30] the modulated action of these two kinds of receptors could give rise 'to an increase of the so-called signal-to-noise ratio of the neuron' (p. 373), depending on their respective activations. Moreover, dopamine D_4 receptors abundant in the frontal cortex are also inhibitory.[31] Finally, histamine was first shown to inhibit cortical neurons by H_1 and H_2 acting receptors.[32,33] It was later shown that H_1 receptors are in fact excitatory.[34,35] However, pharmacological evidence has suggested that histamine may not play a crucial role in cortical processes during waking.[36] Its main influence could be subcortical.[37] The decisive influence of all these transmitters is dependent upon the sensitivity (affinity) of each of their receptors.

These monoaminergic neurons are most active during the waking state.

Mental functioning during the waking state is therefore dependent upon two types of neurotransmitters. The first are activators which support the cortical function. The second are partly at least inhibitors controlling this activation and 'standardizing' mental function, as it were. This hypothesis is supported by the causal link between the disruption in the noradrenergic and/or serotoninergic inhibiting influences and the occurrence of the psychological disturbances associated with nervous depression.

SLOW WAVE SLEEP PROCESSES

Slow wave sleep is composed of cortical slow waves and spindles. It occurs principally during the early periods of sleep. During this phase, neuronal firing decreases, gamma activity diminishes considerably[38,39] and the blood flow in the cortex lessens, except for the visual cortex and, to a lesser degree, the secondary auditory cortex.[12,40,41] This overall reduction in cortical vitality is concurrent with decreased acetylcholine release.[42]

Inhibitory neurotransmitter activity also slows down. The histaminergic neurons become totally silent with the onset of slow wave sleep,[43] while firing of noradrenergic[44,45] and serotoninergic[46,47] neurons is more sporadic. Only the firing of dopaminergic neurons remains unaffected,[48,49] although there is an increase of release[50] which could be consecutive to noradrenergic and serotonergic partial disinhibition.[51,52]

On the psychological level, Foulkes has shown that the nervous system is never silent since he was able, during slow wave sleep, to record 'thought-like' contents corresponding to diurnal reality.[53] He also mentions certain 'dreams' as is confirmed by more recent results,[54–56] however, the current data rather suggest that true dreams, with their characteristic visual components, can only occur in the physiological conditions of REM sleep[57–60] even if this stage is 'covered'.[59] The mental activity specific to slow wave sleep, therefore, is mainly the product of weakened activating and inhibitory factors, which perhaps accounts for the fairly poor psychological content of this phase of sleep.

RAPID EYE MOVEMENT SLEEP PROCESSES

Rapid eye movement sleep (REM sleep), also called paradoxical sleep,[61] is characterized by eye movements often occurring in bursts, low voltage EEG activity as first shown by Aserinski and Kleitman[62] confirmed by Dement and Kleitman[63] (which led Dement[64] to refer to 'activated sleep') and muscular atonia in animals[64,65] and in humans.[66]

Rapid eye movement sleep and the waking state share a host of common features: a similar low-amplitude EEG, the number of cortical action potentials,[7] the same gamma rhythm (but unlike waking, uncoupled between frontal and perceptual cortical regions[67]) and even increased acetylcholine release.[68,69] Cerebral circulation is also similar, and even greater in the phylogenetically older limbic cortex. This could explain the affective involvement in dreams. However, it is lower in the dorsolateral prefrontal cortex, in part of the parietal cortex and in the primary visual cortex.[12,70] The deactivation of this part of the prefrontal cortex might already explain the decrease of mental control during REM sleep. However, in the connection established by positron emission tomography methodology between REM sleep dreaming state and schizophrenia, although chronic drug-free schizophrenics show a lower dorsolateral prefrontal level of activation (all the more so when the results of cognitive tasks are impaired[71]), there is an increase in dopamine synthesis in drug-free schizophrenics. This increase is thought to be consecutive to activation of (not highly specific) monoamine decarboxylases.[72]

In parallel with this 'tonic' activation, ponto-geniculo-occipital (PGO) spikes occur during REM sleep in the cat[73–76] and in humans.[77,78] These are concomitant with 'phasic' cortical superactivation.[79] The PGO spikes, which occur principally in the visual structures[76] and are generally associated with rapid eye movements, are sometimes claimed to be responsible for dream activity.[77,78] Steriade *et al.* stated that because prior to REM sleep entrance there are very high amplitude spikes (without eye movements), vivid imagery may occur during these short periods.[80] However, verbal reports of this period do not reveal visual contents but rather 'a feeling of indefinable discomfort, anxious perplexity and harrowing worry'[81] (p. 279). Also, Larson and Foulkes showed that mental contents during this stage of sleep 'are inconsistent with the hypothesis of an intensification of mental activity or cerebral vigilance at pre-REM EMG suppression. They seem, rather, to point to a reduction in reportable mentation and in efficient cognitive reactivity at the point of transition from non-REM to REM sleep' (p. 552).[82] Moreover, as already mentioned, the primary visual cortex, which receives inputs mainly from the lateral geniculate nucleus, has been shown to be deactivated during REM sleep.[70] However, it is worth mentioning that PGO spikes are recorded in several thalamic nuclei and cortical areas[83] and that the visual associative cortex is activated during REM sleep.[70,84] It is our opinion,[85] however, that the timescale of dreaming is ill-matched to wave lengths with a maximum duration of 100 msec[77,78] unless we accept that the successive spikes are responsible for rapid changes of dream content which currently seems unlikely. Finally, to conclude on Steriade *et al.*'s hypothesis,[80] it is noteworthy that in the transition between slow wave sleep and paradoxical sleep, it has been shown in mice,[86] rats[87] and cats[88] that there is also a short-lasting 'intermediate stage' during which the forebrain seems to be disconnected from the brainstem[88,89] (functional cerveau isolé preparation[90,91]), as also shown by the spontaneous and evoked[92] EEG field activities. However, a slight increase in cortical neuron firing[93] and these rare isolated PGO waves are the first discrete signs of REM sleep. Thus, it could be that the forebrain structures involved in mentation generating processes, transiently lacking in brainstem issued activating and inhibitory main influences, generate such unusual somewhat painful mentation as defined by the above studies.

Thus, during both waking and REM sleep, the electrophysiological, circulatory and neurochemical variables demonstrate the strong activation of the cortex, which is in a position to generate mental activity in both these behavioral states. However, the main difference of REM sleep with the waking state concerns the inhibiting monoaminergic neurons which become silent, with the exception of dopaminergic neurons the firing of which remains unchanged, although it has been shown that dopamine release is increased during REM sleep in some cases.[50] In fact, the 'wet'[94] (in[95]) neurochemical disinhibition resulting from the silence of noradrenergic and serotoninergic neurons only confirms the 'dry' electrophysiological disinhibition previously demonstrated. Indeed, as early as 1964, Evarts[8] (see above), explaining the regular firing of pyramidal neurons, spoke of a 'frequency-limiting' process involving inhibitory influences taking place at the cortical level during waking and disappearing particularly during REM sleep. Similarly, Demetrescu *et al.* in 1966, using a complex paradigm of thalamocortical evoked potentials, concluded that activating and inhibitory influences act together at the cortical level during waking, and both decrease during slow wave sleep.[96] However, during REM sleep there was activation and massive disinhibition. In those early days we already underlined the importance of Demetrescu *et al.*'s finding[96] in accounting for the different kinds of mentation encountered during sleep-waking stages.[97–99]

CEREBRAL NEUROCHEMISTRY AND MENTAL ACTIVITY

Acetylcholine is the main neurotransmitter responsible for cortical activation (its muscarinic antagonist, atropine, produces a slow wave sleep EEG[100]) and constitutes the mainstay of mental activity.[101,102] However, glutamate might also contribute to this activation. During the waking state, nevertheless, this activation appears to be modulated by the noradrenergic and serotonergic partly inhibitory neurotransmitters. The two types of influence, activating and inhibitory, work together therefore to generate waking mental activity in the normal subject. During REM sleep, with the extinction of the bulk of the inhibiting processes, cortical activation becomes dominant. The balance between activation and inhibition ceases, and with it a barrier seems to fall leaving the field open for dream activity marked by inconsistency, irrational associations of ideas and of recurrent dreams which are often the resurgence of highly emotional situations experienced in the past. This disinhibition might also explain the difficulty, even the impossibility, that many people experience when trying to recall their dreams. It has been shown in animals that during the seconds prior to waking the inhibiting mechanisms immediately come into action again.[45] If, as one might well suppose, it is also at work in humans, then it could hinder the recording, in the waking mnemonic system, of the psychic contents occurring in another brain state. Freud utilizes the image of child's 'mystic writing-pad' to explain this specific forgetting.[103]

This quasi-total cortical disinhibition during REM sleep is complicated by yet another neurochemical phenomenon which no doubt contributes to the weird nature of dreams. The typical features of dreams ('sensorimotor hallucinations, bizarre imagery . . . diminished self-reflective awareness, orientational instability . . . intensification of emotion, instinctual behaviors')[104] are highly reminiscent of schizophrenic symptoms (however, in spite of strong similarities there are also differences; dreams are predominantly made up of visual contents, while schizophrenia most often gives rise to auditory hallucinations, although there are also erroneous interpretations of visual data). It happens that the only monoaminergic neurotransmitter which continues to function during REM sleep is dopamine, which is known to be dysfunctional in cases of psychosis, and especially among schizophrenic patients. In a 'normal' subject, when the dopamine level increases in the extracellular environment of the brain, under the influence, for example, of amphetamines,[105] nightmares occur[106] (a possible prelude to psychotic decompensation[107]), as well as psychotic-type disturbances.[108] Conversely, in schizophrenic patients, when the action of dopamine is diminished by the administration of neuroleptics, the delirium and hallucinations vanish.[109]

However, as we have seen, dopaminergic neurons continue to discharge in the same way during the different phases of the waking-sleep cycle. Other factors must play a part therefore in the elaboration of the psychotic-like mode of thought characteristic of dreaming. If this were not the case, there would be no distinction between dreaming and the waking state, except the disinhibition. We suggest that the silence of the noradrenergic neurons during REM sleep might enhance the impact of dopamine on the cortex. The heteroreceptors α_{2a}, located on the cortical dopaminergic endings[52] which inhibit the release of this neurotransmitter during wakefulness, become non-operational during REM sleep. This potentation of dopamine also occurs with the postsynaptic α_1 receptors which impede the action of the dopaminergic D_1 receptors of the target neurons[110] which could be involved in psychotic symptoms.[111] However, today the prefrontal norepinephrine–dopamine interaction is still slightly open for discussion.[112]

For the time being, the impact of serotonin (5-HT) remains more ambiguous. The stimulation of the postsynaptic 5-HT_{1A} receptors located on the as-yet-unidentified neurons enables dopamine release[113] while in 5-HT_{1A} knockout mice with suppression of both pre- and postsynaptic receptors there is an increase of dopamine release and turnover.[51] Up to now, the influence of 5-HT_{2A} receptors gave rise to contradictory results.[114,115] 5-HT_{1B} and 5-HT_6 receptors seem to favor dopamine release.[116] Other studies, however, have shown that the inaction of the 5-HT_6 receptors, which have a strong affinity for neuroleptics, does not modify dopamine release but rather induces behavioral problems in animals which can be relieved with atropine.[117] In addition, inactivation of this 5-HT_6 receptor would seem to increase cortical release of glutamate, aspartate and acetylcholine,[118] thus enhancing the dynamics of the cortex. The release of this last neurotransmitter might also enable the release of dopamine by acting on the nicotinic receptors.[119,120] Consequently, during REM sleep, there should also be an increase of dopamine release.

Nevertheless, the functioning of the nucleus accumbens could also be involved in the mentation of REM sleep. Indeed, while the prefrontal cortex is often thought to be responsible for the 'negative' components of schizophrenia (flat affect, lack of motivation, poverty of speech, poor attention span, etc)[121–123] through a reduced dopamine level, an increase of dopamine influence in the nucleus accumbens is generally considered to be responsible for the 'positive' symptoms of this disease (hallucinations, delusion, etc.) generally encountered in REM sleep mentation. It should be mentioned that 5-HT_{1B} knockout mice show an increase of extracellular dopamine release in the accumbens nucleus[124] and an increase of its turnover.[51] This result could be the consequence of an increased number of 'phasic' discharges of dopaminergic neurons[125] which induce high levels of transmitter release[126] and could be related to both local and area A_{10} serotonergic disinhibition.[52,127] Thus, there should be the same increase of dopamine release during REM sleep. Two experimental arguments strengthen this hypothesis. First, Miller *et al.* showed that in A_{10} area the 'variability' of neuron firing is higher than during slow wave sleep.[48] Second, De Saint Hilaire *et al.* showed that in some cases cortical dopamine release is higher than during slow wave sleep.[50] The same could be true for the nucleus accumbens because both the mesocortical and mesolimbic tracts emanate from the same A_{10} area. However, the silence of noradrenergic afferents, which are principally issued from the medulla A_2 area,[128] could also be involved because β noradrenergic antagonists[129] and α_2 agonists[130] increase dopamine release.

Consequently, while the possible increased influence of dopamine at cortical level during REM sleep might explain the low occurrence of schizophrenic-like negative components of mentation,[112] the increased release at the accumbens level could be responsible for the psychotic-like positive symptoms[131,132] most often encountered in dreaming activity. We hypothesize that the influence of dopamine seems to reach the threshold value at which psychotic disturbances begin to manifest during wakefulness. Finally, the importance of forebrain dopamine for dreaming was also underlined by Solms, who provided clinical evidence that the lesion of forebrain dopaminergic afferents suppresses dreaming without affecting REM sleep.[133]

In summary, the current experimental and clinical data support the following equation: 'activation (principally acetylcholine) + disinhibition (suppression of the inhibitory influence of norepinephrine, serotonin and histamine) + dopamine (excessive influence)' for the genesis of dream activity and its retinue of psychological disorders and 'activation + inhibition + dopamine' for waking mentation (Fig. 1). Despite the plurifactorial character of brain functioning (a deficit in excitatory amino acids also seems to be involved in schizophrenia[125,134,135]), dopamine thus seems at present to constitute a cornerstone of mental activity, a possible factor in nervous depression[136] and the disturbing shared feature of dreams and schizophrenia. (Incidentally, it is of interest to note that both depression[137,138] and schizophrenia[139,140] show a similar reduced latency for REM sleep appearance.) As such,

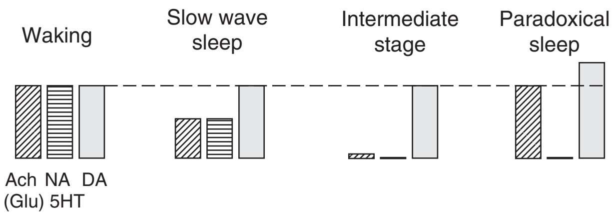

Figure 1. The hypothesis for central regulation of mental activity. The diagram represents the functional power of transmitter influences at cortical and limbic level during sleep-waking stages. During waking the cortex is activated by acetylcholine and also certainly glutamate. Thus, mental activity can be generated. However, inhibitory influences, particularly supported by norepinephrine and serotonin, take place at cortical level and probably have to cooperate with the activating processes to generate the acute, rational mental activity of waking. Dopamine neurons fire at a given rate. During slow wave sleep, activating and inhibitory processes both decrease because of the reduced cortical acetylcholine release and the decreased firing (and release) of norepinephrine and serotonin. The dopaminergic neurons fire globally as during waking. Prior to REM sleep, during the intermediate stage which nearly corresponds to a cerveau isolé preparation, the activating influences of waking are at their lowest level or suppressed, while the noradrenergic and serotonergic neurons become silent. We indicated a trace of activating influences because cortical neurons already begin to fire slighty prior to REM sleep entrance. Dopamine release is probably unchanged. This could perhaps explain the existence of some type of unpleasant mental activity (see text). During REM sleep, there is again a significant release of acetylcholine (i.e. there is strong cortical activation), except in the dorsolateral prefrontal cortex. Consequently, it is likely that mental activity can be generated and the prefrontal deactivation could already explain some disturbances of mentation during this sleep stage. However, the silence of noradrenergic and serotonergic neurons generates an original activation–disinhibition state which could also explain the generally irrational mentation. Moreover, this disinhibition should create an increase in dopamine release at both prefrontal and nucleus accumbens level. At the cortical level it could explain the scarcity or absence of schizophrenic negative symptoms during dreaming; at the limbic level it may reach the threshold of psychotic symptom appearance during waking and be responsible for all positive schizophrenic symptoms (hallucinations, delusion) encountered during dreaming.

dopamine will provide a pedestal for all future research dealing with the neurochemistry of normal and pathological mental activity. This highlights the advantages that can be drawn from studying this neurotransmitter and monoamines as a whole in order to consider the opinion of neuropsychiatrist Henri Ey[141] who claimed ‘It is obvious, it cannot be but obvious that dreams and madness spurt out from the same sources’.

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