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The fundamental neural mechanisms of electroencephalography

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Abstract

We are at an interesting time in the evolution of the EEG. Studies are opening the door to understanding the intrinsic neuronal properties and network operations responsible for the generation of EEG oscillations. I will review some of our knowledge regarding the physiology of the normal and abnormal EEG. Both epileptic and non-epileptic activity will be discussed. Less is known about the latter, because of difficulties in developing appropriate models. The major dichotomy for both types of EEG phenomenon will be focal and generalized (or widespread. Certain distinctive abnormal EEG patterns including burst suppression, periodic phenomena and intermittent rhythmic delta will also be addressed. © 1998 Elsevier Science Ireland Ltd.

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1. Introduction

Electrical activity of the brain results from ionic currents generated by biochemical processes at the cellular level. Over the last decade there has been an increase in understanding of intrinsic neuronal properties and circuit operations that may account for electroencephalographic (EEG) oscillations. The forward problem of EEG refers to how ionic currents generate EEG signals. The inverse problem of EEG refers to the estimation of intracerebral sources responsible for a given scalp potential. The latter is the problem of the clinical electroencephalographer.

2. Field events

Convoluted dipole layers of pyramidal neurons in the cortical gray matter are the principle EEG generators. A dipole is an element with two adjacent opposite charge sites. Positive current (Na^+, Ca^{2+}) is absorbed at one end of the dipole (the sink) and emanates from the other end (referred to as the source). The electrical field around a pyramidal cell conforms to a dipole because a long axis dominates neuronal morphology, and synaptic contacts are segregated such that membrane potential changes occur at either end of the elongated element, depending upon the type of input being activated.

Volume conduction theory describes the flow of current through the extracellular space and the relationship between recordings at some distance (the scalp) from the generator. There are complex mathematical approaches to volume conduction, but the solid angle theorem of volume conduction is a simpler and more intuitive approach to visualizing how cortical generators of EEG signals lead to the waves recorded on the scalp surface. The theorem states that the potential generated by a dipole layer in a volume conductor measured at any point in the conductor is proportional to both the generator's potential and the solid angle subtended by the dipole layer at the point of measurement. Intuitively, this is the visual angle of the 'seeing' electrode. It depends on the apparent size of the dipole layer from the electrodes vantage point. Postsynaptic potentials (PSPs) rather than action potentials are responsible for scalp recorded EEG waves. Although action potentials are higher in amplitude, synaptic potentials are longer in duration and involve a larger membrane surface allowing both temporal and spatial summation. Action potentials occupy a relatively small

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membrane surface at any one instant, and, therefore, the solid angle is a very small. The duration of an action potential is 10–30 times shorter than a synaptic potential, and this would necessitate almost perfect synchronization (to a fraction of a millisecond) for them to overlap in time and summate. Synchronization and coherence in time of potentials also explains the relationship between frequency and amplitude. High-frequency activity is usually lower in amplitude than slow activity. Delta waves may last as long as one-quarter to one-half of a second, and, even if generators are 10–30% out of synchrony, a great proportion of the generator surface will be in relative synchrony at any one time and therefore generate a large potential (Gloor, 1985).

The factors that influence the size, shape, and duration of EEG waves are: (1) the distance of the recording electrode from the current generator, (2) the duration of the PSPs, (3) the number of synchronously activated PSPs, and (4) the anatomical orientation of the layer of pyramidal cells generating the current. The electrical field generated from convoluted layers of pyramidal neurons is referred to as an open field. The field potential around an open field decays inversely to the distance from the generator and can be viewed from almost any distance in a volume conductor (i.e. the scalp). There are structures in the central nervous system in which groups of cells and their processes are not aligned as dipoles and are referred to as closed fields. Structures in the thalamus and brain-stem generate closed field potentials and are not large enough to be detected by scalp electrodes.

3. Depth EEG

The assumption is often casually made that depth electrodes 'see more' than surface scalp electrodes. Potentials in an electric field decrease in amplitude approximately with the square of the distance from the source (parabolically). Scalp electrodes record at a relatively large distance from the generator layer, whereas depth electrodes are in close proximity to the source of the potential. Depth electrodes record a high potential from a very small area of brain, whereas EEG activity at some distance from the depth contact may not be detected. Therefore, scalp electrodes (at ordinary gains) emphasize large generator surfaces 'seen' at a distance, whereas depth electrodes emphasize small generator surfaces 'seen' close up (Gloor, 1984).

4. Rhythmicity

Because of the similarity of rhythmic alpha waves (8–13 cycles/s posterior rhythm seen in the waking state and disappearing with eye opening) to barbiturate-induced sleep spindles in animals, the latter have been studied as a model of the alpha rhythm. Even though alpha waves and spindle waves overlap in frequency, they have distinctly different origins.

4.1. Sleep spindles

In the 1940s, Morrison and Dempsey (1942) described rhythmic cortical phenomena in response to repetitive low frequency midline (ventromedial and centrolateral nuclei) thalamic stimulation. This 'recruiting response' is a widespread sequence of potentials appearing similar to sleep spindles. Spindles were assumed to be generated from medial thalamic structures as were the recruiting waves. As to whether this thalamocortical response is primarily due to circuitry in the thalamus or in the cortex is unclear (Steriade, 1993).

It is now thought that neurons in the nucleus reticular thalami are the spindle pacemaker. This nucleus is a sheet of GABAergic neurons surrounding the anterodorsolateral thalamus. These oscillatory neurons set rhythmicity. They discharge rhythmically and through input to thalamocortical relay (TCR) cells lead to 100–150 ms hyperpolarization in the latter. When a TCR cell is hyperpolarized to −85 mV a rebound action potential is generated (due to a low threshold Ca^{2+} conductance). This postinhibitory rebound burst of action potentials leads to synchronous excitatory postsynaptic potentials (EPSPs) in neocortical neurons (Steriade et al., 1990).

4.2. Alpha waves

Coherence refers to the relationship of waves in one area to those in another region and varies from 0 to 1. Spontaneous alpha activity in dogs and monkeys has corticocortical coherences that are much larger than the thalamocortical coherences (Lopes da Silva et al., 1973). The number and density of corticocortical connections is also far larger in man than thalamocortical connections by a ratio of at least 20:1. Connections parallel to the cortical surface are more important in alpha generation than thalamocortical inputs. Alpha waves are generated in cortical areas acting as epicenters with local spread. The precise cellular mechanism is unknown and in vitro approaches to studying alpha are limited because an awake connected neuronal circuit is necessary to generate the rhythm.

5. Pathophysiology

The development of our concepts regarding mechanisms and significance of different abnormal EEG phenomena is based on: (1) EEG correlations with clinical observations in disease states, (2) EEG correlations with autopsy and computerized tomography (CT) scan data, (3) experimental animal studies (especially in cats, dogs, rabbits and monkeys) and (4) correlation of surface EEG phenomena with neuronal activity at the extracellular and, recently, intracellular level (Steriade, 1993) with computer modeling of some features of the EEG.

6. Epileptiform activity

The electrical marker of a person's susceptibility to have a seizure is the cortical spike seen on the surface electroencephalogram. This is the telltale sign of an epileptic disturbance at a time when the patient is asymptomatic. Spikes are not an epiphenomenon or a neurophysiological curiosity (Hughes, 1989) for they have a relationship to ictal activity, cognitive change and clinical responsiveness. Only 1% of non-epileptic people have spikes whereas as many as 60–90% of patients with epilepsy have spikes in their EEG.

Spikes have morphological features that can help to distinguish them from other similar electrographic phenomena. The epileptiform spike (or sharp wave, or slow sharp wave) is: (1) an asymmetrical wave, (2) usually followed by an afterwave of slower frequency, (3) generally bi-, tri- or multiphasic, and (4) distinctly different in duration than the ongoing background activity (Gloor et al., 1977).

The EEG can help distinguish the two major categories of epileptiform activity. The focal spike indicates that the patient's epilepsy comes from a focal area, whereas generalized spikes (or spike and slow wave complexes) indicate a generalized epileptic process. The prototype of generalized epileptiform abnormalities is the sudden onset of bilaterally synchronous 2.5–4 cycles/s spike and wave activity (S&W). Although described as S&W, the morphology of the complexes is somewhat more complicated. Two spikes, a positive transient and a slow wave, make up the complex. Spike I is negative and low in amplitude (25–50 μV), short in duration, and usually not seen in the first few complexes of the burst. A positive transient lasting 100–150 ms follows spike I; this is followed by spike II which is high in amplitude (three times spike I) and lasts 30–90 ms. The slow wave following spike II is a surface negative wave, and, if one can distinguish it from the positive transient, its duration is in the 150–250 ms range. In addition to sudden near simultaneous diffuse onset, the S&W phenomenon usually stops simultaneously over both hemispheres and is followed by an abrupt return of normal background activity.

At the intracellular neuronal level, focal epileptic spikes are associated with large paroxysmal depolarization shifts (PDS). A PDS is a prolonged (50–100 ms) high-amplitude (20–30 mV) slow membrane depolarization with an overriding train of action potentials (APs). It is followed by an afterhyperpolarization lasting 1–2 s. The cortical spike is a surface field event due to simultaneous PDS in many neurons. The postspike cortical slow wave is due to the hyperpolarization that occurs after the PDS. It has been proposed that local inhibition surrounding the focus may result in the continuous or intermittent slow activity frequently seen in the region of an epileptic focus. Epileptic neuronal activity is related to an alteration in brain metabolism, but there is no direct correlation with excitation and inhibition. Increased metabolism correlates with strong inhibition or strong excitation (increased synaptic activity). Hypometabolism is associated with reduced synaptic activity and a tonic increase in the resting membrane potential (Bruehl and Witte, 1995).

The spike of generalized S&W epilepsy also is a field event generated by underlying neuronal activity. It is caused by synchronous EPSPs. The slow wave of the S&W burst is due to simultaneous inhibitory postsynaptic potentials (IPSPs) secondary to local recurrent inhibition. The S&W phenomenon can be considered an aberrant age-dependent thalamocortical oscillatory rhythm (Gloor and Fariello, 1988; Snead, 1995). The TCRs involved in spindle generation have special Ca^{2+} channels, called T channels, which endow them with the ability to burst fire when stimulated. Nucleus reticularis thalami (NRT) neurons impose oscillatory behavior on the TCR cells. Alterations in the NRT-TCR-cortical neuron loop are responsible for S&W bursts. In the feline generalized penicillin epilepsy model, spindles are gradually converted to S&W complexes after parenteral penicillin. Spindles are surface waves resulting from summation of EPSPs. Most of these EPSPs are not associated with cell discharge. After penicillin the spindle producing thalamocortical volley generates neocortical EPSPs that are high enough in amplitude to reach the threshold for cell firing and a cortical AP is generated. Synaptic efficacy is enhanced. The synchronous APs now activate intracortical recurrent inhibitory pathways which lead to a 200–300 ms period of inhibition and it is this which sets the frequency of the S&W complexes at 3–5 cycles/s. In the cat model, the spike component of each S&W burst is seen first in the cortex and two to 3 complexes later in the thalamus, suggesting that the primary hyperexcitable area is the cortex. In some genetic rat models the spike occurs first in the thalamus.

7. Non-epileptiform abnormal activity

Non-epileptiform abnormalities generally consist of a distortion, disappearance or slowing of background rhythms and the appearance of a new phenomenon—slow waves (the term 'slow-waves' refers to activity below 8 Hz in the adult awake EEG, whereas the term 'delta waves' will refer to activity below 4 Hz). Focal slowing and background alterations usually occur concurrently rather than sequentially. Abnormalities may be focal or lateralized, indicating focal or regional structural pathology, or they may be widespread, which usually suggests diffuse cerebral pathology.

8. Focal slow activity

The most common phenomenon encountered in clinical EEG that is indicative of a localized structural lesion is the appearance of circumscribed slow activity. Focal slow activity is assessed with regard to amplitude, frequency, topography and persistence, and reactivity of focal disturbances is the most reliable indicator of degree of dysfunc-

tion. An EEG/CT scan correlation study by Schaul et al. (1986) showed that field, amplitude and frequency of focal slow waves do not distinguish lesion size, density or mass effect. Reactivity and the persistence of focal abnormalities (continuous versus intermittent) were considerably better indicators of degree of damage. Continuous slow wave activity suggests severe brain damage (likelihood of increased mass effect, large lesion, or deep hemispheric involvement), whereas intermittent slow activity usually indicates a small lesion and the absence of mass effect (Schaul et al., 1981a). Patients with reactive focal slow activity consistently had evidence of less cerebral damage than did patients with non-reactive slow activity. There are few positron emission tomography data regarding non-epileptiform EEG phenomena. In a series of patients with hemispheric tumors, cortical metabolic suppression did not correlate with focal slowing or with background activity attenuation. Hypometabolism was seen in about equal percentages of patients with and without focal EEG alterations (Newmark et al., 1983).

Lindsley et al. (1949) showed that the EEG in lower brain-stem transections in cats remained normal. More rostral lesions of the brain-stem or basal diencephalon caused spindles and high-voltage irregular slow waves. In a series of experiments Gloor (1977) investigated the location of structural pathology that produced localized, lateralized, or generalized slow activity in the electroencephalogram. Purely cortical gray matter lesions did not produce slow activity. The pure cortical lesion presumably destroys the neuronal generators located in the cortex. Thus, the first response of the EEG to ischemia is loss of all cortical frequencies (see Jordan, 1997). Localized lesions of subcortical white matter cause irregular delta activity in the cortex overlying the lesion. Thalamic lesions generally produced focal or unilateral delta activity, but the slow activity varied in time of onset, amplitude, and degree of focality. Bilateral hypothalamic and bilateral upper mesencephalic lesions produced bilateral slow waves. The observation that cortical lesions failed to produce delta activity, but that interruptions of the afferent input to the cortex either in white matter, thalamus, hypothalamus or mesencephalon produced delta activity, suggests that some type of deafferentation of cortical neurons may be responsible for slow activity.

Theoretically, either glia or neurons could be responsible for generating delta activity. Laminar analysis indicates that delta waves due to brain lesions are generated by neuronal elements rather than glia (Ball et al., 1977). Spontaneous delta band activity (physiological delta) in rabbit visual cortex also has source sink current distributions (dipoles) indicating that PSPs are the generators (Rappelsberger et al., 1982).

Extracellular neuronal firing patterns suggests that PSPs at synapses located relatively close to the nucleus in layer 5 are probably responsible for the surface phenomena seen as the EEG. This type of evidence is indirect and the possibility that membrane processes other than PSPs may be responsible cannot be excluded. An intrinsic dorsal thalamic rhythm of 1–2 cycles/s has been described (McCormick and Pape, 1990). Normally depolarizing corticothalamic inputs prevent the manifestation of the thalamic delta rhythm. When areas of the cortex are ablated and the corticothalamic impingement upon thalamic neurons is diminished, the thalamic cells become more hyperpolarized. At this point, the intrinsic thalamic delta oscillation appears. The delta oscillating thalamic cells 'passively transfer' the rhythm to the cortex by thalamocortical pathways (each thalamic action potential in the 'delta network' cause synchronous cortical EPSPs) and a corresponding slow wave. This suggests that thalamic deafferentation from the cortex rather that cortical deafferentation from below may be the slow wave mechanism.

9. Widespread slow activity

In a study of diffuse encephalopathies correlating EEG patterns with sites of histopathology, Gloor et al. (1968) observed continuous diffuse polymorphic delta activity (PDA) in patients with disease processes which extensively involved hemispheric white matter or white and gray matter. PDA was rare in pure cortical gray matter disease. These findings suggested that a disconnection of the cortex from afferent input was the common factor in those with PDA.

In circulatory hypoxia produced in dogs (Gurvitch and Ginsburg, 1977), both PDA and monomorphic slow waves were recorded. The authors distinguish the location of origin of these two types of slow waves. PDA are cortical in origin and due to a disruption of corticocortical and thalamocortical relationships (Ginsburg et al., 1977). The generalized monomorphic slow complexes are considered a more severe manifestation of cerebral damage. It was suggested that the latter may be generated in a subcortical area. Bilateral mesencephalic reticular formation and bilateral hypothalamic lesions in cats produce continuous PDA. This PDA is similar to focal PDA produced by white matter lesions. The relationship of delta activity to neuronal discharge in the cortex is such that it suggests that surface positive delta waves represent an inhibitory phenomenon (hyperpolarization). This may be due to: (1) sypnaptic IPSPs at the soma or basal dendrites, or possibly (2) intrinsic Ca^{2+}-mediated K^{+} afterhyperpolarization. The cell discharge to surface wave relationship is also seen with continuous generalized PDA due to systemic atropine (Schaul et al., 1978). This drug blocks or limits cholinergic transmission. The electrophysiological similarity of lesion-induced and atropine-induced slow waves raises the possibility that a defect in cholinergic pathways may play a role in pathological slow waves.

10. Burst suppression pattern

EEG burst suppression consists of transient sequences of

high-voltage slow waves intermingled with sharp waves, alternating with periods of depressed background activity. It is seen in deep anesthesia, and as an endstage pattern in coma due to anoxia or trauma. Steriade et al. (1994), studying burst suppression induced by various anesthetics in adult cats, showed that almost all (95%) cortical neurons become electrically silent during flat EEG epochs. Hyperpolarization of cortical neurons precedes EEG flattening. The hyperpolarization is due to increased K^+ conductance which in turn is secondary to increased GABAergic inhibition at cortical synapses. This inhibition leads to functional disconnection from thalamic input, but 30–40% of thalamic cells continue firing while the cortex is silent. This is due to the intrinsic pacemaking properties of the thalamic neurons at modest levels of hyperpolarization. Volleys from these thalamocortical neurons account for the cyclic EEG wave bursts.

11. Bilateral paroxysmal slow activity (BPSA)

This EEG phenomenon is also called intermittent rhythmic slowing, rhythmic delta activity and frontal intermittent rhythmic delta activity (FIRDA). Early workers (Daly et al., 1953; Jasper and van Buren, 1953) thought that compression of midline thalamic nuclei by a dilated third ventricle and some 'irritative' phenomena may cause abnormal corticopetal discharges. Gloor et al. (1968) noted bilateral paroxysmal slow activity (BPSA) in 18 of 19 patients in which the pathological process involved both cortical and subcortical gray matter. He also observed BPSA in two of 5 cases when the main pathology was in the cortical gray matter. They concluded that an abnormal interaction between cortical and subcortical neuronal systems may be responsible for these discharges. Gloor later hypothesized that two factors were involved in BPSA: (1) overactive thalamocortical circuits, and (2) some degree of cortical pathology (Gloor, 1976).

Ralston and Ajmone-Marsan (1956) produced 3.5–5 Hz bursts of bilateral slow activity after injecting penicillin into various areas of the thalamus in cats under pentobarbital anesthesia. They regarded BPSA as pathologically slow thalamocortical induced spindles. Ohgami (1973) observed a reciprocal relationship between BPSA and sleep spindles and favored a pathological slow spindle hypothesis. Quesney and Gloor (1978) also injected penicillin into the thalamus of awake cats and, although BPSA-like rhythm was observed in the thalamus, the EEG at the cortical surface failed to show it. Kaada et al. (1967) also produced BPSA experimentally. Reticular formation stimulation under moderate pentobarbital anesthesia lead to BPSA whereas a deeply anesthetized or a fully awake animal failed to have BPSA. These findings suggest that BPSA is due to an interaction between the thalamus and the cortex. Penicillin or electrical stimulation acts to trigger thalamocortical relay cells, but the cortical neuron must be at a specific level of excitability (moderate anesthesia) to respond to these volleys with rhythmic high-amplitude slow waves. A similar mechanism has been proposed to account for the triphasic waves seen in hepatic encephalopathies (Karnaze and Bickford, 1984).

In clinical studies it appears that BPSA is a non-specific finding generally related to disease states effecting neurons at cortical and subcortical levels (Schaul et al., 1981b; Fariello et al., 1982), and not specific to deep midline pathology or intracranial pressure.

12. Background activity

Normal background in posterior head regions in awake adults is 8.5 Hz and above. In anterior regions beta frequencies predominate, whereas in the central and temporal regions beta, alpha and theta activity may be seen. Abnormalities of background activity may be focal or bilateral and consist of an intermixture of slow components (background irregularity), slowing (adult awake background activity below 8.5 Hz), attenuation or diminished background activity reactivity. Unilateral background activity disturbances are also associated with diencephalic, basal ganglia or large hemispheric lesions.

Bilateral background activity abnormalities are a more difficult issue. Background disturbances are present in metabolic, toxic, and degenerative encephalopathies. As to whether intrinsic properties of single groups of neurons (pacemakers) or synaptic interactions of large neuronal pools are responsible for brain waves of different frequencies is unclear. Using a computer simulation model, Lagerlund and Sharborough (1989) showed that IPSP duration in local feedback circuits containing inhibitory neurons could account for a change in BA frequency. A change in the output of the nucleus reticularis thalami could also account for a change in background oscillations.

13. Periodic EEG phenomena

Gloor et al. (1968) observed that periodicity usually correlated with cortical gray matter pathology. They proposed that the cortex was in an abnormal functional state that permitted rapid generalization of neuronal discharges. Traub and Pedley (1981), extrapolating from experimental evidence and computer models of epilepsy, suggested that synchrony and periodicity in Creutzfeld-Jakob disease were related to virus-induced fusion of neuronal processes, leading to electrotonic coupling between cells. This coupling provided a basis for increased excitatory interactions, allowing large cellular aggregates to fire in synchrony. Subsequent to each discharge, a long lasting afterhyperpolarization lead to the refractory state that set the interval duration. A triggering discharge for each complex is probably subcortical (Gloor et al., 1968; Celesia, 1973). Therefore, the substrate for periodic pathological phenomena is

some form of diffuse increase in cortical excitability. The excitability is followed by a period of inhibition which is due to intrinsic membrane processes (presumably hyperpolarization due to K^+ currents), and the inhibitory period is in turn followed by an excitatory trigger from subcortical structures (Brenner and Schaul, 1990).

14. Summary

The EEG is due to temporal and spatial summation of PSPs from cortical pyramidal cells. The epileptiform spike is an excitatory event. In focal epilepsy it represents a summation of synchronous depolarization shifts whereas in generalized epilepsy it represents summated EPSPs. The following slow wave is an inhibitory event related to synchronous afterhyperpolarizations in focal epilepsy and recurrent inhibition in generalized epilepsy.

The evidence is convincing that pathological slow waves are neuronal in origin and generated by dipole layers of pyramidal cells located in the cerebral cortex. Synchronized activity must involve a relatively large area of cortex (estimated at 6 cm^2) in order to yield potentials that can be recorded on the scalp (Abraham and Ajmone-Marsan, 1958; Cooper et al., 1965). Some of the literature suggests that certain types of slow waves may originate in subcortical structures such as the thalamus (Gurvitch and Ginsburg, 1977); however, this is difficult to reconcile with the dipole hypothesis. Neurons in the thalamus are multipolar and not layered in parallel, representing what is termed a closed field rather than an open field, and the voltage necessary to be detected on the scalp would be enormous (Gloor, 1985). It is likely that all scalp recorded slow waves originate in cortical neurons. The network responsible for the slow rhythm may be located in the thalamus (Steriade, 1993), but the cellular events (EPSPs, IPSPs and afterhyperpolarizations) responsible for the generation of scalp recorded slow waves occur in cortical pyramidal neurons and their processes.

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