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Research report

Are neocortical gamma waves related to consciousness?

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Abstract

Previous research has shown that neocortical gamma waves (approximately 30–80 Hz) are continuously present during low voltage fast neocortical activity (LVFA) occurring during waking or active sleep. Gamma waves occur in a burst-suppression pattern in association with large amplitude slow waves during quiet sleep or anesthesia. The present experiments show that continuous gamma activity is also present in rats during LVFA occurring during surgical anesthesia (with ether, isoflurane or urethane) and that a burst-suppression pattern of gamma activity occurs during large amplitude slow waves occurring in the waking state either spontaneously in undrugged rats or as a result of treatment with parachlorophenylalanine and scopolamine. The amplitude of gamma activity occurring during anesthesia is variable but is often greater than it is in the normal waking state. It is concluded that the pattern of neocortical gamma wave activity is strongly related to the presence or absence of large amplitude slow waves but is quite independent of the state of behavioral arousal. Whether or not gamma wave activity is related to subjective awareness is a very difficult question which cannot be answered with certainty at the present time.

Keywords: Anesthesia; Behavior; Consciousness; Dementia, Electrocorticogram; Gamma wave; Neocortex

1. Introduction

A number of recent papers have suggested that gamma waves (electrical oscillations in the 25–100 Hz or 30–80 Hz bands) generated by the neocortex and thalamus may be responsible for perception and consciousness [11,13,32]. In opposition to this, Steriade et al. [37,38] suggest that since gamma waves occur not only in the waking state, but also during slow wave sleep and anesthesia, they may not have any close relation to consciousness. However, the temporal distribution of gamma waves differs in the different states investigated by Steriade et al. Gamma waves were present in an essentially continuous pattern during a low voltage fast activity (LVFA) wave pattern in the waking state or in active sleep but were suppressed during the deep positive (surface negative) component of the slow waves present during anesthesia and slow wave sleep. It is conceivable that consciousness is associated only with continuous gamma wave activity while a lack of consciousness might be associated with an interrupted pattern of gamma waves. Further complications are introduced by the fact, known for many years, that a LVFA pattern of neocortical activity may be present during surgical anesthesia [2,4,8,27,28] and during quiet sleep as well as during active or rapid eye movement sleep [3]. In addition, large amplitude slow waves, rather than an activated LVFA pattern, may be present in the waking state, as first pointed out by Wikler [46] and abundantly confirmed since that time [45], both in normal animals and following treatment with a variety of drugs. These facts raise the following question: Does the temporal distribution of gamma waves (continuous vs. a burst-suppression pattern) correlate with the level of behavioral arousal and consciousness or with the pattern of neocortical slow wave activity independent of behavioural arousal and consciousness? This question has not previously been addressed.

It is essential, in work in this field, to be very clear about what is meant by the words ‘‘conscious’’ and ‘‘consciousness’’. Thus, the word ‘‘conscious’’ is often used to refer to a state in which a normal posture is maintained together with species-appropriate spontaneous behavior and reactivity to environmental stimuli. Coma or unconsciousness has been defined as a behavioral state resembling ‘‘deep sleep from which neither internal nor external stimuli can evoke wakefulness or consistent purposeful responses’’ [24]. Coma and stupor are sharply distinguished from delirium or dementia [16,24]. In objective terms, ‘‘dementia’’ appears to refer to a condition in which there

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is a severe generalized impairment of adaptive behavior together with a preservation of waking postures, spontaneous motor activity and reactivity to some environmental stimuli. The term ''dementia'' has been used in this sense in reference to animals since at least 1929 [12].

The terms ''consciousness'', ''coma'', and ''dementia'' may also refer, not to objectively observable motor activity, but to the presumed state of subjective awareness. Thus, the Multi-Society Task Force on PVS [19] has defined consciousness and unconsciousness in terms of the ability to experience the environment.

In this paper, I describe studies of the occurrence of neocortical gamma wave activity in rats in the waking or anesthetized state (induced with diethyl ether, isoflurane or urethane) and following treatment with *p*-chlorophenylalanine (PCPA, an inhibitor of tryptophan hydroxylase, an enzyme required in the synthesis of serotonin) plus scopolamine (a centrally-acting muscarinic antagonist). The latter drug combination produces continuous delta wave activity in the electrocorticogram in rats, together with a behavioral syndrome resembling human dementia [40,42,43]. The general anesthetics, diethyl ether and isoflurane, have been used extensively in both human and animal surgery. Urethane, in a dose of 1.0–2.0 g/kg, has long been used as a general anesthetic in animal experiments [14].

2. Materials and methods

Sixteen male hooded rats, weighing 436–720 g, were anesthetized with pentobarbital (60 mg/kg). Using a stereotaxic instrument [7,23], electrodes were placed in the left sensorimotor neocortex (at bregma, 2.0 mm lateral to the midline) and in either the same point in the right cortex ($N = 12$) or in the left parietal cortex (3.0 mm posterior to bregma, 2.0 mm lateral to the midline, $N = 4$). The electrodes consisted of stainless steel wire, 125 μm in diameter, insulated with Teflon except for the cross-sectional area of the tip, and soldered to subminiature gold-plated connectors. Screw-type electrodes fixed in the skull provided a ground connection (frontal bone) and an electrically quiet indifferent site (interparietal bone, over the cerebellum). At each site, one electrode was placed on the cortical surface and one was lowered to a depth of 1.0 mm. The deep electrode in such cases is usually located in or near layer 5 [44]. The horizontal separation of the electrodes was not rigorously controlled but was kept below 1.0 mm. The entire assembly was fixed to the skull with stainless steel screws and dental cement.

Experiments began after a recovery period of at least 2 weeks and each rat was used repeatedly in different experiments separated by an interval of 4 days or longer. Rats treated with PCPA were allowed 3–4 weeks to recover before being used in a terminal experiment involving the administration of urethane. Bipolar (surface-to-depth configuration) or monopolar differential records were taken from the cortex using an ink-writing polygraph (Grass Instruments) or a storage oscilloscope (Tektronix) using frequency bands of 0.1 or 0.3–90 Hz in the case of the ink writer and 0.1 or 0.3–10,000 Hz (half amplitude points) in the case of the oscilloscope. Activity was also recorded on a parallel channel in the frequency band of 30–90 or 30–100 Hz and activity in the band of 30–80 Hz was rectified, integrated over 1.0-s intervals, and displayed on the polygraph. For statistical purposes, the amplitude of this integrated activity was measured to the nearest 0.5 mm in 10 s/condition/rat. Amplified signals were also lead to a window discriminator and delay line, permitting the display of multiple sweeps of pretriggered wave forms on the oscilloscope. Finally, the oscilloscope was used to display multi-unit activity (frequency band of 300–10,000 Hz) and to construct $X–Y$ plots showing the phase relation between monopolar surface and monopolar deep recordings.

Recordings of cortical activity were taken while the rats were on a light plexiglass platform (34.5 × 34.5 cm) with a raised edge 1.7 cm high. This platform was mounted on four foam rubber pads. A bar magnet with one end cemented to the lower surface of the platform projected into a coil obtained from a relay. Voltages generated in the coil were displayed on one channel of the polygraph. This entire apparatus and its attached frame was isolated from outside vibration by a heavy concrete block resting on four rubber stoppers. The output from this movement sensor, supplemented by written notes, provided an objective record of behavior. In addition, in one experiment, rats were placed in a vertical position on a piece of hardware cloth held against one side of the movement sensor and records of cortical activity were taken as the rats climbed up.

Drugs used in the experiments included: diethyl ether (BDH), isoflurane (Abbot Laboratories), PCPA, (Sigma), scopolamine hydrobromide (Sigma), and urethane (ethyl carbamate, Fisher Scientific) Urethane and scopolamine were dissolved in 0.9% saline and PCPA was prepared as a fine suspension in a solution of saline (0.9%) plus gum arabic (0.5%).

The volatile anesthetics (ether and isoflurane) were initially administrated by placing rats in a large glass vessel containing room air nearly saturated with the anesthetic. Subsequently, anesthesia was maintained by holding near the snout a small jar containing surgical cotton squares soaked with the anesthetic. Depth of anesthesia was assessed by noting the status of: (a) the righting response; (b) the corneal reflex elicited by a light touch; (c) the flexion reflex elicited by pinching the fore or hind paws; (d) the pinna reflexes elicited by tickling or pricking the inside surface of the pinna with a fine wire; and (e) general observations such as muscle tone, skin color, and the rate and character of respiration. The response to severe pinching of the tail was also observed in deep anesthesia.

The rectal temperature was maintained at 36.5–37.5°C by heating with a lamp when required.

Numerical data were evaluated using the non-parametric Wilcoxon test for within-subject comparisons [31].

At the completion of all the experiments, the rats were deeply anesthetized and perfused through the heart with a formaldehyde solution. Rats anesthetized with urethane (2 g/kg) were perfused at the end of the experiment. The brain was extracted and stored in the formaldehyde solution.

3. Results

3.1. Normal waking state

When tested in a drug-free condition, the rats usually displayed a neocortical record consisting of LVFA. Activity in the 30–90 Hz band was continuously present, varying in amplitude from about 50–100 μV (peak to peak) in both monopolar and bipolar surface-to-depth derivations. When monopolar surface and monopolar deep traces were displayed on the oscilloscope, some potentials were almost exactly superimposable but others, not necessarily differing in frequency or amplitude, displayed large phase differences, sometimes approximating a 180° phase reversal. *X–Y* plots revealed a thick oval or oblong distribution inclined at about 45°, indicating a positive but rather loose association between the two signals. A comparison of the amplitude of integrated 30–80 Hz activity recorded from different electrode configurations (based on 10 1-s samples taken during complete behavioral immobility accompanied by LVFA in each of six rats) showed that the average output (in mm of pen deflection) was 4.0 ± 0.6 (mean ± standard error of the mean) in monopolar surface recordings, 4.2 ± 0.8 in surface-to-depth recordings, and 5.4 ± 0.9 in monopolar deep recordings. In each case the monopolar deep records had a slightly larger amplitude than records derived from the other two configurations ($p < 0.05$, Wilcoxon test). The monopolar surface and surface-to-depth values do not differ significantly.

Any change from undisturbed behavioral immobility such as spontaneous locomotion, passive stroking of the fur, or pushing the rat to make it walk, tended to increase slightly the level of integrated 30–80 Hz activity. In 13 rats, the average amplitude of this integrated activity was 2.6 ± 0.5 mm during undisturbed immobility and 3.5 ± 0.6 mm during stroking of the fur ($p < 0.001$, Wilcoxon test).

Five of the rats displayed multiple episodes of rhythmical 1–2 mV slow waves with a frequency of 7–9 Hz. These waves occurred only when the rats were standing absolutely motionless with eyes open and the head held up against gravity. They appeared in both the anterior and the posterior recording sites and were usually accompanied by a tremor of the vibrissae and head. Activity in the 30–100 Hz band was invariably strongly suppressed during the deep positive phase of these slow waves but the deep negative phase, which terminates as a sharp wave, often with a notch of varying amplitude immediately following the peak, generated large potentials in the 30–100 Hz record (Fig. 1).

3.2. Anesthesia

Rats given ether or isoflurane were initially anesthetized to a point at which neocortical activity and corneal, pinna, and flexor reflexes were suppressed but rhythmical respiration continued. The anesthetic treatment was then discontinued until the rat could right itself. At this point, the anesthetic was readministered and the cycle repeated (Fig. 2). During very deep anesthesia, essentially complete suppression of neocortical slow wave and gamma activity was observed for periods of as long as 20 s. As the depth of anesthesia was reduced, the electrocorticogram returned, initially in the form of complex slow wave bursts with a duration of about 0.5–2.0 s separated by interburst intervals that were initially as long as 11 s but were reduced to 1 s or less within 1–2 min after the anesthetic was discontinued. Activity in the 30–100 Hz band was strongly

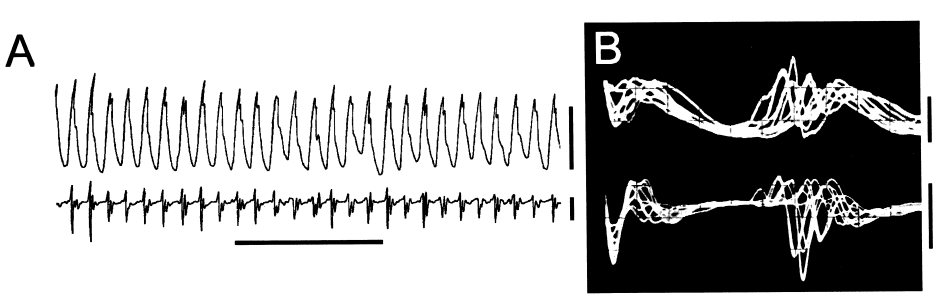

Fig. 1. Spontaneous rhythmical 7–9 Hz potentials occurring in sensori-motor neocortex in a waking immobile rat. (A, top) Surface-to-depth bipolar record; 1–90 Hz frequency band; deep negative up; vertical bar, 1.0 mV; horizontal bar, 1.0 s. (A, bottom) Similar to A, top, but the frequency band is 30–90 Hz and the vertical bar represents 0.2 mV. (B, top) Oscilloscope traces (10 sweeps) triggered by the deep negative peak (deep negative up) of the slow waves; frequency band, 0.3 Hz to 10 kHz; vertical bar, 1.0 mV; horizontal bar, 100 ms. (B, bottom) Similar to B, top but the frequency band is 30–100 Hz and the vertical bar represents 0.5 mV.

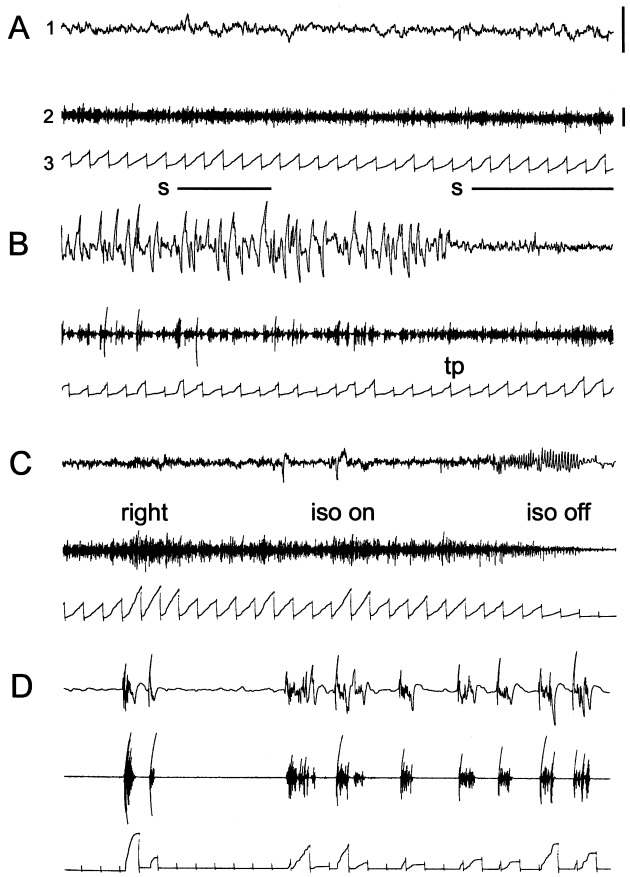

Fig. 2. Spontaneous field potentials in the sensori-motor neocortex before and during isoflurane-induced anesthesia. (A) Normal waking state. A1: surface-to-depth derivation; deep negative up; frequency band, 0.3–90 Hz; vertical bar, 1.0 mV. A2: similar to A1 except that the frequency band is 30–90 Hz and the vertical bar represents 0.1 mV. A3: 30–80 Hz activity, rectified and integrated over 1.0-s intervals. At ''S'' the fur was stroked lightly. (B–D) are continuous records except that 30 s was deleted between C and D. (B) Light anesthesia accompanied by continuous slow waves and a burst suppression pattern of gamma waves. At ''tp'', a light tail pinch produces cortical activation followed by a righting response accompanied by high amplitude continuous gamma activity. Isoflurane was administered between ''iso on'' and ''iso off''. The electrocorticogram was largely suppressed for about 30 s and the corneal, pinna, and flexion reflexes were absent but breathing persisted. Note that during recovery of the electrocorticogram, gamma activity occurs in high amplitude bursts separated by long silent periods.

suppressed during these interburst intervals but reappeared with an amplitude of 500 μV or more (5–10 times the amplitude during normal waking behavior) during the intermittent slow wave bursts (Fig. 2). This effect was clear in both monopolar and bipolar derivations. As the level of anesthesia was further reduced and neocortical slow wave activity became continuous, 30–100 Hz activity continued to be suppressed for 100–200 ms during each deep positive slow wave. This periodic gamma-wave suppression disappeared as spontaneous or elicited LVFA reappeared at a moderate level of surgical anesthesia.

The enhanced amplitude of gamma activity during anesthesia continued for at least several minutes after the righting response had recovered and as the rats were allowed to return to a normal state. In 13 rats, anesthetized with either ether ($N = 6$) or isoflurane ($N = 7$), integrated 30–80 activity soon after the return of righting, and occurring during continuous LVFA and behavioral immobility, averaged 2.9 ± 0.4 mm of pen deflection. This is very slightly higher than the level observed during undisturbed waking immobility prior to anesthesia in the same rats (2.6 ± 0.5, $p < 0.05$, Wilcoxon test). If the fur was stroked at this time, integrated 30–80 Hz activity rose to 5.1 ± 0.7 ($p < 0.001$, Wilcoxon test.) This level of integrated 30–80 Hz activity is also significantly greater than the level seen during stroking of the fur in the waking state in the same rats (3.5 ± 0.6 vs. 5.1 ± 0.7, $p < 0.01$, Wilcoxon test).

Urethane was administered in successive 500 mg/kg doses (i.p.) given at 15–30 min intervals in nine rats. A dose of 500 mg/kg had a marked sedative effect but 1000 mg/kg produced a light anesthesia (no spontaneous righting but good corneal, pinna, and flexor reflexes present) usually associated with nearly continuous LVFA. After doses of 1500–2000 mg/kg, the reflex responses were progressively attenuated or absent and the electrocorticogram consisted of continuous slow waves or of a burst-suppression wave pattern (Fig. 3). Deep negative waves were generally associated with rather high amplitude bursts of gamma waves but deep positive waves were associated with suppressed gamma activity. The occurrence of LVFA during undisturbed periods was usually associated with gamma waves of less than normal amplitude but at all levels of anesthesia, a firm pinch of the tail or a foot could produce clear LVFA associated with

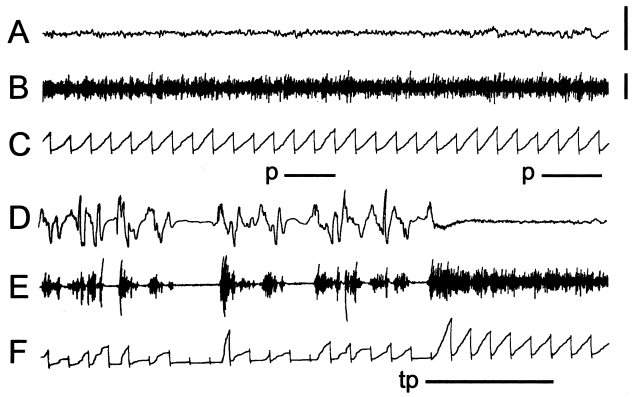

Fig. 3. Spontaneous field potentials in the sensori-motor cortex before (ABC) and during (DEF) anesthesia induced by urethane (1500 mg/kg, i.p.). (A,D) Surface-to-depth bipolar activity; deep negative up; frequency band 0.3–90 Hz; vertical bar represents 1.0 mV. (B,E) Similar to A,D but the frequency band is 30–90 Hz and the vertical bar represents 0.1 mV. (C,F) 30–80 Hz activity rectified and integrated in 1.0-s intervals. At ''p'', the rat is handled and stroked. In DEF, the rat displays no flexion reflex to pinching but there is a corneal reflex and a feeble pinna reflex. At ''tp'', a severe tail pinch produced a slight increase in the rate of respiration but no movement. Cortical activation was accompanied by high amplitude gamma activity.

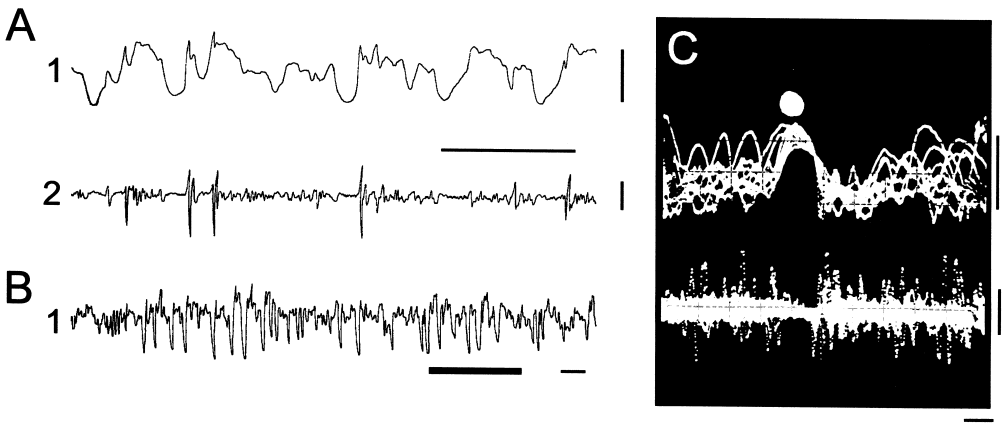

Fig. 4. Spontaneous field potentials in the sensori-motor cortex in a rat following treatment with PCPA (500 mg/kg, i.p., on each of the three preceding days) plus scopolamine (5.0 mg/kg, s.c.). (A1) Surface-to-depth bipolar record; 0.3–90 Hz frequency band; deep negative up; vertical bar represents 1.0 mV. (A2) Similar to A1 except that the frequency band is 30–90 Hz and the vertical bar represents 0.1 mV. (B1) Record as in A1 but at a lower speed. Thin horizontal lines represent 1.0 s. At the heavy horizontal line in B1 the rat was placed on a vertical metal screen and allowed to climb upwards (see Fig. 5). (C, top) record as in A1 except that deep positive is up and the frequency band is 0.3–10 kHz; vertical bar represents 1.0 mV; horizontal bar represents 100 ms. Ten sweeps are shown in which the waves marked by the large white dot triggered the oscilloscope (pretriggered multiple sweeps). (C, bottom) Similar to C, top except that the frequency band is 30–100 Hz and the vertical bar represents 0.1 mV. Ten sweeps were taken after the 10 sweeps shown in C, top had already been recorded.

gamma activity with an amplitude as great or even greater than in the normal waking state (Fig. 3).

3.3. Effects of PCPA and scopolamine

Recording were taken in six rats on the day following treatment with PCPA (500 mg/kg/day, i.p.) on the three preceding days. The neocortex displayed normal LVFA or rhythmical slow waves, normal gamma wave patterns, and largely normal behavior, as previously described [42]. Following treatment with scopolamine (5.0 mg/kg, s.c.) all LVFA disappeared; the electrocorticogram consisted of a pattern of continuous slow waves with an amplitude of 1–2 mV (Fig. 4). Gamma wave activity was of a burst-suppression type with suppressed periods of 100–200 ms duration associated with the deep positive component of the accompanying slow waves. This was true during both immobility and during behaviorally active periods such as climbing up a vertical piece of hardware cloth (Fig. 5). These rats were hyperactive and had to be restrained (by holding the tail or placing them in a deep plastic rat cage) to prevent them from walking over the edge of the movement sensor platform.

In six rats, records were taken after treatment with scopolamine alone (5.0 mg/kg, s.c.) without preceding treatment with PCPA. In this condition large amplitude slow waves associated with a burst-suppression pattern of gamma waves were present during behavioral immobility or tremor but was replaced by LVFA and a more continuous gamma pattern whenever the rats made spontaneous head movements or walked about.

No consistent differences were observed between anterior and posterior cortex in any of the observations reported here.

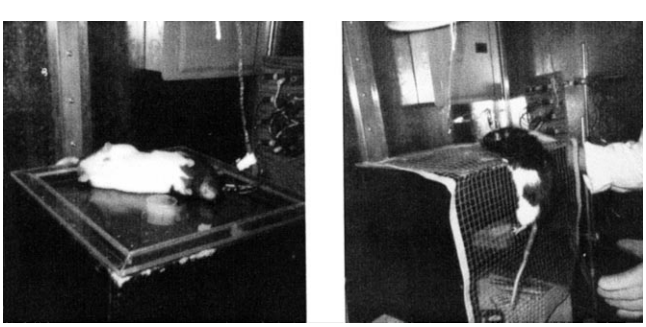

Fig. 5. The behavioral effects of urethane (left) and a combination of PCPA and scopolamine (right). (Left) This rat displays continuous LVFA (not shown but other records from this rat are shown in Fig. 3) and good flexion, corneal, and pinna reflexes but does not right spontaneously after urethane (1000 mg/kg, i.p.) (Right) This rat (records shown in Fig. 4) displays continuous high amplitude slow waves (corresponding to delta waves of the human EEG) together with vigorous spontaneous motor activity while climbing up a vertical wire screen.

4. Discussion

The results show that gamma waves with an amplitude of about 50–100 μV are continuously present during LVFA in the waking rat. According to Steriade et al. [37], gamma waves are synchronized in 1–2 mm diameter columns throughout the thickness of the neocortex while the larger amplitude low frequency waves observed during quiet sleep and anesthesia display a clear phase reversal across the thickness of the cortex. In the experiments reported here, only a partial synchrony of gamma activity was observed between the surface and the deep layers of the cortex, as shown by: (a) direct inspection of the analogue records; (b) *X–Y* plots; and (c) the fact that bipolar

surface-to-depth records revealed gamma activity with a substantial amplitude (equal to the amplitude of the records from monopolar surface electrodes). These observations could be accounted for by assuming that the electrodes sampled activity from multiple partially independent generators.

The experiments reported here provided a clear answer to the question of whether the temporal distribution of gamma activity is related to the state of behavioral arousal or to the accompanying slow wave pattern independent of the state of arousal. LVFA accompanied by continuous gamma activity was observed both in the normal waking state and in deep surgical anesthesia produced by urethane as well as in more moderate levels of anesthesia produced by ether and isoflurane. In contrast, an interrupted pattern of gamma activity with wave bursts occurring only during the deep negative (surface positive) component of the slow waves was observed not only during anesthesia but also during rhythmical 6–9 Hz, 1–2 mV slow waves occurring during behavioral immobility in the waking state. These rhythmical waves have been interpreted as analogous to: (a) the human alpha or wicket rhythm [30,40]; or (b) the spike-and-wave pattern of human petit mal epilepsy [5]. What is important for the present discussion is that rats displaying this pattern maintain a normal posture (head held up against gravity, eyes open) and are normally reactive to mild stimuli such as a light touch by an observer. Thus, the rats are not asleep or stuporous. Furthermore, rats treated with a combination of PCPA and scopolamine displayed a continuous pattern of 1–2 mV, 1–8 Hz slow waves in which the deep positive (surface negative) components of the slow waves were associated with 100–200 ms periods of gamma wave suppression while the deep negative (surface positive) components were associated with bursts of gamma waves. Rats in this condition retain normal waking postures and are capable of vigorous motor activity such as climbing, swimming or jumping. However, the overall temporal and spatial distribution of behaviour, both learned and instinctive, is grossly deranged [6,35,39,40,42,43]. Therefore, these rats could be said to be demented but not comatose or stuporous. It is clear that the temporal distribution of gamma activity (continuous vs. a burst-suppression pattern) has no relation to the waking–comatose or waking–sleeping dimensions of behavior. This is also true of the occurrence of cortical activation [40,45]. The conventional position that cortical activation is associated with the waking state while non-activation is associated with sleep or coma and that cortical activation is mediated via a reticulothalamocortical pathway [17,36] can be maintained only at the cost of ignoring much of the available data [9,40].

The question of whether gamma wave activity is related to subjective awareness [13] is far more difficult to solve than the question of the relation of gamma waves to other aspects of cerebral electrophysiology or to overt behavior. For example, one must consider the question of whether an anesthetized rat, displaying a strong cortical activation response with high amplitude continuous gamma activity when pinched, is experiencing pain even though it does not react in a behavioral sense. Human surgical patients, similarly anesthetized, sometimes complain of severe pain when they recover and can give accurate accounts of events that occurred during their surgical procedure [29]. However, studies carried out in rats indicate little transfer of a learned habit from a state of very light anesthesia to the normal waking state. Overton [21,22] trained rats to escape continuous electric shock by entering one arm in a T-maze with a metal grid floor. Rats treated with small doses of general anesthetics, such as light ether anesthesia or a 750 mg/kg dose of urethane, i.p., were capable of learning the correct response in the maze but this acquired habit usually did not transfer to the normal state when the rats were retested the next day. Similarly, patients anesthetized with ether pass through a stage in which they respond to pain and are capable of answering questions but remember nothing about this after recovery [1]. Both rats and humans in very light anesthesia could be described as consciously aware but amnesic. Whether awareness persists but is masked by subsequent amnesia at deeper levels of anesthesia, when behavioral reactivity has disappeared, is open to debate. It has generally been assumed that a human patient is adequately anesthetized if there is no response during surgery and no recall afterwards [47]. According to this criterion, rats given urethane or volatile anesthetics may be fully anesthetized even though they may react to a nociceptive input by generating neocortical activation and continuous gamma activity.

A major difficulty in the attempt to study subjective awareness with the methods of natural science is that we cannot specify negative cases with much confidence. According to traditional ideas in this field, we can be completely certain only of our own awareness and must accept varying degrees of uncertainty when we consider the possibility of awareness in: (a) other normal intact humans, (b) humans whose behavior has been substantially altered by brain damage or the effects of drugs; (c) other vertebrates; (d) invertebrates; (e) single celled organisms; and (e) the inanimate world. For example, Eccles [25] has proposed that consciousness is linked *only* to the dominant hemisphere in patients in whom the forebrain commissures have been surgically divided. In contrast, Sperry [33,34] proposed that both hemispheres are conscious in cases in which forebrain commissures have been divided. Eccles [10] has also proposed that ''consciousness appears to have come into the mindless world of biological evolution with the origin of mammals''. Margulis and Sagan [15] suggest that bacteria are conscious and Romijn [26] has recently revived the theory of hylozoism which holds that all material things possess subjective awareness [18]. Although one may have one's own intuitions about such proposals, there is no known way of refuting or confirming any of them [41].

An inevitable consequence of our inability to identify clear-cut non-occurrence of subjective awareness is the logical impossibility of identifying the biological basis of such awareness. It may be proposed that some specific behavioural, physiological, anatomical, or chemical feature (such as gamma activity) is related to consciousness or awareness but, apparently, we cannot be certain that the non-occurrence or experimental removal of the feature will mean that consciousness is absent. Neither is it possible to be certain that consciousness is invariably present whenever the specific feature is present. It seems, therefore, that proposals that neocortical gamma activity provides a basis for subjective awareness are ultimately untestable.

What, then, is the neurobiological significance of neocortical gamma activity? Steriade et al. [37,38] have proposed that gamma waves are generated by cross membrane currents associated with excitation. Many observations made in the present investigation are consistent with this view. Gamma activity is prominent during the deep-negative component of large amplitude slow waves both in the waking state and in anesthesia but is suppressed during the deep positive component of such waves. It is well known that unit potentials tend to cluster on the deep negative component of large slow waves and are suppressed during the deep positive component [40]. It is also well known that cortical unit activity is suppressed during very deep anesthesia when the electrocorticogram has disappeared, and further, that the slow wave bursts that appear as the level of anesthesia is reduced are associated with grouped discharges of unitary activity. In these cases gamma waves are closely correlated with unit activity. Finally, events that are associated with increased cortical activity, such as spontaneous movement or stroking the fur, produced an increase in cortical gamma activity in the present experiments.

It is rather puzzling that the amplitude of gamma activity may actually be higher during anesthesia than during the waking state. This observation (rather surprising if one supposes that gamma waves are related to consciousness) may result from the fact that both volatile anaesthetics and urethane tend to hyperpolarize neurons [20]. Intense excitatory inputs would be expected to produce particularly large membrane currents under these circumstances, thereby producing gamma waves of an amplitude greater than normal.

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References

[1] J.F. Artusio, Ether analgesia during major surgery, J. Am. Med. Assoc. 157 (1955) 33–36.
[2] H.K. Beecher, F.K. McDonough, Cortical action potentials during anesthesia, J. Neurophysiol. 2 (1939) 289–307.
[3] B.M. Bergmann, J.B. Winter, R.S. Rosenberg, A. Rechtschaffen, NREM sleep with low voltage EEG in the rat, Sleep 10 (1987) 1–11.
[4] F. Bremer, Action de différents narcotiques sur les activités électriques spontanée et réflexe du cortex cérébral, Compt. Rend. Soc. Biol. (Paris) 121 (1936) 861–866.
[5] G. Buzsáki, I. Laszlovzky, A. Lajtha, C. Vadász, Spike-and-wave neocortical patterns in rats: genetic and aminergic control, Neuroscience 38 (1990) 323–333.
[6] J.C. Cassel, H. Jeltsch, Serotonergic modulation of cholinergic function in the central nervous system: cognitive implications, Neuroscience 69 (1995) 1–41.
[7] R.K. Cooley, C.H. Vanderwolf, Construction of wire leads and electrodes for use in slow wave recording in small animals, Brain Res. Bull. 3 (1978) 175–179.
[8] E.F. Domino, S. Ueki, Differential effects of general anesthetics on spontaneous electrical activity of neocortical and rhinencephalic brain systems of the dog, J. Pharmacol. Exp. Ther. 127 (1959) (1959) 288–304.
[9] H.C. Dringenberg, C.H. Vanderwolf, Involvement of direct and indirect pathways in electrocorticographic activation, Neurosci. Biobehav. Rev. 22 (1998) 243–257.
[10] J.C. Eccles, Evolution of consciousness, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 7320–7324.
[11] C.M. Gray, W. Singer, Stimulus-specific neuronal oscillation in orientation columns of cat visual cortex, Proc. Natl. Acad. Sci. U. S. A. 86 (1989) 1698–1702.
[12] K.S. Lashley, Brain Mechanisms and Intelligence: a Quantitative Study of Injuries to the Brain, University of Chicago Press, 1929.
[13] R.R. Llinás, D. Paré, Of dreaming and wakefulness, Neuroscience 44 (1991) 521–535.
[14] C.A. Maggi, A. Meli, Suitability of urethane anesthesia for physiopharmacological investigations in various systems: Part 1. General considerations, Experientia 42 (1986) 109–114.
[15] L. Margulis, D. Sagan, What is Life? Simon and Schuster, New York, 1995.
[16] O.N. Markand, Organic brain syndromes and dementias, in: D.D. Daly, T.A. Pedley (Eds.), Current Practice of Clinical Electroencephalography, 2nd edn., Raven Press, New York, 1990, pp. 401–423.
[17] D.A. McCormick, T. Bal, Sleep and arousal: thalamocortical mechanisms, Annu. Rev. Neurosci. 20 (1997) 185–215.
[18] W. McDougall, Body and Mind: a History and Defense of Animism, Methuen, London, 1911.
[19] Multi-Society Task Force on PVS, Medical aspects of the persistent vegetative state, N. Engl. J. Med. 330 (1994) 1499–1508.
[20] R.A. Nicoll, D.V. Madison, General anesthetics hyperpolarize neurons in the vertebrate central nervous system, Science 217 (1982) 1055–1057.
[21] D.A. Overton, State-dependent learning produced by depressant and atropine-like drugs, Psychopharmacologia (Berlin) 10 (1966) 6–31.
[22] D.A. Overton, Comparison of the degree of discriminability of various drugs using the T-maze drug discrimination paradigm, Psychopharmacology 76 (1982) 385–395.
[23] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, 2nd edn., Academic Press, Sydney, 1986.
[24] F. Plum, Coma and related global disturbances of the human conscious state, in: A. Peters, E.G. Jones (Eds.), Cerebral Cortex, Normal and Altered States of Function, Vol. 9, Plenum, New York, 1991, pp. 359–428.

[25] K.R. Popper, J.C. Eccles, The Self and Its Brain, Springer-Verlag, Berlin, 1977.
[26] H. Romijn, About the origin of consciousness: a new multidisciplinary perspective on the relationship between brain and mind, Proc. Kon. Ned. Akad. Wetensch. 100 (1997) 181–267.
[27] G.F. Rossi, A. Zirondoli, On the mechanism of the cortical desynchronization elicited by volatile anesthetics, Electroencephalogr. Clin. Neurophysiol. 7 (1955) 383–390.
[28] J. Schlag, H. Brand, An analysis of electrophysiological events in cerebral structures during ether anesthesia, Electroencephalogr. Clin. Neurophysiol. 10 (1958) 305–324.
[29] P.S. Sebel, B. Bonke, E. Winograd, Memory and Awareness in Anesthesia, Englewood Cliffs, Prentice-Hall, NJ, 1993.
[30] K. Semba, H. Szechtman, B.R. Komisaruk, Synchrony among rhythmical facial tremor, neocortical ''alpha'' waves, and thalamic nonsensory neuronal bursts in intact awake rats, Brain Res. 195 (1980) 281–298.
[31] S. Siegel, Nonparametic Statistics for the Behavioral Sciences, McGraw-Hill, New York, 1956.
[32] W. Singer, C.M. Gray, Visual feature integration and the temporal correlation hypothesis, Annu. Rev. Neurosci. 18 (1995) 555–586.
[33] R.W. Sperry, Lateral specialization in the surgically separated hemispheres, in: F.O. Schmitt, F.G. Worden (Eds.), The Neurosciences: Third Study Program, The MIT Press, Cambridge, MA, 1974, pp. 5–19.
[34] R.W. Sperry, Consciousness, personal identity and the divided brain, Neuropsychologia 22 (1984) 661–673.
[35] T. Steckler, A. Sahgal, The role of serotonergic–cholinergic interactions in the mediation of cognitive behavior, Behav. Brain Res. 67 (1995) 165–199.
[36] M. Steriade, Arousal: revisiting the reticular activating system, Science 272 (1996) 225–226.
[37] M. Steriade, F. Amzica, D. Contreras, Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation, J. Neurosci. 16 (1996) 392–417.
[38] M. Steriade, D. Contreras, F. Amzica, I. Timofeev, Synchronization of fast (30–40 Hz) spontaneous oscillations in intrathalamic and thalamocortical networks, J. Neurosci. 16 (1996) 2788–2808.
[39] C.H. Vanderwolf, Near-total loss of 'learning' and 'memory' as result of combined cholinergic and serotonergic blockade in the rat, Behav. Brain Res. 23 (1987) 43–57.
[40] C.H. Vanderwolf, Cerebral activity and behavior: control by central cholinergic and serotonergic systems, Int. Rev. Neurobiol. 30 (1988) 225–340.
[41] C.H. Vanderwolf, Brain, behavior, and mind: what do we know and what can we know?, Neurosci. Biobehav. Rev. 22 (1998) 125–142.
[42] C.H. Vanderwolf, G.B. Baker, Evidence that serotonin mediates non-cholinergic neocortical low voltage fast activity, non-cholinergic hippocampal rhythmical slow activity, and contributes to intelligent behavior, Brain Res. 374 (1986) 342–356.
[43] C.H. Vanderwolf, G.B. Baker, C. Dickson, Serotonergic control of cerebral activity and behavior: models of dementia, Ann. N. Y. Acad. Sci. 600 (1990) 366–383.
[44] C.H. Vanderwolf, G.C. Harvey, L.-W.S. Leung, Transcallosal evoked potentials in relation to behavior in the rat: effects of atropine, *p*-chlorophenylalanine, reserpine, scopolamine, and trifluoperazine, Behav. Brain Res. 25 (1987) 31–48.
[45] C.H. Vanderwolf, T.E. Robinson, Reticulo-cortical activity and behavior: a critique of the arousal theory and a new synthesis, Behav. Brain Sci. 4 (1981) 459–514.
[46] A. Wikler, Pharmacologic dissociation of behavior and EEG ''sleep patterns'' in dogs: morphine, *N*-allylnormorphine, and atropine, Proc. Soc. Exp. Biol. Med. 79 (1952) 261–265.
[47] W.D. Winters, T. Ferrer-Allado, C. Guzman-Flores, The cataleptic state induced by ketamine: a review of the neuropharmacology of anesthesia, Neuropharmacology 11 (1972) 303–315.