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# REGIONAL ORGANISATION OF BRAIN ACTIVITY DURING PARADOXICAL SLEEP (PS)

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## INTRODUCTION

As early as 1962, Michel Jouvet already envisioned how the regional brain activity was distributed during paradoxical sleep (PS), initially referred to as the rhombencephalic phase of sleep (10). He also foresaw how this functional distribution could account for the main characteristic features of PS:

> *"The rhombencephalic phase of sleep (RPS) is dependent upon the triggering of a system situated [...] in the pontine reticular formation. This system controls the somato-vegetative phenomena which are highly characteristics (sic) of the RPS (Disappearance of all muscular tonic activity [...], variation in respiration and cardiac rhythms). The [...] rhythmic hippocampal activities occuring (sic) during the RPS [...] are suppressed by lesion of the ventral mesencephalon, the hypothalamus and the septum. It is suggested that connections between the pontine reticular formation and the limbic system may take the "limbic midbrain circuit" described by Nauta. [...] Such results suggest that dreaming occurs periodically during sleep when a ponto-limbic system is brought into play by a neurohumoral mechanism.".*

Fifty years later, many of these assumptions have been confirmed while some remain valuable working hypotheses. A particularly challenging task has been to provide experimental evidence for these hypotheses in humans, due to the limited experimental access to the human brain function. In this paper, we concentrate on the contribution of functional neuroimaging to the understanding of mechanisms of human PS. The important activity in pontine and limbic areas has been confirmed. The functional implication of these regional activities in some aspects of PS such as the instability of the neurovegetative system has also been investigated. However, the neurophysiological mechanisms which produce this peculiar organization of brain function remain unclear. Some evidence exists that activities similar to pontine waves or ponto-geniculo-occipital (PGO) waves are present in Man. They might play a prominent role in shaping the pattern of regional brain activity during PS.

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Finally, although the distribution of brain activity may be compatible with the general characteristics of dreams, a considerable work remains to be done to fully confirm Michel Jouvet's farsighted hypothesis that the activity in this ponto-limbic system is causally related to the phenomenology of dreaming in humans.

## THE PONTO-LIMBIC SYSTEM

Paradoxical sleep is characterized by a sustained neuronal activity (9, 34) and, correspondingly, by high cerebral energy requirements (13, 17) and blood flow (5, 13). In this sleeping but working brain, some areas are more active than others; in contrast, other regions have lower than average regional activity. With the advent of neuroimaging technique, the characterization of the regional distribution brain activity became possible. Early studies reported a high regional glucose metabolism in the limbic system in rats (12, 26) and cats (27). In humans, the functional neuroanatomy of normal PS has been investigated by several laboratories that have provided highly consistent results. The activation of mesopontine tegmentum and thalamic nuclei has been systematically reported during PS (1, 19, 24). In the forebrain, PET data showed that limbic and paralimbic areas were among the most active areas in PS: amygdala, hippocampal formation, anterior cingulate, orbito-frontal and insular cortices (1, 19, 24). Temporal and occipital cortices were also shown to be very active (1), although this result is less reproducible. Finally, more recent data demonstrated that the motor and premotor cortices were also very active during PS (18). While the activation of the ponto-limbic system in humans during PS has been linked to the dreaming activity (see below), recent analyses of neuroimaging data assessed the participation of the ponto-limbic system in other key PS features. For instance, we recently showed that the large variability in heart rate during PS can be explained by a prominent influence of the amygdaloid complexes (Desseilles *et al.*, in preparation).

An original contribution of human functional neuroimaging was to demonstrate the relatively low activity in the multimodal associative cortices of the prefrontal cortex and inferior parietal lobule (1, 19). The latter feature is also observed in deep slow wave sleep (1, 16). In contrast, these cortical areas are the most active regions during wakefulness (14). Another important contribution of human functional imaging was to show that the functional relationships between distant brain areas are different during PS and wakefulness. The functional relationship between striate and extrastriate cortices, usually excitatory, is inverted during PS (2). Likewise, the functional relationship between the amygdala and the temporal and occipital cortices is different during PS than during wakefulness or SWS (20). These results indicate that a considerable change in functional integration might occur during PS, which is probably as important as the pattern of regional activity in understanding the functions of PS.

## WHY BRAIN ORGANIZATION IN PS IS SO DIFFERENT FROM WAKEFULNESS

The issue is now to understand why the functional neuroanatomy of PS is so different from the distribution of regional brain activity during wakefulness. A change in neuromodulation might participate to a modification of forebrain activity and responsiveness during PS, as PS is characterized by a prominent cholinergic tone and a decrease in noradrenergic and serotonergic modulation (34). Unfortunately, at present, there is no report exploring how changes in the neuromodulation may affect the regional brain function during PS.

The influence of pontine waves or ponto-geniculo-occipital waves should also be considered. Several observations suggest that PGO waves also occur during human sleep. In epileptic patients, direct intracerebral recordings in the striate cortex showed monophasic or diphasic potentials during PS, isolated or in bursts (29). In normal subjects, surface electroencephalography (EEG) revealed transient occipital and/or parietal potentials time-locked to REMs (21). Source dipoles of magnetoencephalography (MEG) signal were localized in the brainstem, thalamus, hippocampus and occipital cortex during PS (8).

We also tried to get some evidence that activities like pontine or PGO waves exist in humans and result in a hemodynamic signal detectable by positron emission tomography and cerebral blood flow measurements. Since rapid eye movements during PS have been shown to correlate with the occurrence of the so-called PGO waves in animals, we reasoned that the presence of such waves in humans implies that the neural activity of the brain regions from which PGO waves are the most easily recorded in animals (i.e. the dorsal meso-pontine tegmentum, the lateral geniculate bodies and the occipital cortex) should be more tightly related to spontaneous ocular movements during PS, than during wakefulness. We could confirm this hypothesis by showing that the activity in the lateral geniculate bodies and the occipital cortex is more closely related to rapid eye movements during PS than during wakefulness (25). These results support the assumption that pontine or PGO waves do exist in humans. This finding has important functional implications. Although most easily recorded in the pons (11), the lateral geniculate bodies (22) and the occipital cortex (23), PGO waves are observed in many parts of the cat brain (6), including limbic areas (amygdala, hippocampus, cingulate gyrus). Moreover, in rats, the generator of the pontine waves, which has been located in the dorsal part of the subcoeruleus nucleus project to a set of brain areas shown to be active in human PS: the occipital cortex, the entorhinal cortex, the hippocampus, the amygdala as well as brainstem structures participating in the generation of PS (3). Taken together, these various experimental elements warrant the hypothesis that activities similar to pontine or PGO waves play a prominent role in shaping the distribution of regional brain activity during PS in humans.

## CEREBRAL CORRELATES OF DREAMING

The study of cognitive processes during PS assumes that the anatomical segregation of brain functions is preserved during sleep (7). Dream features can therefore be potentially mapped onto a specific distribution of brain activity. Indeed, quantitative analyses of dream content have been obtained from various sampling methods, and revealed several frequent and stable features of dream phenomenology which fit remarkably well with the distribution of brain activity during PS (7, 18, 19, 32).

Dreams are characterized by their perceptual features. The sensory modalities represented in dreams are very consistent across studies: visual elements are present in almost all dreams, auditory elements occur in about 40-60% of dreams, movement and tactile sensations in about 15-30%, while smell and taste appear in less than 1% of the dream reports (35). The abundance of visual aspects in dreams is in good accordance with the activation in associative visual brain areas during PS (1, 2).

Another well-documented regularity in dreaming is the prominence of negative emotions, anxiety and fear (35). It is sensible to relate this common fear experience in dreams to the activation of the limbic system, in particular the amygdala (15). In animals and humans, the amygdala mediates responses to threatening stimuli or stressful situations (28); it is thus in a perfect position for organizing emotional processing during sleep, favoring fearful experience in dreams.

Motor activity is also very present in dreams (4). However, because of the characteristic muscular paralysis in PS, no coordinated motor behavior is observed unless (pathological) conditions remove this atonia. For instance, after pontomedullary lesions, cats seem to act out their dreams (30). Likewise, in human patients suffering from REM sleep behavior disorder the coordinated motor behavior during PS is often related to the dream content that the patient reports upon awakening (31). The PET results observed in normal subjects suggest that these coordinated behaviors are programmed centrally, in the motor and premotor cortical areas (18).

Other characteristic features of dreams such as the lack of insight, distortion of time perception, and amnesia on awakening have been tentatively attributed to the relative hypoactivation of prefrontal cortex (7, 15). However, lesions to lateral prefrontal cortex do not affect the ability to experience and report dreams in human patients who suffer stroke or head injuries (33).

These observations provide only a general perspective on the plausible match between global dream characteristics and typical PS pattern of brain activity. More insight into PS mechanisms can be gained if the content of each individual dream was to be used as an explanatory variable to model neuroimaging data. Unfortunately, in our experience, the use of standard scales to parameterize dream content in terms of the motor, perceptual or emotional content has not been successful in describing dream-related brain correlates. Theoretical tools have been developed to run these experiments but it remains that dream reports can be adversely influenced by several factors – forgetting, reconstruction mechanisms, description in verbal description, censorship (32). Future research will take these facts into account in its attempt to specify the exact cerebral correlates of dreaming.

## CONCLUSIONS

Despite the wealth of data accumulated about the generation of PS and the cerebral correlates of dreaming, both from animals and human studies, the conclusion which Michel Jouvet came to forty years ago still holds:

> *"Pour le neurophysiologiste, la porte des rêves est à peine entrouverte et la clef des songes n'est pas encore découverte. Si certains mécanismes de l'activité onirique semblent se dévoiler, les fonctions du rêve nous demeurent toujours inconnues."* (10).

## SUMMARY

Human brain function is regionally organised during paradoxical sleep (PS) in a very different way than during wakefulness or slow wave sleep. The important activity in the pons and in the limbic/paralimbic areas constitutes the key feature of the functional neuroanatomy of PS, together with a relative quiescence of prefrontal and parietal associative cortices. Two questions are still outstanding. What neurocognitive and neurophysiological mechanisms may explain this original organization of brain function during PS? How the pattern of regional brain function may relate to dream content ? Although some clues are already available, the experimental answer to both questions is still pending.

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