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Brain and Cognition

Asleep but aware?

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ABSTRACT

Despite sleep-induced drastic decrease of self-awareness, human sleep allows some cognitive processing of external stimuli. Here we report the fortuitous observation in a patient who, while being recorded with intra-cerebral electrodes, was able, during paradoxical sleep, to reproduce a motor behaviour previously performed at wake to consciously indicate her perception of nociceptive stimulation. Noxious stimuli induced behavioural responses only if they reached the cortex during periods when mid-frontal networks (pre-SMA, pre-motor cortex) were pre-activated. Sensory responses in the opercular cortex and insula were identical whether the noxious stimulus was to evoke or not a motor behaviour; conversely, the responses in mid-anterior cingulate were specifically enhanced for stimuli yielding motor responses. Neuronal networks implicated in the voluntary preparation of movements may be reactivated during paradoxical sleep, but only if behavioural-relevant stimuli reach the cortex during specific periods of "motor awareness". These local activation appeared without any global sleep stage change. This observation opens the way to further studies on the currently unknown capacity of the sleeping brain to interact meaningfully with its environment.

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1. Introduction

Sleep has frequently been assimilated to a little death, to such an extent that the Greek mythology establishes a fraternal link between Hypnos, the God of Sleep and Thanatos the God of Death. The loss of behavioural control and the fading of consciousness are the distinctive features of sleep that underlie this phenomenon. The accompanying lack of responsiveness towards nocturnal stimulation led to hypothesize a functional disconnection between the cerebral cortex and the external world (Steriade, 1994). This disconnection is especially intriguing in the period of paradoxical sleep (PS), during which the electroencephalographic pattern is similar to that of waking state.

In order to explain this paradox, Foulkes (1966) and later Llinas and Ribary (1993) suggested that PS "is a state of hyperattentiveness during which sensory input cannot address the machinery that generates conscious experience". They hypothesized that the oniric activity integrally focuses the attention of the sleeper, excluding the possibility for external sources of stimulation to be processed. However, this view is challenged by the well-known fact that external events can interfere with, or be incorporated into, the ongoing oniric activity (Dement & Wolpert, 1958).

Modern behavioural and neurophysiological studies indicate that the sleeper keeps the possibility to perceive and process external information. Accordingly brain responses related to cognitive activity (e.g. P300) have been recorded during PS in response to frequency- or intensity-deviant stimuli (Bastuji, Garcia-Larrea, Franc, & Mauguière, 1995; Cote & Campbell, 1999; Takahara, Nittono, & Hori, 2006; Macdonald, Jamshidi, & Campbell, 2008), and likewise to more complex stimuli such as the subject's own name (Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999; Pratt, Berlad, & Lavie, 1999). The persistence of a differential brain response ("N400 effect") to incongruous words during PS further indicates that the sleeper's brain keeps some capacity to analyse semantic contents (Brualla, Romero, Serrano, & Valdizan, 1998), even if linguistic absurdity appears to be accepted to a greater extent than during waking (Perrin, Bastuji, & Garcia Larrea, 2002). These results confirm that the sleeping brain remains able to detect and categorize some particular traits of external stimulus significance, even if the processes engaged are not identical to those implicated during wakefulness.

Notwithstanding the importance of the above work, the question of consciousness of external events during sleep remains unanswered. An empirical criterion used to assess the awareness of information is its "reportability" (Dehaene & Naccache, 2001; Gazzaniga, LeDoux, & Wilson, 1977; Weiskrantz, 1997) defined as "all voluntary communicative acts that are used to report conscious content" (Baars, 1997). In the context of sleep, Laberge (2000) has shown that "lucid dreamers" can voluntarily produce eye movements, to indicate that they are aware of dreaming, during ongoing PS. It has also been demonstrated that operant responses learned during wakefulness may be reactivated by stimuli presented during sleep (Bonnet, 1982; Burton, Harsh, & Badia, 1988; Granda & Hammack, 1961; Lauerma, Kaartinen, Polo, Sallinen, & Lyytinen, 1994). Evans, Gustafson, O'Connell, Orne, and Shor (1970) succeeded to observe complex behavioural responses to verbal suggestion during PS (i.e. "Whenever I say the word "itch," your nose will feel itchy until you scratch your nose") without sleep interruption. These behaviours remain rare and inconsistent suggesting that stimulus awareness during PS may be fluctuating.

In parallel to this, a critical and unsolved question concerns, the brain regions or activity supporting the production of these apparently 'intentional' responses while EEG recordings indicate unequivocal PS sleep, characterised by atonia and fading consciousness. Using brain imaging, Dresler and colleagues recently showed that dreamed motor actions performed during PS elicited neuronal activation in the sensorimotor cortex and the SMA, comparable to those observed during movements really acted during wakefulness (Dresler et al., 2011).

Here we describe the results of intracerebral EEG investigation that fortuitously captured a spontaneous reactivation of an actual motor behaviour previously used during wakefulness as an indicator of conscious perception of nociceptive stimulation in a patient affected by drug-resistant epilepsy recorded during presurgical assessment. Intra-cerebral recordings demonstrated that pre-activation of mid-frontal networks was determinant to allow this adapted behaviour to an external input, whereas activity in sensory cortices appeared irrelevant and global sleep stage unchanged.

2. Materials and methods

The subject was a 37-year-old women involved in a study protocol evaluating nociceptive processes during sleep using laser stimulations (Bastuji et al., 2011). She presented with refractory epilepsy and was being investigated using stereotactically implanted intracerebral electrodes before functional surgery. Depth EEG recording electrodes were implanted according to the stereotactic technique of Talairach and Bancaud (1973). The cortical targets were identified on the patient's MRI. The implantation procedure has been described in detail elsewhere (Frot & Mauguière, 1999; Frot, Rambaud, Guénot, & Mauguière, 1999; Guenot et al., 2001).

The patient was fully informed about the fact that Laser Evoked-Potential (LEP) recordings during sleep were not a part of the diagnostic procedure but were performed with research purposes, and gave her written informed consent. The laser stimulation paradigm was submitted to, and approved by, the local Ethics Committee (CCPPRB Léon Bérard-Lyon) and the study was promoted by the French National Agency for Medical Research (INSERM).

2.1. Laser stimulation procedure and parameters

Nociceptive heat pulses of 5 ms were delivered with a Nd:YAP-laser (Yttrium Aluminium Perovskite; wavelength 1.34 µm; El.En.®). Series of laser stimuli were delivered on the dorsum of the right hand (radial territory contralateral to the hemisphere of electrode implantation). The pain threshold was determined at wake. The patient was instructed to lift her left index finger to indicate that she had perceived the stimulation and score its intensity using a Likert-type scale where 0 was "no sensation", 8 = unbearable pain, and 4 was defined as "pricking, moderately painful"). An energy level of 80 mJ/mm^2, yielded for this patient the expected painful sensation defined as "pricking, moderately painful". After that, ten stimulations, at this pain threshold, were delivered to obtain wakefulness LEP responses. During LEP recordings, the patient was lying, immobile.

Then, the patient was allowed to sleep at her own time. During the night, series of up to 30 nociceptive laser pulses were delivered when definitive stages of sleep were reached, as determined on-line by an experienced sleep researcher. The staging was later confirmed off-line. The laser intensity was kept stable during the whole night (80 mJ/mm^2). Laser pulses were transmitted through the optic fibre from the laser stimulator. This 10-m optical fibre connecting the laser generator with the stimulating probe allowed stimulating conveniently the hand dorsum despite subject position during the night. Both the sleeping subject and the stimulating investigator wore eye protections.

After preliminary work showing that delivering stimuli at short (<6 s) and constant intervals increased the probability of awakening, inter-stimulus interval (ISI) was pseudo-randomly adjusted on-line and varied between 10 and 20 s. The laser beam was slightly moved over the skin surface between two successive stimuli to avoid habituation and especially peripheral nociceptor fatigue (Schwarz, Greffrath, Buèsselberg, & Treede, 2000).

Due to environmental bad conditions (noisy storm), this night session ended prematurely. A second night of stimulation was planned one week later, during which, the emergence of behavioural responses was observed. This night recording was conducted 14 days after electrodes implantation; at that time, anticonvulsant drug intake was drastically reduced for at least one week. EEG recordings were performed with sampling frequency of 256 Hz and a 0.03–100 Hz bandpass (Micromed®, Mâcon, France) in referential mode (the reference electrode being an implanted contact located in the skull).

In order to limit the lack of comfort induced by the monitoring device, no submental EMG electrodes were placed, but only EKG and 2 EOG electrodes (supero- and infero-lateral right canthus). EEG, EKG and EOG were recorded continuously during the night and stored for off-line analysis. In order to stimulate at well-identified sleep stages, the different states of vigilance were visually identified on-line, according to the criteria of Rechtschaffen and Kales (1968) adapted to intracranial recordings (see Magnin, Bastuji, Garcia-Larrea, & Mauguiere, 2004; Rey et al., 2007).

2.2. Incorporation of stimuli to dreams

In the morning that followed the recording night, a four-level scale adapted from Zimmerman (1970) was used to assess the degree of stimulus incorporation to dreams. The four-levels were (1) no incorporation, the subject had no recall of somatosensory or pain stimulation; (2) possible incorporation, the subject had some somatosensory or pain recall, but unrelated to the stimulations delivered; (3) obvious incorporation, the subject had some somatosensory or pain recall related to the stimulations delivered; (4) awareness of stimulation effectively delivered.

2.3. Anatomical localization of recording sites

The final position of each implanted contact with respect to the targeted anatomical structures was verified via frontal and sagittal X-rays at scale 1, using an X-ray source at 4.85 m from the patient's