A cura di
Oriano Mecarelli

Clinical Electroencephalography

1. Tecniche di registrazione ed analisi del segnale EEG

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TECNICHE DI REGISTRAZIONE ED ANALISI DEL SEGNALE EEG

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Indice

Prefazione

A distanza di oltre 30 anni dalla pubblicazione del mio primo Manuale di EEG in lingua italiana[1], testo che ha avuto una seconda edizione nel 1995[2] e che poi è stato interamente riscritto nel 2009[3], è stato per me un grande onore pubblicare nel 2019 per Springer il volume *Clinical Electroencephalography* in lingua inglese, dal quale sono stati estratti i tre fascicoli *Tecniche di registrazione ed analisi del segnale EEG*, *Epilessia nell'adulto* e *Epilessia pediatrica*. Il textbook *Clinical Electroencephalography* si basa fondamentalmente sulla mia esperienza didattica e clinica in Elettroencefalografia presso la Neurofisiopatologia dell'Università La Sapienza di Roma e può essere quindi considerato l'espressione della scuola romana di EEG presso cui mi sono formato e che ho contribuito a far sviluppare negli ultimi trent'anni. Ma il volume è stato realizzato anche grazie al contributo di importanti esperti italiani nei vari settori specifici, che operano in Università ed Istituti a carattere scientifico in varie città del nostro Paese. Inoltre sono particolarmente grato ad alcuni colleghi stranieri che hanno voluto con il loro contributo rendere maggiormente prestigioso il libro stesso. Si tratta comunque del primo Manuale di EEG in lingua inglese quasi interamente scritto da autori italiani (alcuni dei quali operanti attualmente all'estero), ed esso vuol essere quindi la dimostrazione di quanto la cultura elettroencefalografica sia viva nel nostro Paese.

Il Manuale vuole soprattutto essere utile ai fini didattici ed è rivolto sia ai Tecnici di Neurofisiopatologia che ai medici di branca neurologica che intendono avviarsi ad una approfondita conoscenza dell'Elettroencefalografia, per poterla correttamente utilizzare in campo clinico. Sinteticamente quindi nel Manuale vengono affrontati tutti gli aspetti dell'EEG, partendo dalla metodologia tecnica, proseguendo con la descrizione dei pattern normali per arrivare quindi alla descrizione dei pattern EEG correlati con le varie patologie del SNC e sistemiche. I tre fascicoli si occuperanno in particolare di fornire le conoscenze di base riguardo le modalità di acquisizione ed elaborazione del segnale EEG e descrivere i pattern peculiari delle varie sindromi epilettiche in età evolutiva ed adulta.

Nell'ultimo trentennio l'Elettroencefalografia ha subito una vera e propria rivoluzione, non tanto perché sono stati individuati e descritti quadri EEG prima sconosciuti o perchè la metodica abbia trovato campi di utilizzo diagnostico diversi dal passato, ma perché lo sviluppo tecnologico ha permesso la completa digitalizzazione delle apparecchiature e quindi anche dell'acquisizione, registrazione ed archiviazione del segnale bioelettrico cerebrale. Quando cominciai io ad occuparmi di refertazione degli EEG alla fine degli anni '70 i tracciati erano registrati su carta ed il medico elettroencefalografista si trovava sulla scrivania pacchi di carta più o meno voluminosi, da sfogliare e risfogliare alla ricerca di eventuali alterazioni, con parametri e montaggi prefissati e note segnate dal tecnico con la matita sul tracciato stesso.

Oggi gli EEG vengono acquisiti esclusivamente in digitale e visualizzati per la refertazione su monitor; i file possono essere trasmessi via rete ed essere rivisti dinamicamente in qualsiasi reparto dell'ospedale o anche al di fuori di esso, potendone modificare tra l'altro anche i parametri di visualizzazione; per preparare l'iconografia basta catturare le immagini dal monitor, sapendo utilizzare semplici programmi computerizzati di grafica. Negli ultimi decenni insomma, anche se non abbiamo scoperto molto di nuovo per quanto riguarda la reale

"sostanza" dell'Elettroencefalografia, la metodica è diventata di utilizzo sia clinico che didattico più agevole e con possibilità applicative in continua espansione.

Senza voler togliere nulla alle neuroimmagini, a tutt'oggi l'Elettroencefalografia rimane un'indagine neurofunzionale utile ed insostituibile, poco costosa, accessibile un po' ovunque. Purtroppo però nelle Scuole di specializzazione di branca neurologica il tempo dedicato allo studio ed all'applicazione dell'EEG è per lo più carente e ciò si traduce in una scarsa preparazione alla materia, con conseguenti risvolti negativi nella pratica clinica, sia per quanto riguarda la richiesta dell'esame che per la sua refertazione. L'obiettivo quindi, preparando il Manuale, è stato soprattutto quello di mettere a disposizione di tutti coloro che vogliono dedicarsi all'EEG un testo completo ma sintetico e di taglio estremamente pratico e didattico, che nulla vuol quindi togliere ai tradizionali Manuali che da molte edizioni vengono pubblicati oltreoceano e che restano insostituibili.

Come già feci in occasione dell'edizione del 2009 in lingua italiana[3] questa nuovo libro di EEG è stato dedicato alla memoria del mio maestro, il professor Gianfranco Ricci (Palermo 1925 – Roma 2000), che è stato un ricercatore ed un clinico particolarmente preparato e sensibile, pioniere della Neurofisiopatologia nel nostro Paese. Egli infatti fondò nel lontano 1972 presso l'Università Sapienza di Roma la Scuola Speciale per Tecnici di Neurofisiopatologia, che nello stesso anno ebbe l'avvio anche presso l'Università di Bologna grazie al Professor Elio Lugaresi. Successivamente tutta la sua carriera universitaria è stata dedicata alla formazione sia dei tecnici che dei medici in Elettroencefalografia clinica ed Epilettologia, come Direttore della Scuola di Specializzazione in Neurofisiopatologia, da qualche anno purtroppo soppressa.

Un ringraziamento particolare vorrei ancora una volta porgere ai miei collaboratori (tecnici, specializzandi, dottorandi, etc) che mi hanno supportato durante le fasi di progettazione, di preparazione dei manoscritti e di scelta del materiale iconografico, proveniente in gran parte dai nostri Laboratori. È per me anche un onore che alcune parti del Manuale siano state attivamente preparate da tecnici di Neurofisiopatologia. Spesso infatti i tecnici sono relegati al ruolo di meri esecutori di indagini diagnostiche; credo invece che abbiano le necessarie competenze per partecipare in prima persona alla discussione dei problemi specifici e all'elaborazione del materiale ad uso didattico e scientifico.

Oriano Mecarelli

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Neurophysiological Basis of EEG

2

Marianna Brienza and Oriano Mecarelli

2.1 Central Nervous System: Anatomo-physiological Considerations

Nervous tissue is composed of nerve cells, the neurons, together with a supporting tissue called neuroglia, which is found only in the brain and medulla spinalis [1]. Neurons are highly differentiated and specialized cells, and they are distinguished from the other cells because of their complex and polarized structure. They are constituted of: 1) a cell body called "soma" whose morphology characterizes the cell type, qualifying it as stellate, pyramidal, etc. ; 2) two types of cytoplasmic prolongations: the dendrites and the axon, anatomically and functionally different: while dendrites converge on the soma, the axon conveys activity to distant locations.

Dendritic arbors receive synaptic inputs. The various dendritic morphologies have been used for classifying neuronal types by Cajal. Type-specific dendritic morphology is directly linked to the neuronal function. The location and density of the dendritic arbors determine the type and the number of inputs that a neuron can sample. The size and shape of dendritic trees govern their passive electrotonic properties, while the dendritic distribution of ion channels endows active membrane conductance [2–4].

In the mature nervous system, the primary purpose of the axon is to propagate and regenerate action potentials at a consistent speed and, secondarily, to provide support for the energetic and signalling needs of its distal processes [5].

Morphologically, each neuron consists of two distinct domains: the somatodendritic domain contains the cell body (soma), multiple dendrites and a short region of the proximal axon adjacent to the soma (axon hillock); the axonal domain projects a long axon away from the axon hillock toward the next neuron, in the neural circuitry or toward a target tissue where it branches into multiple axon terminals that form the synapses. Functionally, information flow starts from the somatodendritic domain, which receives synaptic input from neighbouring or distant neurons, and it is subsequently transmitted to the axonal domain which s sends signals to the next neuron in the neural circuitry or to a target tissue (Fig. 2.1) [6].

Glial cells are more numerous than neurons. The generic term "glial cells" includes various cell types (astrocytes, oligodendrocytes, microglia, ependymal cells, etc.) with a trophic and supportive function: they are essential for providing metabolic support to neurons and for myelination of axon fibers [7].

Macroscopically, human Central Nervous System (CNS) is composed of different structures that, in the cranio-caudal sense, are the spinal cord, the brainstem (oblongata, pons, midbrain), the cerebellum, the diencephalon and the telencephalon (basal ganglia, white matter and cortex). The telencephalon is divided into two hemispheres by the interhemispheric fissure. Each hemisphere is divided in lobes and each lobe is crossed by the sulci that delimit the circumvolutions.

On the basis of the cytoarchitectural characteristics, the cerebral cortex is organized in six layers with different functions, depending on the type of cortex (visual, somatosensory, motor, etc.), but with a similar columnar organization. In rostro-caudal sense, they are numerated from I to VI and they are composed of different cellular types, reflecting their differentiation in function and connectivity. Although apparently separated, cortical layers are structurally inter-connected: for example, layer IV contains spiny apical dendrites of layer V pyramids and spiny basal dendrites of layer III pyramids. As a matter of fact, we can distinguish an ascending and a descending pathway. The first pathway has layer IV as a primary target, also called the "granular layer" that receives inputs from the thalamus and relays signals to layers III, II and IIIb [8]. The descending pathway does not instead involve the middle layers. Inputs from layers II-III reach the layers V (of the giant pyramidal cells) and VI which are interconnected. Layer V proj-

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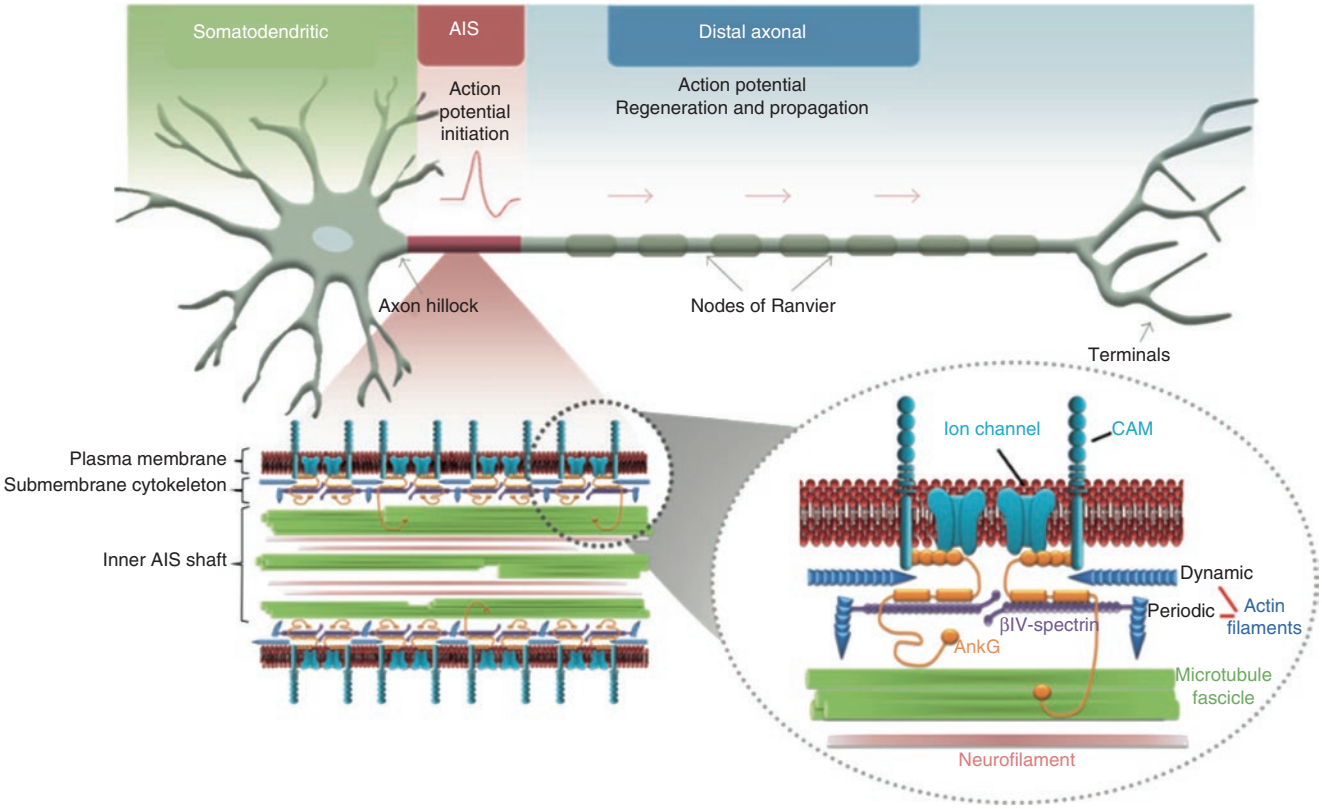

Fig. 2.1 Architecture of the Axon Initial Segment (AIS) and its key protein components. Polarized neurons receive synaptic inputs in the somatodendritic domain (green), which transmits the signals through the axon hillock to the axon initial segment (red). The AIS integrates synaptic inputs and initiates an action potential that propagates along the distal axon (blue) and is amplified at nodes of Ranvier. Molecular organization of the AIS (bottom part of the figure). The AIS can be divided into three layers, the plasma membrane, submembrane cytoskeleton and inner AIS shaft (left), each having AIS-specific features (zoomed view at bottom right). The scaffolding protein Ankyrin G (AnkG) recruits many other proteins to the AIS and can interact with components in the different AIS regions. In the plasma membrane, AnkG - through its N-terminal membrane-binding domain - binds voltage-gated ion channels, important for action potential initiation and regulation, and Cell Adhesion Molecules (CAMs). The submembrane cytoskeleton contains AnkG, βIV-spectrin and actin filaments. These proteins form a periodic network along the entire length of the AIS. Periodic actin is spaced ~190 by at least two βIV-spectrin subunits, which attach to the membrane through interactions with AnkG. In addition to periodic actin, relatively long, randomly oriented, dynamic actin filaments also exist in the submembrane cytoskeleton, and these filaments may have functions distinct from periodic actin. The inner AIS shaft contains microtubule bundles (fascicles), neurofilaments and potentially also actin filaments (not shown). AnkG can extend its C-terminal tail into the inner AIS shaft where it is predicted to interact with microtubule fascicles (modified from Jones SL and Svitkina TM. Axon Initial Segment Cytoskeleton: Architecture, Development, and Role in Neuron Polarity. Neural Plast. 2016;2016:6808293,with permission)

ects to the subcortical structures through the axon that originates from the cell body or from one of the basal dendrites and, after being covered by the myelin sheath, constitutes the projection and association fibres. Layer VI contains multiple distinct classes of pyramidal neurons defined by their apical dendritic arborization patterns, a broad category of oddly shaped excitatory neurons and a variety of inhibitory neurons; however, the typical neurons are short and tall pyramidal neurons, which constitute the majority of excitatory cells in layer VI (Fig. 2.2) [9].

It is important to underline that the ascending and descending pathways represent only a schematization of the cerebral circuits, organized with much more complexity: in addition to the "vertical" information flow, many signals run also "horizontally" and/or reverberate among the various layers, to optimize and integrate the final output (associative fibres).

The functionality of the neuron is guaranteed by the cell membrane. The cell membrane is a selective filter, extremely thin (0.005 μm) and consists of a phospholipids double layer. Specific receptors for chemicals (exogenous and endogenous) and specific ion channels are located on the cell membrane. The voltage-dependent channels on the presynaptic cell membrane perform a double function: to depolarize the presynaptic membrane then triggering the action potential and to produce a current of such intensity to generate a variation of action potential also in the postsynaptic cell. All the neurons, pyramidal and nonpyramidal, establish interneuro-

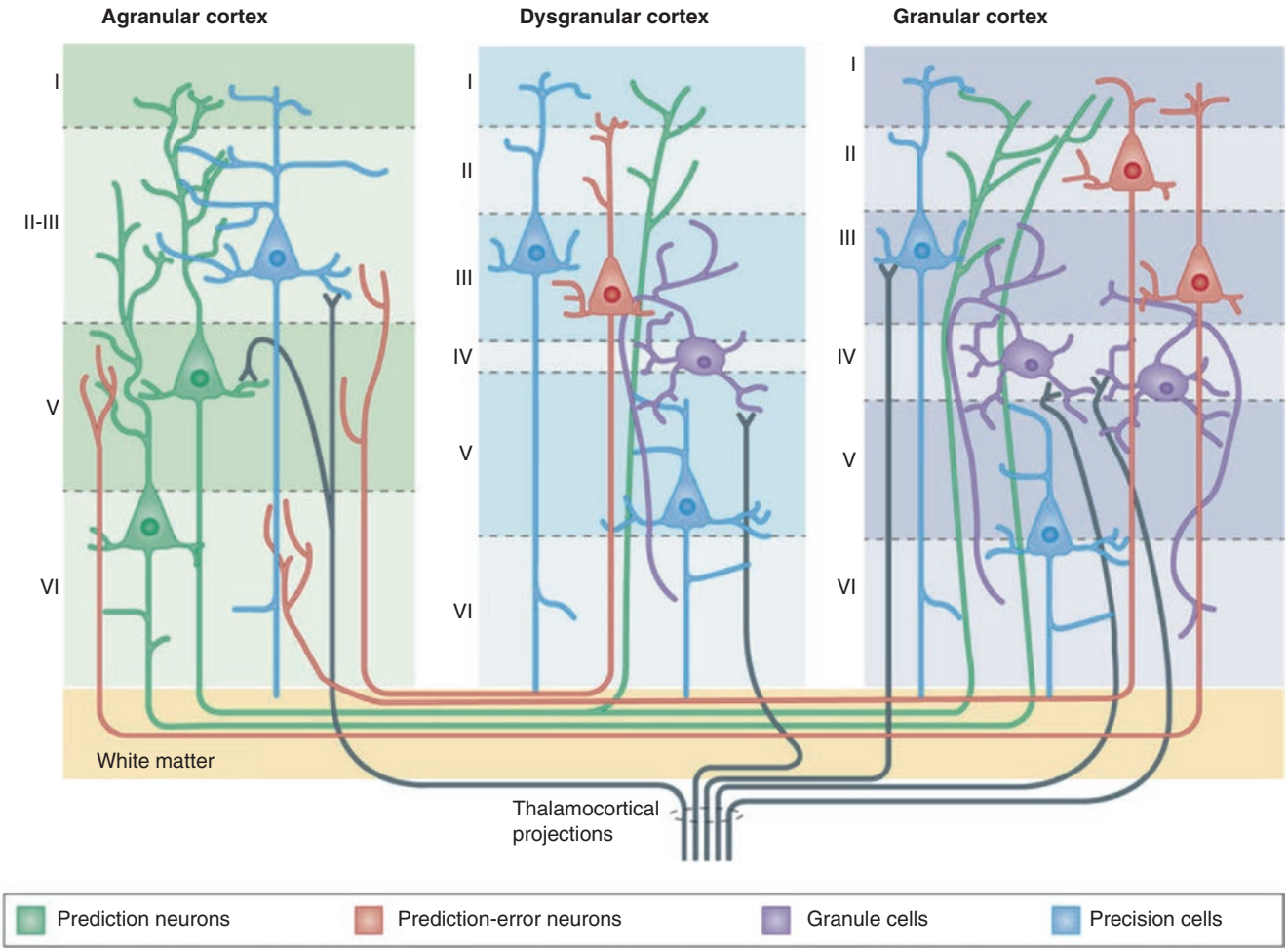

Fig. 2.2 Organization and cellular architecture of cortical layers. Cortical columns are defined by different numbers of layers (also called laminae), with each layer having characteristic cell types and pathways of intracortical and intercortical connectivity. Granular cortex (right) is characterized by six differentiated laminae (layers I-VI), with layer IV containing granule cells, which are excitatory spiny stellate neurons (purple) that amplify and distribute thalamocortical inputs throughout the column. Granular cortex also contains many spiny pyramidal neurons throughout its infragranular and supragranular layers. Pyramidal neurons have a triangular soma, from which basal dendrites project; an ascending apical dendrite, often with large dendritic tufts in layer I; and a single axon that descends and projects out of the cortical column (sometimes with multiple collaterals). Conversely, agranular cortex (left) does not have a fully expressed layer IV and has a poorly differentiated boundary between layer II and layer III. These upper laminae contain relatively fewer pyramidal neurons than does granular cortex. However, agranular cortex contains relatively greater numbers of large pyramidal neurons in layer V and layer VI than in its upper layers. Despite not having a defined layer IV with granule cells, agranular cortex still receives thalamic projections; however, the sensory information that enters agranular cortex is less amplified and less well redistributed throughout the column than in granular cortex. Dysgranular cortex is found in transition zones between granular and agranular regions and contains a small but defined layer IV and a distinctive (although rudimentary) layer II and layer III (modified from Barrett LF, Simmons WK. Interoceptive predictions in the brain. Nat Rev Neurosci. 2015;16:419–429, with permission)

nal connections through the synapses that can be achieved at the level of the cell body, of the dendrites and of the axon.

Synaptic transmission can be electrical or chemical. In the case of electrical synapses, there is a cytoplasmic continuity between the pre- and postsynaptic terminal (gap junction). Nerve transmission through the electrical synapses is very rapid, because it is the result of the direct passage of the current generated by the voltage-dependent channels of the pre-synaptic cells, with a virtually absent delay. Electric synapses often interconnect entire populations of neurons and, in these cases, the function is to synchronize their responses. When many cells are interconnected by electric synapses, the threshold necessary to evoke an action potential becomes high and, if this threshold is exceeded, the whole group of electrically coupled neurons will tend to discharge synchronously and maximally as the action potential is "all-or-nothing". These synapses are typical of the pyramidal cells. Most of the electrical synapses are able to transmit both depolarizing and hyperpolarizing currents [10]. In the chemical synapses the presynaptic and postsynaptic terminals are divided by the syn-

aptic cleft, an intersynaptic space of 30–50 nm. The electrical potential generated in the axonal terminal induces release of a chemical neuromediator by the presynaptic vesicles which spreads in the synaptic cleft binding specific receptors and determining the opening of ionic channels which then modify the postsynaptic membrane potential. The synaptic delay ranges in this case from 0.3 to several ms.

Postsynaptic potentials may be excitatory or inhibitory, depending on the neuromediator released. The action of a neurotransmitter on the postsynaptic membrane does not depend necessarily on the chemical structure of the neurotransmitter, but rather on the properties of the binding receptors: acetylcholine is almost always an excitatory transmitter; noradrenaline, dopamine and serotonin can be excitatory or inhibitory. The main inhibitory neuromediator of the CNS is the Gamma-Amino Butyric Acid (GABA); postsynaptic GABA receptors form permeable channels to Cl^- ions. The activation of these channels determines the entry of Cl^- ions which hyperpolarize the membrane of the neurons and increases their conductance during the resting state.

The main excitatory neurotransmitter is Glutamate (Glu). Many types of postsynaptic receptors for Glu have been identified, basically represented by α-Amino-3-hydroxy-5-Methyl-4-isoxazol-Propionic Acid receptors (AMPA), quisqualate and kainate, and *N*-Methyl-D-Aspartate) (NMDA) receptors. AMPA receptors form permeable channels to both Na^+ and K^+ ions. Ionic currents that pass through these channels are responsible for the early stage of a fast excitatory postsynaptic potential. The NMDA receptors form a channel that is permeable to Ca^{++}, Na^+ and K^+ ions; this receptor-channel complex is also voltage-sensitive. In resting conditions, the channel is blocked by extracellular Mg^{++} ions. To open the NMDA channel, the neurotransmitter Glu and a depolarizing current are necessary. Given the delay with which this channel opens, the ionic currents crossing the channel cause the appearance of a late component of the postsynaptic excitatory potential.

Excitatory synapses are usually located on dendrites, while inhibitory synapses are mainly found on neurons cell body where they are able to effectively counteract the effects of excitatory afferents from the axon and the dendrites. The final integration of synaptic inputs is made at the axon hillock, which is the area of the cell body closest to the initial segment of the axon. It has the highest density of Na^+ channels of the whole cell and, therefore, it will also have the lowest threshold for triggering an action potential.

Nerve cells communicate through direct or mediated synaptic contacts, and the electrical impulse is generated and transmitted through the input and output of ions with positive or negative electrical charges. In resting conditions, the concentration of K^+ ions inside the cell is about 30–50 times higher than outside, and Na^+ ions are 10 times more concentrated outside than inside. The ion concentrations are kept stable by an active ion pump and, in resting conditions, K^+ channels are open and Na^+ channels are closed. In resting state, the membrane potential then depends: on the electrochemical gradient created by the transmembrane Na^+/K^+ ATPase, located at the plasma membrane of all mammalian cells, which utilizes energy from ATP hydrolysis to extrude three Na^+ cations and import two K^+ cations into the cell [11]; on the high membrane permeability to the K^+ ions and, on the other hand, by the low permeability to the Na^+ ions. This corresponds to a potential difference of about −70 mV, with more negative charges inside the cell.

Due to the high basal K^+ permeability, the resting potential of living cells is normally dominated by the high and low concentration of K^+ ions inside and outside the cell, respectively. The action potential that underlies the propagation of the nerve impulse reflects the rapid opening and closing of Na^+- and K^+-selective channels in response to changes in the transmembrane potential. After a stimulus, the very fast opening of voltage-activated Na^+ (Nav) channels causes a depolarization of the membrane. While the Nav channels are transiently open, the membrane potential is briefly dominated by the different Na^+ ions concentrarion, low inside and high outside the cell. The transient membrane depolarization subsequently triggers the slower opening of the voltage-activated K^+ (Kv) channels, which then repolarize the membrane toward the resting potential [12].

One of the most critical functional aspects of Kv channels is their high selectivity for K^+ over Na^+ ions. In comparison, Nav channels, which serve as a trigger to initiate the action potential with their fast-gating kinetics, do not need to be as highly selective as Kv channels. Thus, the difference in selectivity is consistent with the respective functional contribution of these channels to the generation of the action potential. The large conductance and high selectivity of K^+ channels, in particular, are absolutely critical to ensure rapid return to the resting potential after membrane depolarization [13]. The action potential is generated in 1 ms; repolarization occurs in 2–3 ms. Immediately after the genesis of an action potential, the membrane is refractory to other stimulations, initially in an absolute and then in a relative way (raising the threshold of excitability). Changes of the electrical charges between inside and outside the cell, less important than those that determine the action potential, can generate other electric potential differences. Excitatory neurotransmitters can make the neuronal membrane highly sensitive to Na^+ ions for 1–2 ms (Fig. 2.3).

During this short time, Na^+ ions enter the cell reducing the negativity of the resting potential of 1–5 mV and realizing an Excitatory PostSynaptic Potential (EPSP), that takes about 15 ms to completely disappear. On the other hand, inhibitory neuromediators can determine an increase in resting potential (−70 mV) up to values of about −75 mV, allowing entry of the Cl^- ion into the cell and the exit of K^+ ions: the Inhibitory PostSynaptic Potential (IPSP) will be achieved, and it will also persist for about 15 ms (Fig. 2.4).

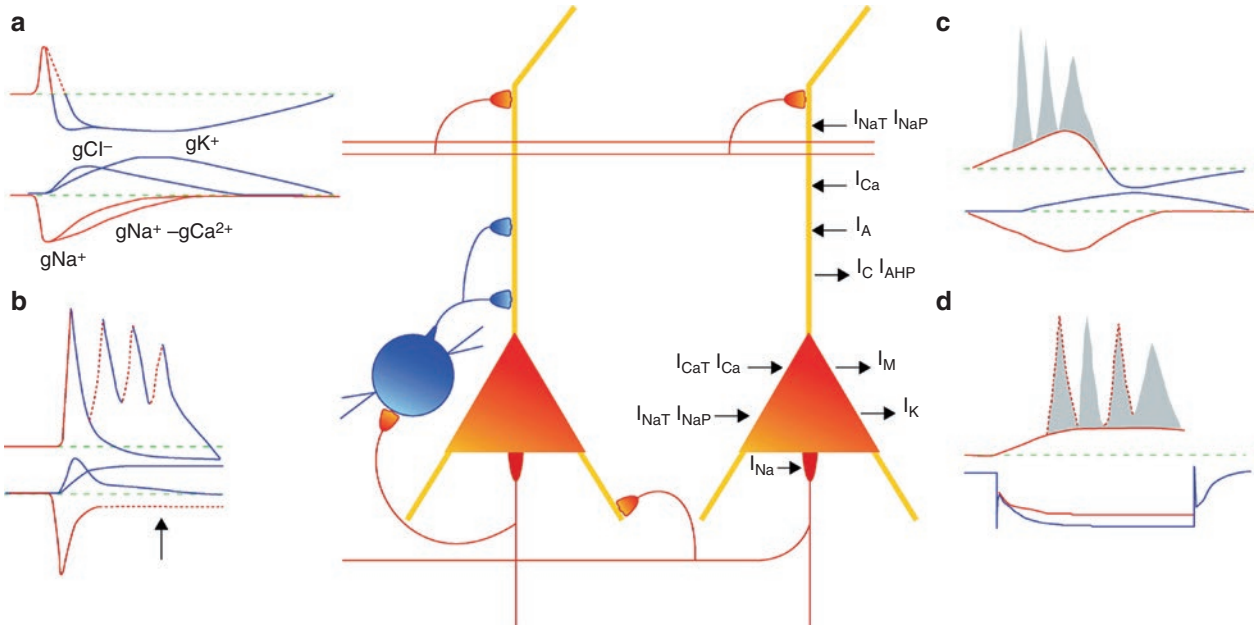

Fig. 2.3 Ionic currents that cause the excitability of cortical neurons. In (**a**–**d**), the upper graph represents voltage recorded with the current clamp technique and the lower graph shows the current signals related to ionic conductance (g) through the open channel. NMDA receptors mediate a long Excitatory PostSynaptic Potential (EPSP; broken red line in **a**). The pyramidal neurons (red) receive inhibitory synaptic input via feedback circuits from local GABAergic interneurons (blue). The action of GABA on postsynaptic receptors generates Inhibitory PostSynaptic Potentials (IPSPs; blue trace in **a**). Membrane depolarizations activate voltage-gated sodium channels producing the rising phase of the action potential (**b**, red traces). Subsequently, various voltage-gated potassium channels, which are involved in the repolarizing phase (**b**, blue traces), are activated. The few channels that fail to inactivate carry the persistent fraction of the sodium current (I_{NaP}; broken red trace in **b**, arrow). The calcium ion-dependent currents (unbroken red lines in **c**) shape the depolarization after an action potential and ultimately sustain hyperpolarizing afterpotentials, which mainly depend on the various potassium currents activated by entry of calcium ions into the cell (Ic, I_{AHP}; blue traces). Under inhibition by muscarine, the membrane may undergo more intense depolarization (**d**, red traces), which favours recurrent, closely spaced action potentials and burst activity (from Avanzini G and Franceschetti S. Cellular biology of epileptogenesis. Lancet Neurol. 2003;2:33–42, with permission)

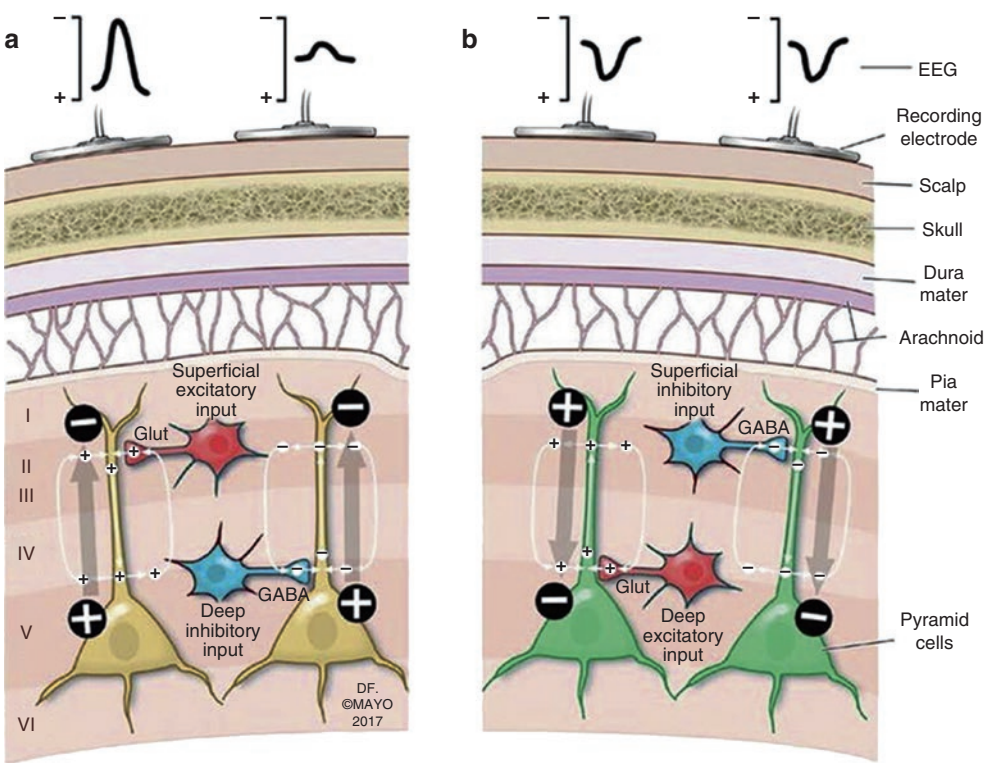

Fig. 2.4 Schematic drawing of the scalp EEG registering negative (**a**) and positive (**b**) deflections elicited from summated EPSPs and IPSPs derived from pooled pyramidal cells. Cells releasing glutamate and GABA provide excitatory and inhibitory superficial and deep synaptic connections resulting in an electrophysiological sink or source. *EEG* electroencephalography, *EPSP* Excitatory PostSynaptic Potentials, *GABA* Gamma-AminoButyric Acid, *IPSPs* Inhibitory PostSynaptic Potentials (Figure courtesy of Anteneh Feyissa M.D. and Mayo Clinic. From Tatum WO, Rubboli G, Kaplan PW, et al. Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. Clin Neurophysiol. 2018;129:1056–1082, with permission)

2.2 Origin of the Electrical Activity of the Brain

Electroencephalography is a graphic representation of the difference in voltage between two different cerebral locations plotted over time [14]. Therefore, the Electro Encephalo Gram (EEG) consists of the recording of the bioelectric activity of the brain from the scalp. The synchronized activity of large cell aggregates can be detected by extracellular recordings; in this case, the signals that are recorded are called field potentials. Surface EEG can be considered the result of field potentials that are produced by fluctuations in the electrical activity of large populations of cortical neurons; these extracellular current flows are generated by the spatial summation of the postsynaptic potentials of the activated cells (Fig. 2.5).

EEG is the graphical representation of the potential difference between an "active" electrode, placed above the seat where the neuronal activity takes place, and an "indifferent electrode", located at a certain distance from the first. It is a dynamic measure, as the potential difference is represented as a function of time. Therefore, the surface EEG measures the electric potential difference between different areas of the scalp and reflects the current flowing in the cerebral cortex during synaptic activation of the dendrites of many pyramidal neurons, which lie just below the surface of the skull.

Although the action potentials - as the larger electrical potentials generated by the neurons - may appear to be the most obvious source of the electrical potentials recorded by the scalp, they contribute minimally to the genesis of EEG graphoelements.

Action potentials cannot be the main cause of the EEG genesis for two main reasons: the amplitude of the electric field produced by the propagation of an action potential decreases much more rapidly than the amplitude of the fields produced by the postsynaptic potentials; the duration of action potentials is very short, 1 ms, and this time is insufficient to obtain an adequate synchronization of large cortical neuronal populations (even a minimal asynchrony of a few milliseconds would make the summation of action potentials impossible). Conversely, the flows of synaptic currents in the extracellular space last for about 10–40 ms, so the postsynaptic potentials can add up together more efficiently than the action potentials and create electric fields large enough to be able to be registered from outside, even without a perfect synchronization.

Moreover, the excitatory or inhibitory postsynaptic potential show other peculiarities that makes it different from the action potential: it does not have a threshold; it is graduated (i.e. its amplitude is proportional to the magnitude of the stimulus and, therefore, does not respond to the "all or none" law, as the action potential); it is a local; it has no tendency to propagate without decrement (as the action potential), but it decreases as moving away from its source.

We have already stated that the genesis of EEG is based on the flow of ionic currents generated by the neurons in the extracellular space. To understand the origin of postsynaptic extracellular potentials, we can imagine an ionic current that flows inward towards the cell through the synaptic membrane and outward through the large surface of the extrasynaptic membrane. The net ionic current is then recorded as the voltage existing through the resistance of the extracellular space. Since the extracellular resistance is very low, compared to the high resistance of the membrane, transmembrane voltage is equal to the product of the current for the resistance of the membrane. Furthermore, the ionic current flowing through the high resistance of the membrane determines a potential difference higher than that caused by the current when it flows through the extracellular resistance. This is one of the reasons why the intracellular potentials are much larger (mV) than the extracellular ones (μV).

The electrical conductivity of biological tissues depends on the distance between generator and recording electrode, on the spatial diffusion and on the orientation of the generator: if the neurons of a population are oriented in parallel and activated synchronously, the amplitude of the signal recorded remotely is greater.

To further understand the importance of the synchronization of cortical cells for EEG genesis, it is also necessary to consider that the electrical contribution of each cortical neuron is very poor and that the signal must cross several layers of non-neural tissues, including the meninges, the cephalorachidian liquid, the bones of the skull and the skin. Each layer has different conduction properties that attenuate the electric signal before it reaches the electrodes on the scalp. As a result, thousands of simultaneously activated neurons are necessary to generate an EEG signal strong enough to be detected from the electrodes on the scalp surface.

Synchronous activation of over 100 cortical neurons in an area of at least 6 cm^2 is required to determine a visible EEG signal from the scalp. Therefore, the amplitude of the EEG signal depends, above all, on the synchronization of the activated cells. If synchronous activation of this group of cells repeats many times, the resulting EEG will be characterized by broad and rhythmic waves. When a layer of pyramidal neurons is not activating coherently, the excitatory current will not be zero, and our baseline EEG signal will consist of fluctuations in the baseline excitatory current. The zero potential surface is located halfway between the positive and negative poles of the dipole. To understand how electrical potentials generated by populations of the pyramidal neurons are recordable on the scalp, it is important to consider the solid angle concept of the volume conduction theory. According to this therory, the potential generated by a dipole layer in a volume conductor (brain and its environs) is proportional to the solid angle subtended by the dipole layer at the point of the measurement.

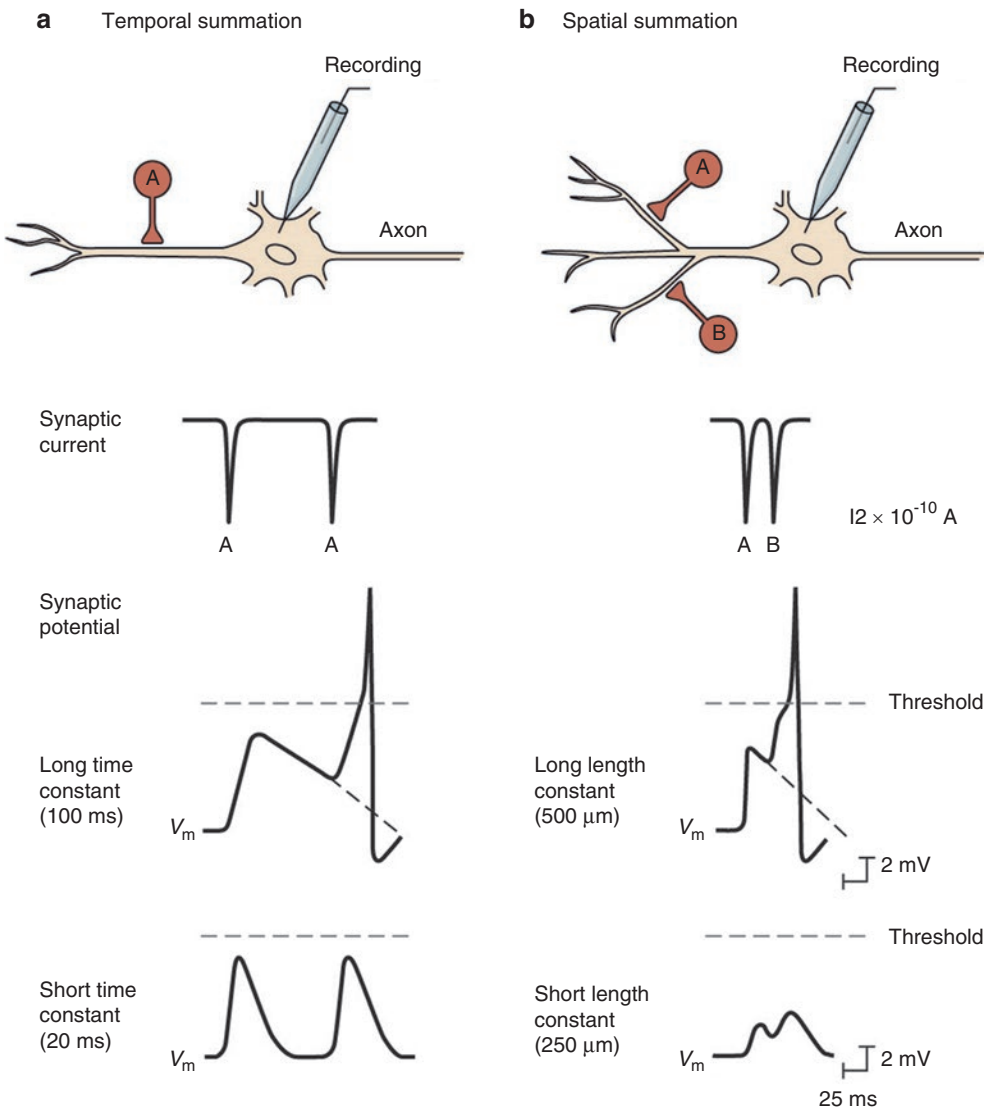

Fig. 2.5 Central neurons are able to integrate a variety of synaptic inputs through temporal and spatial summation of synaptic potentials. (**a**) The time constant of a postsynaptic cell affects the amplitude of the depolarization caused by consecutive Excitatory PostSynaptic Potentials (EPSPs) produced by a single presynaptic neuron (*A*). Here the synaptic current generated by the presynaptic neuron is nearly the same for both EPSPs. In a cell with a long time constant, the first EPSP does not fully decay by the time the second EPSP is triggered. Therefore, the depolarizing effects of both potentials are additive, bringing the membrane potential above the threshold and triggering an action potential. In a cell with a short time constant, the first EPSP decays to the resting potential before the second EPSP is triggered. The second EPSP alone does not cause enough depolarization to trigger an action potential. (**b**) The length constant of a postsynaptic cell affects the amplitudes of two EPSPs produced by two presynaptic neurons (*A, B*). For illustrative purposes, both synapses are the same (500 µm) distance from the postsynaptic cell's trigger zone at the axon initial segment and the current produced by each synaptic contact is the same. If the distance between the site of synaptic input and the trigger zone in the postsynaptic cell is only one length constant (i.e. the postsynaptic cell has a length constant of 500 µm), the synaptic potentials produced by each of the two presynaptic neurons will decrease to 37% of their original amplitude by the time they reach the trigger zone. Summation of the two potentials results in enough depolarization to exceed threshold, triggering an action potential. If the distance between the synapse and the trigger zone is equal to two length constants (i.e. the postsynaptic cell has a length constant of 250 µm), each synaptic potential will be less than 15% of its initial amplitude, and summation will not be sufficient to trigger an action potential (from Kandel ER, Schwartz JH, Jessell TM. Principles of neural sciences. 5th ed. New York: McGraw-Hill; 2012; with permission)

What we observe in EEG is a baseline signal of about 30 µV, which suggests that the fluctuations in the excitatory current during periods of minimal activity are about 2% of the maximum excitatory current during fully coherent excitation. The polarity of the potential recorded from the scalp depends on the site and depth of the synaptic activity onset. To explain this concept, it is important to make a distinction between the site from which the current starts

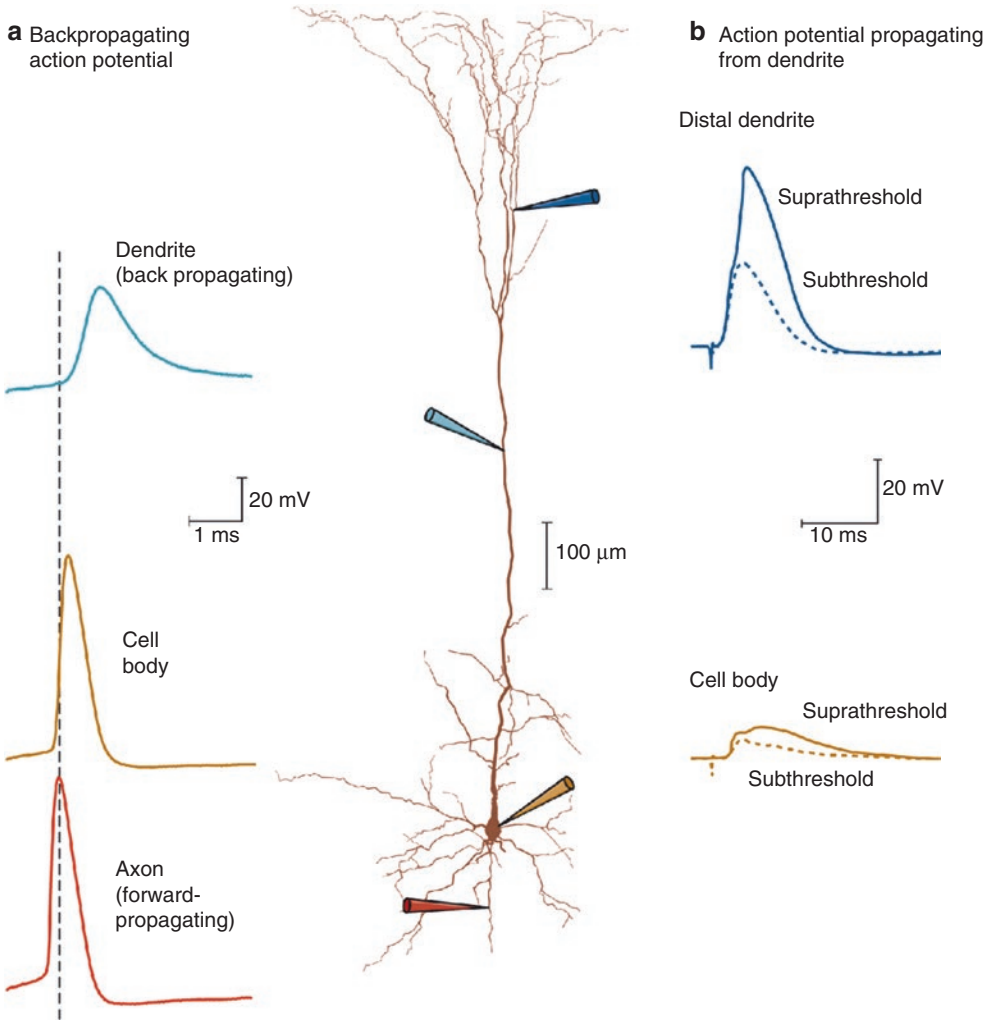

Fig. 2.6 Dendrites support propagation of action potentials to and from the axon initial segment. The figure illustrates an experiment in which several electrodes are used to record membrane voltage and pass stimulating currents in the axon, the soma and at several locations along the dendritic tree. The recording electrode and corresponding voltage trace are matched according to colour. (Adapted, with permission, from Stuart et al. 2000.) (**a**) An action potential can be propagated from the axon initial segment to the dendrites. Such backpropagation depends on activation of voltage-gated Na^+ channels in the dendrites. Unlike the action potential that is continually regenerated along an axon, the amplitude of a backpropagating action potential decreases as it travels along a dendrite due to the relatively low density of voltage-gated Na^+ channels in dendrites. (**b**) A strong depolarizing excitatory postsynaptic potential at a dendrite can generate an action potential that travels to the cell body. Such forward-propagating action potentials are often generated by dendritic voltage-gated Ca^{2+} channels and have a high threshold. They propagate relatively slowly and decrement with distance, often failing to reach the cell body. The solid line shows a suprathreshold response generated in the dendrite and the dotted line shows a subthreshold response (from Kandel ER, Schwartz JH, Jessell TM. Principles of Neural sciences. 5th ed. New York: McGraw-Hill; 2012; with permission)

and moves away (source) and the site to which the current approaches (sink). The activity recorded by EEG is that of the most superficial layers of the cortical grey matter. The potential changes in the cortical EEG are due to the current flow in the fluctuating dipoles formed by the dendrites of the cortical cells and the cell bodies; namely, the current to flow through the volume conductor between "source" at the soma and basal dendrites and the "sink" at the apical dendrites, sustaining the EPSP. At the incoming current (sink), an upward deflection of the potential will be obtained, indicating a negative potential of depolarization (EPSP); at the outgoing current (source), a downward deflection, which indicates a positive hyperpolarization potential (IPSP), will be obtained (Fig. 2.6).

The flows of ionic charges caused by the EPSP-IPSP generate the extracellular field potentials, whose recording from the scalp constitutes the EEG activity. The synapses located on the cell body, near the axon hillock, are generally inhibitory, while those on the dendritic spines are mainly excitatory. The recorded EEG signals are generated mainly by neurons located near the recording electrode and only in small parts by more distant neurons: the broader the population of neurons under the recording electrode, the greater the EEG signal will result.

Moreover, the more the electrode (REF) is placed near the site where the recorded bioelectric activity originates (REC), the more the signal amplitude decreases as a function of the square root of the distance. The small amplitude of the extracellular recorded potentials is due, in addition, to the low value of the extracellular resistance and to their rapid decrease as a function of distance. The amplitude of these potentials becomes a critical factor when the tip of the electrode is far from the activated neurons, as occurring when we record from the scalp with a macro electrode. In such cases, it is not possible to record the activity of individual neurons, because the amplitude of the potentials is too small and the macroelectrodes are not sufficiently selective to discriminate the activity of these neurons from that of neighbouring cells. The EEG recorded from the scalp is, instead, the summary of the activity of a large number of neurons.

Thalamic afferences synchronously activate thousands of cortical neurons. The first response of the cortex to a signal originating from the thalamus is a sink in the deep layers (where excitatory synapses are located) and a source in the superficial layers. A recording electrode placed on the scalp is closer to the source than to the sink. The polarity of the electrical signals will be different depending on the site of the excitatory synapses (in the superficial or deep layers).

In extracellular recordings, an upward deflection indicates a negative potential when the recording electrode is near the synapse in which current is entering. When the recording electrode is located at level of the deeper cortical layers, far from the synapse, the same excitatory postsynaptic potential is recorded as a downward deflection. At rest, there is no potential difference between the soma and the dendrites of pyramidal cells, as both exhibit uniformly positive charges on the membrane surface and negative charges inside the membrane. This changes when, for example, due to the effect of afferent messages, there is a depolarization of the dendrites and an EPSP occurs. Therefore, there is a flow of current from the cell body (source) to the dendrites (sink), generating an electric field whose intensity can be measured as a potential difference between two points on the same line of force generated by two electric charges of opposite sign; this constitutes a dipole, its entity depending on the resistance of extracellular fluids. In practice, neurological generators do not correspond precisely to simple one-dimensional dipoles. Any source of activity large enough to be recorded in EEG will comprise at least a small area of cortex whose neurones are synchronously active. This source may be regarded as a three-dimensional sheet, polarized across its thickness. If it is small enough, it may still be conveniently represented as an "equivalent dipole." A larger area of cortex may be curved or even convoluted, and the equivalent dipole then becomes a complex sum of all the vectors. Furthermore, when many widely scattered generators are active, an infinite number of combinations may give rise to the same pattern of surface potential [15].

While the vector's magnitude is a function of the distance from the recording electrode (regarding the brain bioelectrical signals, the signal strength is inversely proportional to the square of the distance), the vector's direction always remains the same. If two or more vectors are oriented simultaneously towards the same electrode, they can be added together: the result of this sum will correspond to the arithmetic sum of their magnitudes. Depending on the orientation of the dipole compared to the cortical surface, we can distinguish a *vertical* (or radial) dipole oriented vertically to the cortical surface, a *horizontal* (or tangential) dipole located in a groove or in the interhemispheric fissure and an *oblique* dipole, if the positive and negative extremities are not aligned. Therefore, scalp electrodes can record different kinds of signal depending on dipole orientations (Fig. 2.7). The amplitude of signal

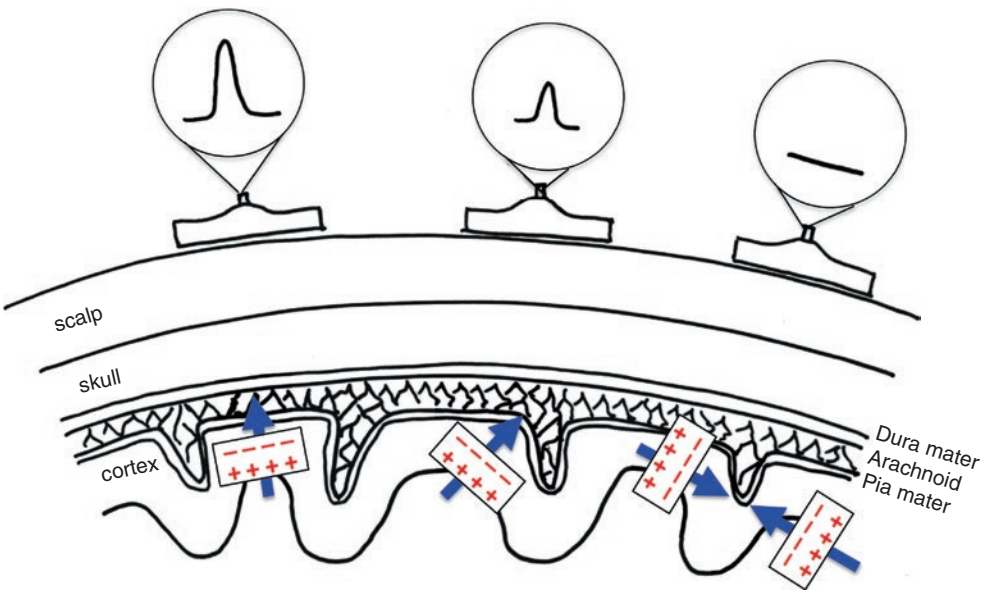

Fig. 2.7 Example of bioelectric signals recordable from the scalp, depending on the orientation and the underlying dipole: vertical, oblique, horizontal

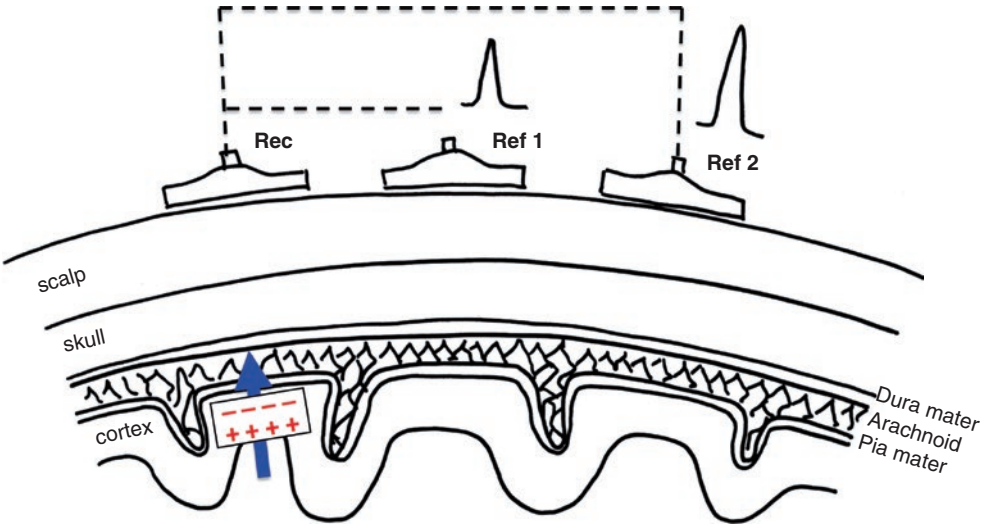

Fig. 2.8 Schematic representation of a population of cortical pyramidal cells. The amplitude of the recorded signals depends on the interelectrode distance: it grows as the distance increases

depends on the distance between the two electrodes and it grows as the distance between the electrodes increases (Fig. 2.8).

Furthermore, the position of the two electrodes compared to the dendrites is very important: for example, the best condition to record a potential gradient is when an electrode is placed on the surface at the main axis of the apical dendrites and the other is located more laterally. If the two electrodes are placed symmetrically and in a lateral position compared to the arborization of the dendrites, it is not possible to record any electrical gradient, as the two recording points are equipotential.

An electrical gradient between cell body and apical dendrites can also occur when the soma is hyperpolarized, due to an IPSP, while dendrites are in rest conditions; in this case the current flow goes from the cell body to the dendritic terminations.

A question that has always been asked over the years and which has found, to date, only partial answers is about the origin of the EEG rhythms. The dorsal thalamus is considered to be the chief subcortical EEG rhythm generator, synchronizing populations of neocortical neurons as voltage generators. In normal conditions, both thalamic nuclei and cortical regions interact to produce the synchrony of cortical PostSynaptic Potentials (PSPs) during wakefulness and sleep. The facultative pacemaker theory assumes that thalamocortical relay neurons send fibres to the cortex as well as give off branches that turn back and end on thalamic inhibitory interneurons (biofeedback servomechanism). Nucleus reticularis hypothesis attributes the pacemaker properties to the nucleus reticularis thalami, whose cells release the inhibitory neurotransmitter GABA in rhythmic bursts of depolarizations directed to the neurons of the dorsal thalamus and rostral brainstem [14]. The thalamus is the major gateway for the flow of information toward the cerebral cortex and is the first station at which incoming signals can be blocked by synaptic inhibition during sleep. This mechanism contributes to the shift that the brain undergoes as it changes from an aroused state, open to signals from the outside world, to the closed state of sleep [16].

2.3 Focus on Alpha Rhythm

Many studies on the normal EEG alpha rhythm have been performed, and they have demonstrated that the Posterior Dominant Rhythm (PDR) changes continuously during life and continues to mature throughout adolescence into early adulthood. It is difficult, therefore, to infer what the age-related increases in PDR frequency observed in human developmental studies actually mean in terms of maturation of the underlying brain functions [17, 18]. In addition to the genesis of the alpha rhythm, the thalamus seems to have a fundamental role. Although the exact contribution of thalamic activity as a generator of alpha rhythm is still not fully clarified, the pulvinar - among the posterior nuclei - is more likely associated with the spontaneous modulation of posterior alpha rhythm and its extensive connections with the entire cortex make it well-suited to finally modulate the alpha rhythm. More generally, the thalamic nuclei, in particular the dorsal ones, can be considered anatomo-functional stations of the ascending reticular activating system; this could explain how the alpha rhythm is closely related to them as it depends on the arousal levels [19]. In this context, alpha waves, defined as the oscillatory activity of the EEG recorded primarily on occipital regions with a frequency range between 8 and 12 Hz [20], behave like sleep spindles, inhibiting incoming information from sensory systems at the thalamic and early cortical level. Recordings from single thalamocortical relay cells (which are responsible of spindle generation) have demonstrated that hyperpolarization of the membrane potential when these cells are less receptive may

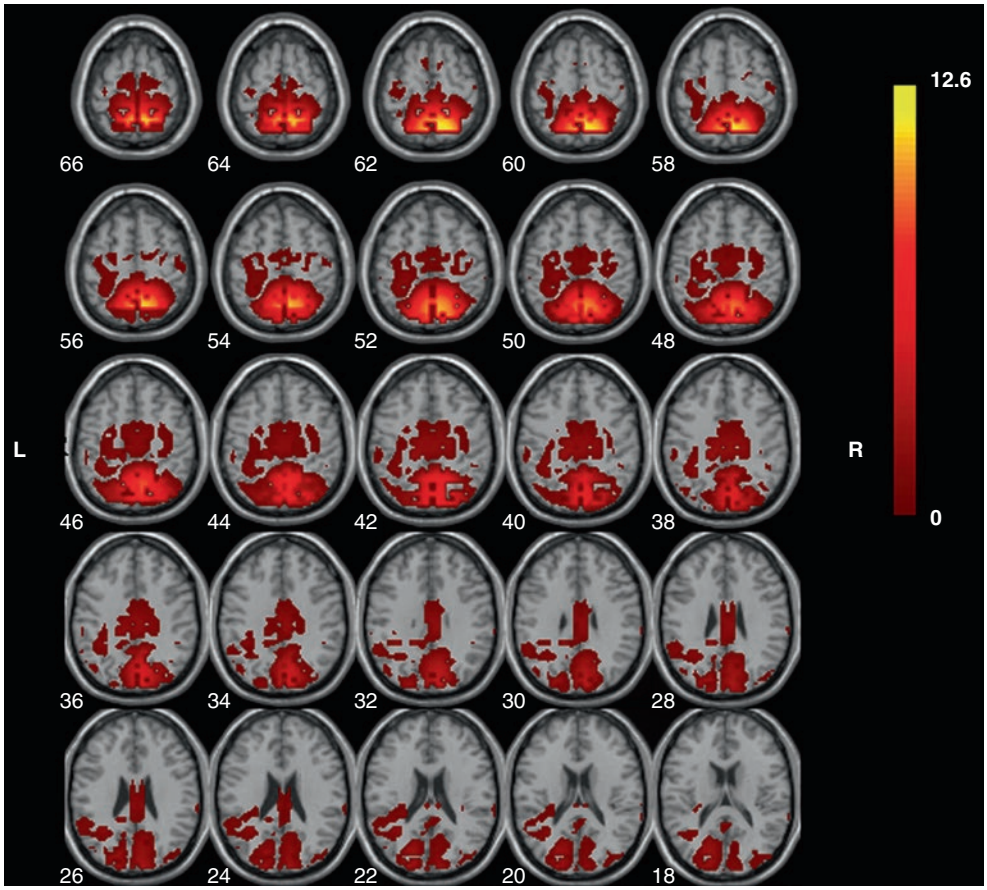

Fig. 2.9 Spatial pattern of the alpha band Default Mode Network (DMN) component that was identified in rest with the eyes closed condition and showed the highest correlation with self-referential-thought-scale (From Knyazev GG, Slobodskoj-Plusnin JY, Bocharov AV, Pylkova LV. The Default Mode Network and EEG alpha oscillations: an independent component analysis. Brain Res. 2011.21;1402:67-79, with permission)

give rise to an oscillation in the alpha range [21]. These kinds of oscillations in the primary visual area may represent a mechanism to stop incoming information and they are at the basis of the "gating function theory", along with the classical alpha desynchronization predicting higher alpha activity in inhibited cortical areas and lower activity in areas engaged in information processing [22]. Great attention has been focused, in recent years, on the study of the correlation between alpha rhythm and Default Mode Network (DMN). DMN is a resting state network, typically defined to include regions of the Medial PreFrontal Cortex (MPFC), Anterior Cingulate Cortex and Posterior Cingulate Cortex (PCC), cuneus/precuneus and temporoparietal junction/angular gyrus. These brain areas appear to be particularly active in resting state, while their activity decreases during the execution of specific tasks: increased activations within this network are related to the processes of memorization and creating associations, being related to the learning and integration processes [23]. Therefore, the relationship between DMN and alpha rhythm is not surprising, if we consider that the alpha rhythm is typically recorded during the quiet awakening and is selectively suppressed during the performance of specific tasks [24]. Correlation studies between EEG and Magnetic Resonance Imaging (MRI) have shown the relationship between alpha rhythm and DMN with conflicting opinions. Some areas of the DMN, such as orbital and medial PFC and PCC, seem to be active during quiet awakening in concomitance with the registration of the alpha activity, while some areas, such as posterior cingulate and parietal cortex, superior frontal cortex and medial frontal and bilateral temporal cortex, seem to have been suppressed [25]. However, given the great overlap and integration between these and other cortical areas, further studies are necessary to confirm and corroborate these results (Fig. 2.9).

2.4 Origin of Slow Brain Rhythms

There are at least two cellular sources of delta activities, originating in the thalamus and in the cortex. The combination of the intrinsic electrophysiological properties of the thalamic and cortical neurons, together with their synaptic connections and glial cells, are responsible for the generation of these oscillations. Thalamocortical neurons are able to display a clocklike delta rhythm, either induced by imposed hyperpolarizing current pulses or spontaneously. It has been described that thalamocortical neurons, recorded in vitro, display rhythmic bursts of high-frequency spikes with an interburst frequency of 1–2 Hz. This oscillation results from the interplay between two membrane currents: [26] the tran-

sient calcium current and a hyperpolarization-activated cation current. Thalamic neurons can be found in two different physiological states: a transmission mode and a burst mode. When the membrane potential of a thalamic neuron is close to the threshold of the action potential, the neuron is in the transmission mode: the synaptic excitatory potentials generated by the afferent signals generate a discharge whose characteristics depend on the sensory stimulus. These thalamic discharges produce low-amplitude signals in a desynchronized EEG pattern. On the other hand, when the thalamic neuron is hyperpolarized by inhibitory afferent signals, it is in the burst mode, because they react to brief depolarization with a burst of action potentials. Each burst produces a volley of EPSPs in cortical dendrites that generates a slow, synchronized and rhythmic EEG activity (delta activity). This pattern is observed in deep sleep and it is also recorded when the blocking of thalamocortical transmission occurs, such as in coma or in some epileptic seizures [27].

However, the presence of a delta rhythm after thalamectomy also suggests its further cortical genesis. Cortical neurons throughout layers II-VI displayed a spontaneous oscillation recurring with periods of 1–1.54–5 s, consisting of prolonged depolarizing and hyperpolarizing components. The long-lasting depolarizations of the slow oscillations consisted of EPSPs, fast IPSPs and fast pre-potentials, reflecting the action of synaptically coupled GABAergic local-circuit cortical cells [28]. A contribution of both NMDA-mediated synaptic excitatory events and a voltage-dependent persistent sodium current to the depolarizing component of the slow oscillation was also demonstrated [29].

A recent comparative study during simultaneous EEG and functional MRI recording in 14 patients after sleep deprivation evaluated positive and negative Blood Oxygenation Level Dependent signal (BOLD) correlations with delta and theta rhythms for left and right temporal electrodes. The two rhythms were almost entirely distinct in either anatomic distribution or correlation. Essentially, the delta rhythm had negative correlations within the frontal and temporal lobes, deep grey nuclei and cerebellum and positive correlations within the occipital and parietal lobes the theta rhythm had negative correlations within the occipital and parietal lobes and positive correlations within the frontal and temporal lobes, cerebral nuclei and cerebellum [30]. Another study by Hofle et al. assessed the EEG delta power with positron emission tomography on subjects progressing from wakefulness to slow wave sleep. They found that delta slow activity had negative correlation with thalamus, brainstem reticular formation, cerebellum, anterior cingulate cortex and orbitofrontal cortex. Positive correlation was indeed present in visual and auditory cortices [31]. However, the high variability of the results of correlation studies is mainly due to the different recording and processing methods and, therefore, needs further investigation.

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Scalp and Special Electrodes

3

Oriano Mecarelli and Ferruccio Panzica

3.1 General Characteristics of Electrodes

Electrodes are the connecting system between the tissues where bioelectric activity is generated, or through which it is conducted, and the amplifier inputs. The electrical current in the human body is the result of ion flow, while the current in electronic circuits and instrumentation is due to electron flow. In order to record bioelectric signals, such as EEG and EMG, the ionic currents must be converted. This function is carried out by electrodes, transducers that sense the ion flow on the surface of the tissue, and convert it into an electron current.

Electrodes can be of different types and shapes, but they are still an interface between the patient and the recording device. The ideal electrode should not distort the signal nor generate significant artifacts. However, in reality, this is very difficult to accomplish. As the first component of the EEG signal acquisition chain, the characteristics of electrodes, namely, electrode–tissue interface, polarisation and impedance, are factors influencing the overall system performance and patient comfort.

The flow of electric current from body to electrode can be understood by examining the electrode–electrolyte interface [1]. When a metal is placed in an electrolyte, such as in the saline environment of tissue or skin, at the electrode–electrolyte interface, reduction/oxidation (redox) reactions occur. Assuming that the metal of the electrode and the cations (positive ions) in the solution are the same, the following reactions occur:

$$\mathrm{C} \rightleftarrows \mathrm{C}^{n^+} + n\mathrm{e}^- \tag{3.1}$$

$$\mathrm{A}^{m^-} \rightleftarrows \mathrm{A} + m\mathrm{e}^- \tag{3.2}$$

In (Eq. 3.1) an atom C gives up electrons (oxidation) and discharges it into a solution as a positively charged ion, while the electrons remain as a charge carrier in the electrode. In (Eq. 3.2) the reaction involves an anion which can become a neutral atom giving off one or more free electrons to the electrode.

When a metal is brought into contact with a solution, the above reactions occur immediately; therefore, the local concentration of cations and anions in the solution at the electrode–electrolyte interface changes, and neutrality of charges is not maintained between the electrode and electrolyte where two layers of oppositely charged ions are produced, called the electrical double layer, similarly to that existing along electrically active biological cell membranes. This charge distribution establishes a potential difference known as the half-cell potential. It mainly depends on the metal involved, the concentration of its ions in the solution and the temperature.

Therefore, when a metal such as silver (of which traditional electrodes are made of) comes into contact with a solution containing ions, a stable electric potential between the metal and the solution can be measured (electrode potential). This property is used, for example, in batteries and accumulators to create a potential difference between the two poles. The stable electrode potential does not distort the bioelectric activity recorded by the electrode, but it adds a fixed value that can be even larger than 1 V; in the case of silver/silver chloride (Ag/AgCl), the half-cell potential is 222 mV. This value of half-cell potential is much larger than the EEG amplitude. Ideally, this would not be problem, because if the electrode potentials of two electrodes - both connected to a differential amplifier - are of the same amplitude, they will simply cancel each other because their difference will be equal to zero, thus permitting a correct recording of potentials. If, however, the electrode potentials are unequal and/or variable, this could generate unreliable signals that

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would add to the bioelectrical activity and could be present at the output of the differential amplifier.

Theoretically, if two electrodes are of the same shape and made of the same metal, their electrode potential should be exactly the same (and the potential difference should be equal to zero), but light impurities and contaminations of the surface can cause imbalances of potentials, in the amount of several mV, for a pair of similar electrodes. Moreover, neurophysiological signal distortion can also happen on the electrode surface because of the metal with which it is built. Silver electrodes, coated with silver chloride, are stable and particularly suitable for surface EEG recordings.

The half-cell potential described above refers to the equilibrium when no electric current exists between the electrode and the electrolyte. In many metal electrodes, the electrochemical interface does not allow electric charge to cross with equal ease in both directions, resulting in a higher electrode resistance to current flow in one direction than the other. Therefore, if there is a current flow, the electrode half-cell potential value could vary from its reference value depending on the direction and magnitude of electrode current flow [2]. In electrochemistry, this process is known as *electrode polarisation*. Electrode polarisation generally refers to the change of electric potential difference at the electrode–electrolyte interface due to the electric current passing through it, so that the equilibrium initially existing is disturbed and altered leading to an overpotential.

Theoretically, two types of electrodes are possible, those that are perfectly polarisable and those that are perfectly nonpolarisable. Ideally, polarisable electrodes are those in which no actual charge (faradic current) crosses the electrode–electrolyte interface (the electrical double layer) when a current is applied between the electrode and the electrolyte. This kind of electrodes are, therefore, characterised by an absence of net faradic current between the electrode surface and the electrolyte. The electrode–electrolyte interface behaves like a capacitor and the current across it is a displacement current. No Direct Current (DC) can flow between it and, therefore, the electrode–electrolyte interface acts as a high-pass filter reducing the transduction and transmission of low-frequency components. Moreover, it shows a very large change in potential upon the passage of small currents.

Perfectly nonpolarisable electrodes are those in which charges can move freely across the electrode–electrolyte interface. Its half-cell potential does not change from its equilibrium value upon application of the current and, therefore, there is no overpotential.

Electrodes made of noble metals such as platinum, iridium and gold behave similarly to perfectly polarisable electrodes. These materials are indeed electrochemically inert and, therefore, they are difficult to be oxidised and dissolved. An electric current changes the concentration of ions at the electrode–electrolyte interface, so the overpotential seen in this type of electrodes is mainly due the concentration of change.

Electrode polarisation could be associated with electric instability and could give rise to high impedance and high noise levels.

The best electrode–electrolyte interfaces for biopotential recordings are those made of a combination of metal and one of its metallic salts, usually chloride. Metallic salt is used as a coating on the metal and acts as an intermediary in the electrode–electrolyte process. A chloride electrode consists of a metallic electrode, placed in contact with one of its insoluble salts and immersed in a solution of soluble salt of the same anion (e.g. silver, in contact with silver chloride, immersed in sodium chloride).

The AgCl outer layer is highly reversible with chloride ions in physiologic electrolytes and the silver is highly reversible with its salt. Thus, current can reversibly flow across the electrode by the following two-stage chemical reaction:

$$\mathrm{Ag} \leftrightarrow \mathrm{Ag}^{+} + \mathrm{e}^{-}$$

$$\mathrm{Ag}^{+} + \mathrm{Cl}^{-} \leftrightarrow \mathrm{AgCl}$$

With the flowing of an external current, so that the silver electrode becomes positive, silver atoms lose an electron and discharges as ions (Ag^+) into the solution and immediately combine with the chloride ions (Cl^-) of the solution to produce neutral insoluble silver molecules that attach themselves on the electrode. Chloride ions are thus removed from the solution.

$$\mathrm{NaCl} \rightarrow \mathrm{Na}^{+} + \mathrm{Cl}^{-}; \mathrm{Ag}^{+} + \mathrm{Cl}^{-} \rightarrow \mathrm{AgCl}.$$

If the current passes through the double electric layer in the opposite direction, silver ions in the solution regain electrons and settle as metallic silver on the surface of the electrode; the solution becomes unsaturated and silver chloride splits into silver and chloride ions:

$$\mathrm{Ag}^{+} + \mathrm{electron} \rightarrow \mathrm{Ag}; \mathrm{AgCl} \rightarrow \mathrm{Ag}^{+} + \mathrm{Cl}^{-}.$$

In this way, chloride ions pass through the solution. The passage of small amounts of charges through the electrode, in both directions, makes the chloride layer thinner or thicker, but it does not change its properties. Unless a substantial amount of charges passes through in the same direction (as what can happen, for example, when executing an imprudent electrode impedance test through a DC source), the electrochemical state of the electrode surface remains stable and the electrode potential unvaried.

This process of electric charge transfers greatly lowers electrode resistance to solution, reduces electrode polarisation to near zero, improves electrode potential stability and reduces electrochemical noise. Therefore, the Ag/AgCl

electrodes have characteristics similar to those of an ideal nonpolarisable electrode.

When a pair of electrodes is connected to a differential amplifier input, the difference between the two electrode potentials, if stable, can be removed by capacitors, called coupling capacitors, acting as low-cut filters (or high-pass filters) and so the potential difference will not be displayed in the recorded signal.

The situation worsens when potentials slowly change in time because of the changes in the conditions of the skin-electrode interface.

The ability to record low frequencies is also strictly connected to the electrode surface: the lower the surface of the electrode, the lower its electric capacity, the bigger the cut to lower frequencies as a result of polarisation. Paradoxically, smaller electrodes are often built with non-chloridisable materials and, therefore, susceptible to polarisation, but there are practical reasons for this:

- Needle electrodes, used for electromyography but also for EEG recordings of the scalp, must be made of stiff metal, like stainless steel, which can also be sharpened.
- Intracerebral electrodes can't be manufactured with non-polarisable materials, like silver chloride, because they are toxic if introduced into the brain. Stainless steel intracerebral electrode also contains a layer of chromic oxide on its surface, acting as another serial capacitor, lowering the resulting capacity value.

Finally, another artifact source not mentioned earlier is the connection between the electrode to a metallic wire of a different material (electrode-copper wire bimetallic junction), used for the connection to the amplifier. Should this junction (weld joint) not be correctly insulated and come into contact with the electrolyte (gel, etc.), it could function as a battery and produce fluctuating potentials of high amplitude, which generate artifacts.

In conclusion, electrodes are of vital importance in the chain of instruments used to record bioelectric signals; therefore, in order to record reliable data, it is necessary that they be prepared and treated with great care.

3.2 Electrode Chloridation

To make traditional silver electrodes nonpolarisable, an electrolytic method is used. Before re-chloriding previously used electrodes, it is necessary to carefully remove the existing layer of silver chloride; this can be achieved electrolytically by immersing the above-mentioned electrodes in a saline solution and making them electronegative (at more or less 9 V) compared with another silver electrode for a few minutes, until the surface is clear of any coloured chloride residue. Electrodes are then placed in a glass container with a saline solution, each of them attached to the positive pole of a 1.5 V battery. The negative pole of the battery is connected to another silver electrode, also immersed in the saline solution. With this method, after approximately 30 s, the electrodes connected to the positive pole will be covered with a layer of silver chloride and they will gain a dark brown or violet colour. The current passes at about 2.5 mA per cm^2 of electrode surface and it must flow for about a minute. The chemical reactions taking place when silver electrodes are immersed in saline solution are described by the following equations: $NaCl \rightarrow Na^+ + Cl^-$; $Cl^- + Ag^+ \rightarrow AgCl$. Na^+ ions react to the cathodic surface, producing hydrogen ions: $2Na^+ + 2H_2O + 2$ electrons $\rightarrow 2NaOH + H_2$.

Electrode chloridation is not necessary - of course - when using newly developed electrodes (gold-plated silver, gold or sintered metal electrodes).

3.3 Standard Recording Electrodes

Electrodes for scalp EEG recordings are: bridge electrodes, cup electrodes and needle electrodes. A bridge or pad electrode is an Ag/AgCl electrode, composed of a distal enlarged plate covered with a cotton pad, and a proximal segment, extended and usually threaded, to which wire connectors are fastened. The electrode is mounted on a plastic bridge (or a tripod) and various kinds of connectors can be attached (alligator clip, spring plug or touch proof) (Fig. 3.1a).

The main benefit of these electrodes is that they guarantee reliable recordings, with flexible and easily adjustable positioning. However, the tampon (impregnated with saline solution) tends to dry over time and this causes an increase in impedance. Moreover, the pressure on the patient's head (caused by the rubber bands of the cap) creates a certain physical annoyance over time and the montage becomes unstable in the event of a seizure or lack of cooperation; lastly, the junction between the electrode and the connector can generate artifacts (Fig. 3.1b).

Cup electrodes (or disc electrodes) are usually composed of an Ag/AgCl disc plate, partially concave in its inner part, with a small hole in the middle. In this case, the cup is integrated with the wire connecting it to the amplifier and this cable can be directly welded to the plate or detachable (bayonet connector). Gold-plated silver or sintered metal cup electrodes are currently available on the market (Fig. 3.2).

Cup electrodes can be secured on the patient's skin by applying them directly or with the help of a small gauze pad soaked in collodion or with a specific adhesive paste (see Chap. 7). To secure the electrodes to the skin with collodion, after having separated the hair and scrubbed the skin, small gauze pads soaked in liquid collodion can be used. Alternatively, liquid collodion can be poured slowly on the

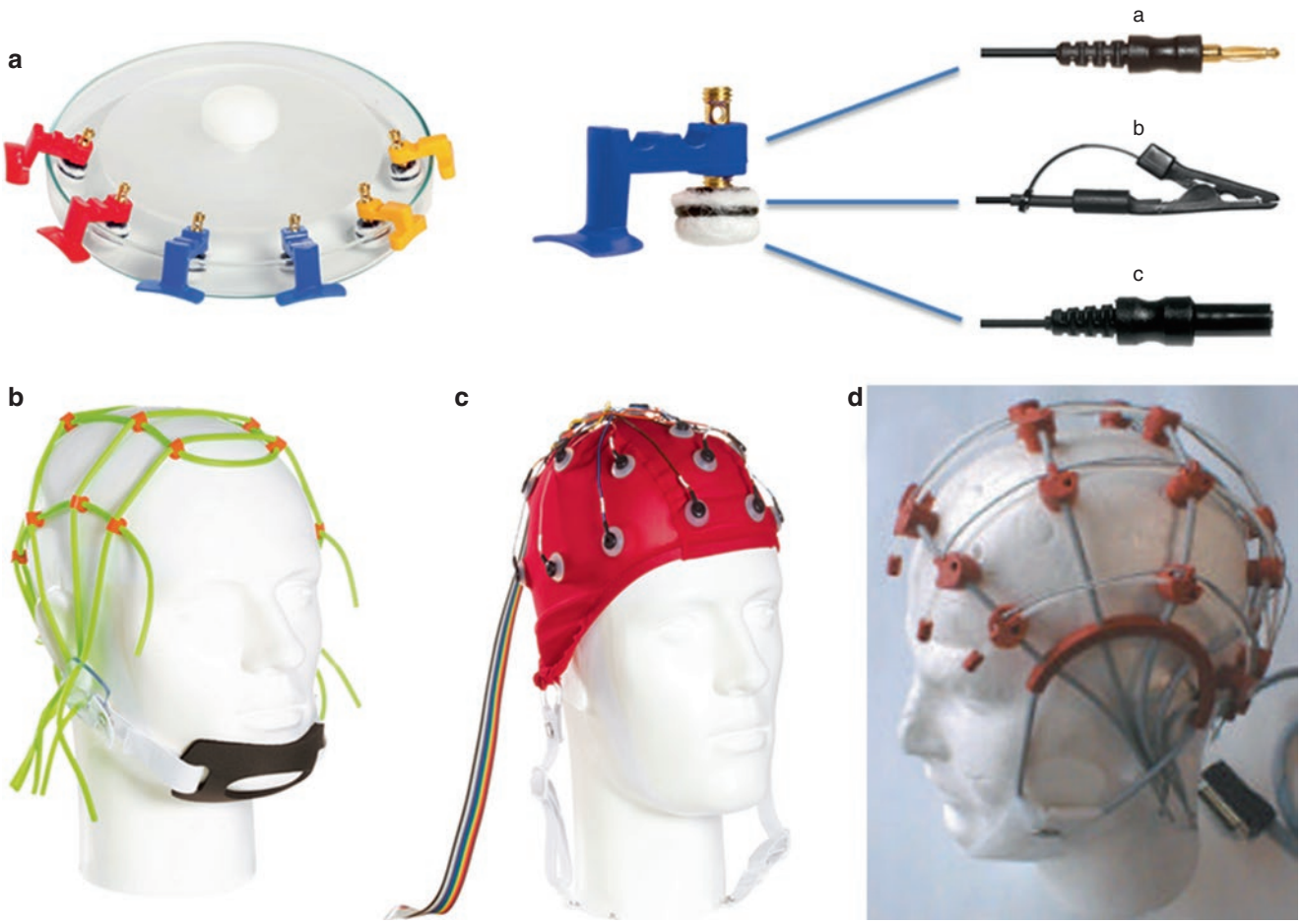

Fig. 3.1 (**a**) Bridge electrodes and their connectors: (*a*) spring plug; (*b*) alligator clip; (*c*) touch proof. (**b**) Cap with rubber bands for positioning bridge electrodes. (**c**) Prewired cap for standard EEG recording. (**d**) Elastic cap with electrodes pre-inserted in junctures

cup electrode with a syringe without a needle. A stream of cold air, discharged by a compressor or a simple hair-drier, can be used to dry the collodion. Once all the electrodes are placed, a conductive gel must be inserted into the hole at the centre of the cup and an impedance check must be carried out. The conductive gel can also be inserted into the concave side of the disc, before it is applied on the skin. This method is consistent over time and is more resistant to wire movements and traction; therefore, it is more suitable for long-term EEG monitoring. Disadvantages include longer preparation times, non-flexibility of the electrode montage and the use of collodion. Collodion is an unpleasant-smelling, flammable and toxic adhesive solution. Since its vapours are heavier than air, they tend to spread along the ground, and thus the room needs to be ventilated and equipped with a vapour extractor. Moreover, when applying collodion, particular care has to be be taken to cover the eyes and other mucous membranes which could accidentally come into contact with it. Removal of the collodion-placed electrodes can be carried out with an acetone-soaked cotton ball. Acetone inhalation can produce nasal and conjunctival irritation, respiratory effects, nausea and vomiting.

Traditional adhesive pastes (such as bentonite paste) can be used instead of collodion, but they don't guarantee the same adhesion to the skin and they also require special storage procedures. In addition, they can cause undesired skin reactions.

New types of adhesive pastes can now be found on the market (e.g. EC2, whose main ingredient is propyl paraben); they don't release vapours, they are non-toxic and they don't require special preservation methods. In addition, their removal can be accomplished with a simple aqueous solution. Electrode positioning with this method has shown stability for a long time and is therefore also appropriate for long-term video-EEG monitoring [3, 4].

Contact electrodes can also be placed on the scalp using prewired caps (Figs. 3.1c and 3.3). They are elastic caps of a textile material (skullcap) in which the electrodes are permanently embedded. These electrodes usually consist in silver discs, contained in a plastic shell with a hole in the middle.

Fig. 3.2 Examples of casted silver Ag/AgCl, stamped gold (Au) and sintered Ag/AgCl cup electrode with central hole

Once the cap is positioned on the patient's head, it is possible to insert a conductive gel through the hole on the electrodes, to facilitate their contact with the skin. All electrodes inserted into the cap are firmly connected to the wires, which in turn are connected to a single cable, inserted into the amplifier through its connector. This method of preparation is usually more comfortable for the patient and it guarantees montages with multiple electrodes achieved in a relatively short time, with good recording reliability, especially in the case of long-term monitoring or motor seizures (electrodes are flat and are not easily moved). Using these caps, however, it is not possible to reduce easily skin-electrode impedances and the electrode placement cannot be modified in case of any particular cranial conformations, skin wounds or pulse artifacts. Slow and large "sliding" artifacts can also occur easily, when an excessive amount of gel is inserted between the skin and the electrode.

Caps having the advantages of both traditional and prewired caps are the rubber band caps in which the contact electrodes are already inserted into the junctures between the rubber bands themselves and they are permanently connected to the wires, which in turn are covered by a single shielded cable; by using this type of cap, the patient preparation time can be reduced and the position of the electrodes can be changed according to individual needs (Fig. 3.1d).

Needle electrodes are made of stainless steel or platinum–iridium needles, about 1.5–2 cm long and about 0.3–0.4 mm in diameter, directly connected to a wire, which ends up in a connector to be then inserted into the amplifier. It must be positioned subcutaneously and obliquely to the surface (30°), after proper disinfection of the affected skin area. To avoid asymmetry in magnitude of the recorded signal, it is essential that the needles be aligned in parallel, in the anteroposterior direction.

Fig. 3.3 Examples of prewired elastic cap for high density EEG

The American Clinical Neurophysiology Society (ACNS) guidelines do not recommend these electrodes for routine clinical use, because of their higher impedances, patient discomfort, risk of injuries to personnel and infection risks [5, 6]. Sterilisation of welded cable electrodes is possible with ethylene oxide (not in autoclave though), but this problem is currently solved with the use of presterilised disposable needles. Actually, this type of electrode is very easy to use for recordings in the intensive care unit or, more generally, in patients with low levels of consciousness, including operating room recordings or for brain death ascertainment. In any case, needle electrodes, by their intrinsic properties, attenuate EEG frequencies lower than 1 Hz and this must be taken into account.

3.4 Recent Developments: Dry and Active Electrodes

Ag/AgCl electrodes with wet conductive gel are still almost universally used for biopotential recordings in clinical and research applications. With proper preparation, they are characterised by a low skin-electrode impedance that reduces artefacts or interference induced by cable movement; they show an excellent signal quality and good Signal-to-Noise Ratio (SNR). However, wet electrodes require skin preparation and professional personnel in order to place them properly. In addition, their impedance could deteriorate in a few hours after gel application and the gel itself can dry out. These drawbacks limit the use of Ag/AgCl electrodes for long-term EEG monitoring, especially when a large number of electrodes should be placed on the scalp.

In order to overcome these drawbacks, in recent years, dry (gel-free) electrodes have been developed. The main advantages are that they do not require the use of conductive gel or paste nor any skin/scalp preparation, thus reducing the setup time and improving subject comfort. However, dry electrodes present a higher impedance comparing with Ag/AgCl electrodes leading to high susceptibility to movement artifacts and to a significant increase in the noise and interference picked up from the environment; moreover, they are much more sensitive to the condition of the skin. Typical dry-electrode impedance ranges from a few hundreds of kΩ to a few tens of MΩ [7]. Therefore, dry electrodes should be used coupled with differential amplifiers with a very high input impedance and shielding in order to come near to the performance of wet electrodes [8].

State-of-the-art superficial dry electrodes for EEG can be grouped in two categories: contact electrodes and non-contact - or capacitive-coupling - electrodes. Dry non-contact sensors isolate the electrode from the skin, but this leads to even higher electrode impedance and makes EEG recordings more susceptible to movement and muscular artifacts. Regarding to subject comfort, dry electrodes implemented with conductive rigid metal pins can provide long-term EEG recordings but at the cost of pain and discomfort. Recently, dry electrodes with soft contact to the skin and an electrode impedance ranging from 20 to 500 kΩ have been developed [9–13].

Recent advances in integrated circuits and sensor techniques have allowed the development of dry Active Electrode (AEs) [12]. These are electrodes with integrated amplifiers that locally buffer and amplify EEG signals. The closeness of electrode to amplifier reduces interference and noise pickup. Furthermore, the low output impedance of the integrated amplifier allows the use of high-impedance dry electrodes, reducing cable motion artefacts, noise and interference from the environment. On the other hand, an AE-based EEG system require more wires (e.g. for power supply) compared to a conventional EEG, especially when additional functions (e.g. impedance measurement) are integrated in AEs.

Early AEs included simple analog buffers, i.e. voltage followers. This is at present the most popular architecture, because of its balanced performances. Moreover, it makes the use of the active shielding technique simpler to reduce the interferences [8, 14].

The main limitation of this classic AE architecture is that an analog buffer only performs impedance conversion without providing any voltage gain. Therefore, follow-on readout circuits are needed, leading to additional power consumption. Other configurations involve the use of inverting or non-inverting amplifiers, each with proper advantages and disadvantages.

Clearly, AE-based EEG systems should be designed to meet the requirements compliant with medical standards, which impose constraints on the electrical performance in terms of input impedance, noise, electrode offset tolerance, signal quality, common-mode rejection ratio, power dissipation and safety. Therefore, development of AEs remains a challenging task [15]. At present, there is an increase for EEG recording systems for research application and mobile, wearable applications, mainly because of their robustness to environmental interference.

3.5 Special Electrodes

From early on in the history of electroencephalography, it was clear that some cerebral regions were difficult to analyse with conventional surface electrodes. In order to obtain more thorough information, adjunctive electrodes, also known as basal electrodes, began to be used. In particular, these electrodes can be useful when identifying epileptiform abnormalities in the mesial and basal surfaces of the tempo-

ral and frontal lobes. They are generally invasive or semi-invasive and they can only be used in specific cases and in adequately specialised laboratories.

3.5.1 Sphenoidal Electrodes

Sphenoidal electrodes were introduced into EEG practice in 1951 [16] to analyse areas of the temporal lobe not recordable from the scalp. They are composed of a stainless steel or platinum wire, insulated along its entire length, except for the 3–5 mm at the extremity (Fig. 3.4). Sphenoidal electrodes are positioned under local anaesthesia, in a sterile environment, using as a guide, a lumbar puncture needle, inserted 3 cm anterior to the external auditory canal, below the zygomatic arch, and through the mandibular notch, targeting the lateral border of foramen ovale (Fig. 3.5). Sphenoidal electrodes denomination is Sp1 and Sp2. These electrodes are generally reliable regarding the quality of the recording, and they can be left in place for up to 3 weeks. As an alternative, shorter sphenoidal electrodes (mini-sphenoidal) can be used; their insertion is associated with less discomfort, but the results of few studies do not demonstrate particular advantages. Sphenoidal electrodes are mostly well tolerated by patients and they cause little artifactual activity. Infrequently, they can cause bleeding, penetration of the salivary duct or lesions of the trigeminal branches with consequent facial pain.

Fig. 3.4 Hook wire electrode, usable also as sphenoidal electrode

3.5.2 Naso-Ethmoidal Electrodes

These curved-end electrodes are applied under local anaesthesia. They are inserted in an upward direction, between the nasal septum and the nasal concha, coming close to the lamina cribrosa of the ethmoid bone. They can be useful for recordings of the basal surface of the frontal lobe. Once in place, this type of electrode is well tolerated, even though at times it can cause irritation of the conjunctiva.

3.5.3 Nasopharyngeal Electrodes

The nasopharyngeal electrodes consist of a solid or semi-solid insulated silver rod, with a small silver ball at the tip. After their lubrication, the electrodes are inserted bilaterally through the nares until they reach the nasopharynx posterior wall. They don't require local anaesthesia nor a sterile environment and are placed in the nasopharynx for the recording time only. This method is not considered invasive and, therefore, these electrodes can be positioned by an adequately trained technician and removed at the end of the recording session.

The nasopharyngeal electrodes may record the bioelectric activity generated in the inferior-mesial surface of the temporal and frontal lobes and so their indications are similar to those of sphenoidal electrodes, although with greater disadvantages. In fact, relevant artifacts can be generated by breathing and pharyngeal muscle contraction and, in relation to motor seizures, electrodes can cause injury to the pharynx itself. For these reasons, nasopharyngeal electrodes are currently rarely used.

3.5.4 Zygomatic Electrodes

The zygomatic electrodes are considered a non-invasive replacement for sphenoidal electrodes, suitable for routine recordings in the study of focal epileptic seizures (Fig. 3.6).

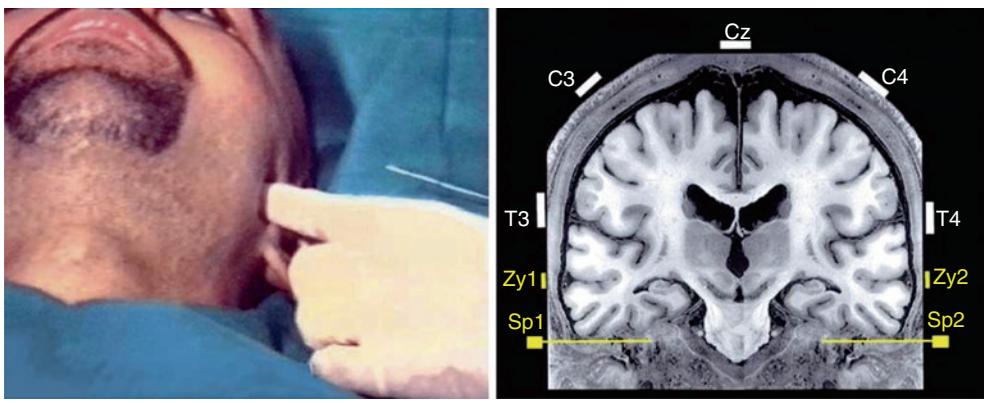

Fig. 3.5 Positioning of bilateral sphenoidal electrodes (courtesy of Francesca Bisulli and Paolo Tinuper, IRCCS Institute of Neurological Sciences, and Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy)

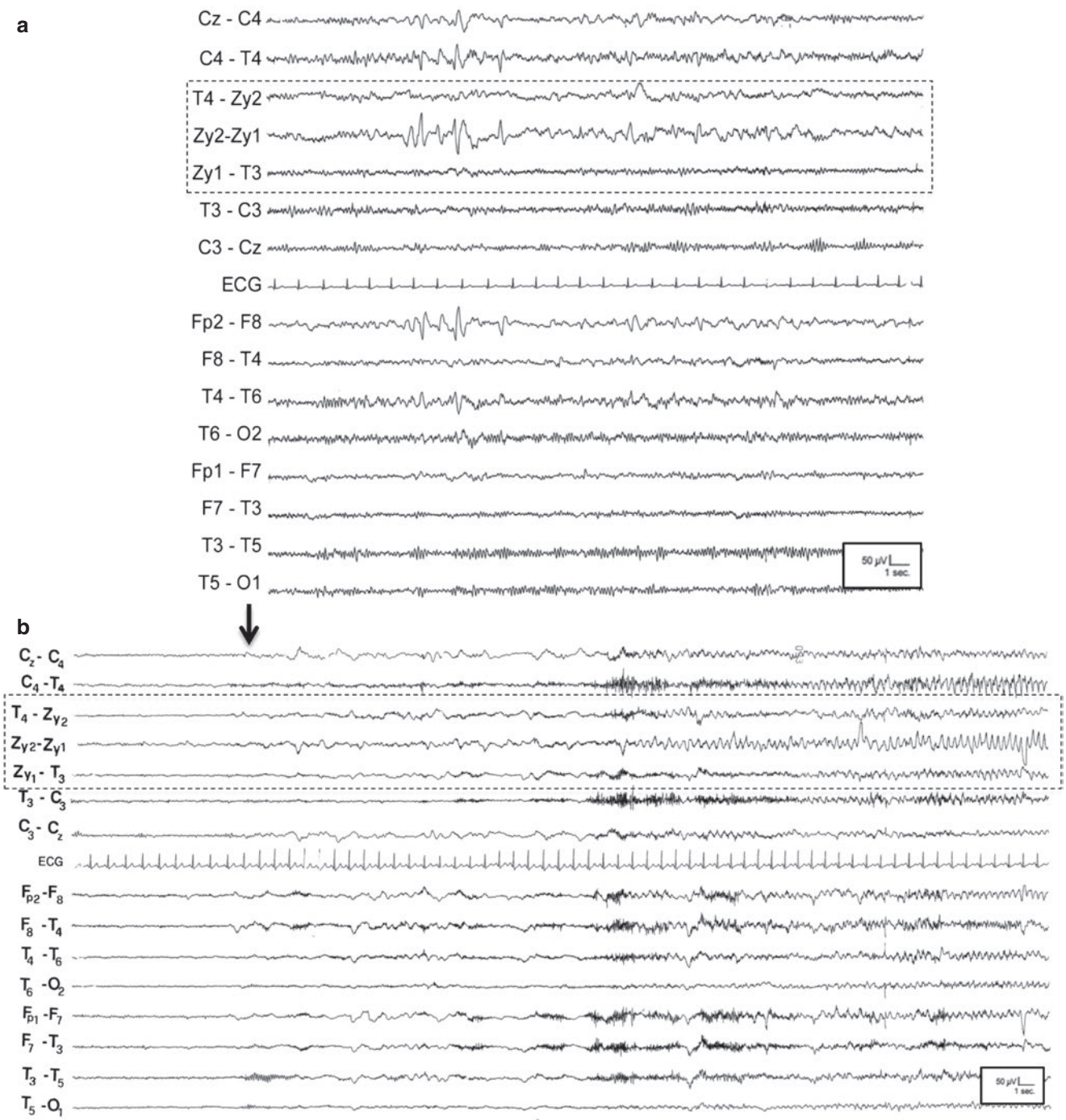

Fig. 3.6 An example of EEG recording with additional zygomatic electrodes in a 35-year-old woman with temporal epilepsy: interictal (**a**) and ictal (**b**, onset of discharge at arrow) epileptic pattern (courtesy of Francesca Bisulli and Paolo Tinuper, IRCCS Institute of Neurological Sciences, and Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy)

Zygomatic electrodes are simple cup electrodes, applied in front of the tragus, on the zygomatic arch, along the line connecting the tragus and the nasion. However, their ability to highlight epileptiform abnormalities that arise from basal and mesial frontotemporal regions is lower than sphenoidal electrodes.

3.5.5 Supraorbital Electrodes

Supraorbital electrodes are cup electrodes which can be applied, with collodion or adhesive paste, below and into the third medialis of the superciliary arch. They can be used when the aim is a more thorough study of the frontal pole

activity. Given their positioning, these electrodes are particularly sensitive to eye movement-generated artefacts and the activity recorded with them must always be compared to the purely electrooculographic one. These electrodes are named as So2 and So1 and they are referred in bipolar derivation to Fp2 and Fp1.

3.5.6 Tympanic Electrodes

Tympanic electrodes are an additional mean of recording brain areas that cannot be explored from the scalp and traditionally they are composed of a small S-shaped, insulated tube, about 6 cm long, terminating in a soft little sphere, of 7 mm in diameter, soaked in physiologic solution. These electrodes are inserted through the ear canal until their soft extremity touches the tympanic membrane (this requires experience and manual sensitivity). They can be used to study epileptic abnormalities that originate from the lower part of the temporal lobe, but they can be useful, rather than for EEG, to better visualise the first component of acoustic evoked potentials. Nowadays, for the evoked potential recording, a miniaturised version can be used, wet EEG electrodes positioned at discreet scalp and ear locations, useful for recording EEG on an everyday basis, and this will increase user acceptance and open up new avenues for the monitoring of the human brain function during daily life situations and actions.

3.6 Infection Control

The problem of transmissibility of certain pathogens, especially in a hospital environment, has always existed, but the attention in this regard has increased after the advent of HIV infection. Many diseases, from viral hepatitis to Creutzfeldt-Jakob disease (CJD), are at risk of being transmitted from patient to staff or other patients, through the use and reuse of contaminated electrodes. The problem is also relevant with regard to forensics.

Detailed recommendations regarding sterilisation of electrodes (or other instruments) were issued by the American Electroencephalographic Society [17] and recently reviewed [18]. For a continuous update on the procedure, you can also consult the Neurodiagnostic Society site at http://www.aset.org.

The highest risk of infection occurs when using needle electrodes. The technician can get infected either by needle pricks or through contact between blood and broken skin. Risks of transmission from patient to patient obviously exists with the reuse of the same electrodes. The preparation of the patient's skin before the electrodes are positioned can also cause bleeding or serous exudates, which can contaminate both the electrodes and the technician's hands. It is, therefore, advisable to avoid abrasions of the scalp, caused by excessive rubbing or by sharp objects, even blunt ones, used - for example - to clear out the hair. Blunt needles used to apply the conductive gel under the electrodes on prewired caps are particularly susceptible to contamination risk.

Disposable gloves can be worn by technical staff during the placement, removal and washing of the electrodes. Particular attention must be paid in trying not to touch other instruments when wearing potentially infected gloves. Application of the electrodes on patients who are known (or suspected) to be suffering from highly transmissible diseases must be carried out using all adequate physical protections: surgical masks, disposable overalls and latex gloves. EEG needle electrodes should be sterile and disposable; otherwise, they must be accurately cleaned and autoclaved (e.g. at 121 °C for 15 min). Needles used to inject conductive gel require similar measures. Bridge electrodes or cup electrodes must be cleaned with an adequate detergent after each use and they should be brushed in order to remove fragments of gel or adhesive paste; subsequently, they must be immersed in a sodium hypochlorite solution for at least 10 min, after each application. In cases of a highly infectious patient (e.g. with CJD), the preferred solution is to use disposable electrodes, to be later destroyed in an incinerator. Intracranial electrodes are at the highest risk of the transmission of diseases like CJD and so they should also be destroyed after use.

The recording system should be cleaned as well, with sodium hypochlorite, if contaminated with fluids at high biological risk. Two percent glutaraldehyde is a very powerful disinfectant for almost any infective disease (except for CJD), but it is not suitable for ordinary cleaning, as it can sensitise the staff. All contaminated linen should be treated according to locally recommended procedures. It is clear, however, that the precautions to be adopted to prevent the risk of infections (especially if not excessively high) should never affect the patient's dignity.

Appendix: Electro-Physical Characteristics of Electrodes

M. Mistretta

Silver (Ag): it is a transition, pliable, biocompatible metal for non-invasive use only. It is characterised by a higher electrical conductivity than the other metals and by a medium/low level of electrode potential. It is subjected to a fast oxidation in contact with ozone and therefore the air. It is often used as a basic material in the production of surface electrodes, and in order to reduce to the minimum the inherent noise, it is essential to use the 999% pure one. The pure silver is a non-magnetic metal.

Silver/silver chloride (Ag/AgCl): it is a mixed material with pure silver base and an external layer of silver chloride. The external match between silver metal and silver chloride salt guarantees unique features for the electrode. This mixed material is characterised by a fixed and specific electrode potential and by a low electrode/skin contact impedance. Therefore, it is perfect for recordings of low levels of AC and DC potentials and shows lower noises in low frequency in comparison with gold and pure silver. The layer of chloride silver that covers silver can be achieved through a chemical or electrolytic process. Both treatments make the electrode to get a characteristic dark grey colouring. Being of a least thickness, this external coat can deteriorate in the long term if high-saline content pastes and gel are used and if they are not removed at the end of use conveniently. Moreover, it is necessary to pay a particular attention to external mechanical abrasions that could take the treatment away. In case of a continuous employment, a treatment of re-chlorinating is needed when you notice the surface of the electrode has lost its original colour.

Sintered silver/silver chloride (Sint Ag/AgCl): it has the same electrical features of Ag/AgCl as it is formed by a mixture of Ag and AgCl very thin powders that are compacted through the sintering process. Therefore, you get an electrode of uniform thickness characterised by a greater stability of electrical features in the long term compared to an average Ag/AgCl. With regard to maintenance, this type of electrode does not need to be re-chlorinated but only to remove the remains of gel and conductive paste carefully.

Gold (Au): it is a transition, pliable, biocompatible metal used also for invasive employment. It is characterised by an excellent electrical conductivity, by a medium/low electrode potential and by the fact it is resistant to most chemical compounds. These features make it perfect for an employment with strong saline-based electrolytes and adhesives or diluents of a various nature. It is often employed as an external coat in the production of cup electrodes to be used in long terms monitoring or for sleep studies, as adhesives and diluents strong like collodion and acetone are applied with the electrode. Owing to a high biocompatibility, it is often used for invasive electrodes for recording of both potentials and electric stimulation.

Tin (Sn): it is a post-transition, pliable and resistant to metal corrosion. It is characterised by a good electrical conductivity, low level of electrode potential and a low level of innate noise. It is the material with the best value/quality relationship in the production of electrodes, and historically it is used in the production of head caps with prewired electrodes.

Carbon/graphite (C): it is a non-metal material with a good electrical conductivity; it has a very low level of electrode potential and shows a low level of noise similar to Ag/AgCL. Moreover, it has the quality to be radium-opaque and non-magnetic. Often, the graphite powder is inserted into plastics and paints to be employed in the production of electrodes. This solution makes the electrical features of this material worse but makes it easily usable in manufacturing systems.

Steel (alloys AISI 304,316): biocompatible, of high hardness and elastic alloy, characterised by a remarkable resistance to corrosion in water and in the air. It gives a medium electrical conductivity. Owing to mechanical and ductile features, it is used in the production of medical needles. Given its wide employment in the medical field, it guarantees the best quality/price relationship.

Platinum (Pt): it is a transition, pliable metal; it has a strong resistance to corrosion and is biocompatible. Usually it is used in alloy with iridium to improve its mechanical resistance. It is recognised for its good electrical conductivity and is employed for cortical electrodes and needles. It is a non-magnetic material.

Titanium (Gr. 5): it is a light and resistant metal, both mechanically and chemically. It is a biocompatible material and customarily is employed in prostheses. As far as the electrical characteristics, they are similar to tins. It is a non-magnetic material and for this feature it is used for MRI compatible products, especially needle electrodes, owing to its physical characteristics like steel. Given its high level of biocompatibility and resistance, it is also used for long-duration applied electrodes and implantable electrodes.

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Electrode Placement Systems and Montages

4

Oriano Mecarelli

4.1 Traditional International 10-20 System

When Hans Berger recorded the first human EEG, he only had two electrodes available, positioned them in the anterior and posterior regions of the head. Berger kept using this method for many years, considering it an efficient system to measure the global cortical activity. Later on, other researchers highlighted how, in reality, EEG activity varied significantly depending on the area of the scalp from which it was recorded. Observation of different regional cerebral rhythms encouraged the use of multiple electrodes and of more recording channels, but standardization of the recording methods soon became necessary, so that the resulting data could be comparable with one another. A committee of International Federation of Societies for EEG and Clinical Neurophysiology (IFSECN), led by H. Jasper, started then working on a specific electrode positioning system to be used in all laboratories. The first standardized system was presented at the 2nd International Congress of IFSECN in Paris in 1949 and published by Jasper in 1958; it is still universally used and known as the International 10-20 System (IS 10-20) [1].

In the development of IS 10-20, the following concerns were addressed:

- Definition of a measuring system for electrode positioning, taking into account clearly defined anatomical landmarks, so that the measurements were as proportional as possible to the shape of the skull
- Electrode distribution in order to guarantee that they cover every part of the skull and electrode identification according to standard positions, regardless whether all, or only some, are used in a specific recording
- Identification of the various electrode positions depending on the underlying brain area (frontal, central, temporal, parietal and occipital), rather than just using numbers, so that communication is more immediate and intuitive
- Execution of appropriate anatomical studies to safely localize brain area projections which, presumably, match the electrode standard positions.

Correct positioning of the electrodes on the scalp according to IS 10-20 is achieved by tracing imaginary lines, starting from specified anatomical landmarks. These circumferential lines are mutually perpendicular and they are represented by:

– Anteroposterior sagittal midline, connecting nasion to inion, through the vertex. Nasion is the depression between the eyes, just above the nasal bridge, at the insertion of the frontal bone and the nasal bones. Inion is the highest point in the midline of the protuberance of the occipital bone.
– Along this sagittal midline, there are five standard positions called frontopolar (Fpz), frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz). The letters F, C, P, and O indicate the underlying cerebral area and the letter z stands for zero. Considering the total distance between nasion and inion in centimeters, Fpz and Oz points are located at 10% of the total distance, respectively, from the nasion and the inion. All other positions are calculated at 20% of the distance between Fpz and Oz (the 10-20 denomination originated precisely from this percentage calculation). The ideal placing along the skull would set the central electrode (Cz) exactly in the middle of the line between nasion and inion; anatomical studies showed that C electrodes are located 1 cm within the central sulcus [2] (Fig. 4.1a).

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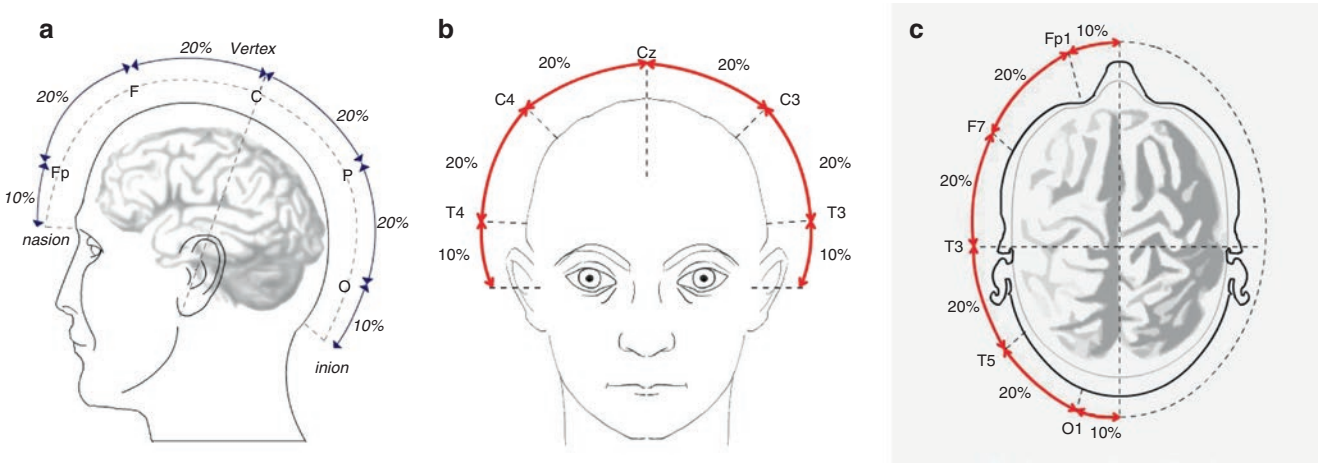

Fig. 4.1 Traditional 10-20 system. (**a**) Anteroposterior mesial line, connecting nasion and inion; (**b**) latero-lateral coronal line, connecting the two preauricular points, through the vertex; (**c**) sagittal lateral longitudinal line, connecting nasion and inion

– Latero-lateral coronal line, from the right to the left preauricular point, through the vertex. The preauricular points are identified as depressions at the root of the zygoma, just anterior to the auditory canal. Along this line, temporal electrodes (T4 to the right and T3 to the left) must be placed at 10% of the total distance, starting from the preauricular point while lateral central electrodes (C4 to the right and C3 to the left) must be placed at 20% from the temporal points (T4 and T3) and from the vertex (Cz) (Fig. 4.1b).

Starting from these two lines(i.e. the antero-posterior sagittal and the latero-lateral coronal) it is then possible to trace another two pairs of circumferential longitudinal lines in the anterior-posterior direction: lateral longitudinal line, from Fp2 to O2, through F8, T4 and T6 on the right; from Fp1 to O1, through F7, T3 and T5 on the left (Fig. 4.1c); longitudinal parasagittal line, from Fp2 to O2, through F4, C4 and P4 on the right; from Fp1 to O1, through F3, C3 and P3 on the left. Frontopolar electrodes (called Fp2 in the right and Fp1 in the left) are placed along the longitudinal line, at 10% of the distance to the side of Fpz, while for occipital electrodes (called O2 and O1) the 10% is measured with reference to Oz. Positions of the inferior frontal electrodes (F8 and F7) and posterior temporal electrodes (T6 and T5) are calculated at 20% of this line starting, respectively, from Fp2/Fp1 and O2/O1. The remaining frontal electrodes (F4 and F3) and parietal electrodes (P4 and P3) are placed along the frontal and parietal coronal lines, equally distant between the mesial and temporal lines on each side.

Standard numbering of the traditional 10-20 system establishes the disposition of even-numbered electrodes on the right side of the skull and of odd-numbered electrodes on the left side, identifying with letters the brain area above which they are positioned: Fp2, F4, F8, C4, P4, T4, T6 and O2 for the right hemisphere and Fp1, F3, F7, C3, P3, T3, T5 and O1 for the left hemisphere.

This measuring system identifies 21 standard electrode positions, including electrodes on the medial line (Fz, Cz, and Pz) and two reference auricular electrodes (A2 and A1) (Fig. 4.2a).

The International 10-20 system defined, in a short period of time, a standard scalp electrode positioning, allowing reliable comparisons of the acquired data from the various laboratories around the world. Nevertheless, the system is not exempt from criticisms. First of all, this system does not take into account that most human heads are asymmetrical. The posterior part of the skull is larger than the anterior one. Moreover, when dividing the skull in four quadrants (starting from nasion, inion and preauricular points), it can be noted that right-handed patients' heads temd to have a larger posterior quadrant on the left side and a larger anterior quadrant on the right side. For this reason, it would be necessary to arrange the electrodes proportionally not to the whole skull, but dividing it into four quadrants, meaning that the montage should be individualized.

For this reason, it is impossible that the interelectrode distances are the same along the longitudinal and transverse lines and, since interelectrode distance has a significant effect on the amplitude of the recorded signal, this problem should be carefully considered.

Furthermore, the relationship between the superficial positioning of the electrodes and the underlying anatomical structure was not correctly identified and, for this purpose, modern neuroimaging techniques should be better utilized. The 21 standard electrodes montage is not necessarily extensive enough to overlay all brain areas. For a correct detection of basal frontotemporal and mesial temporal areas, for example, specific additional electrodes are required.

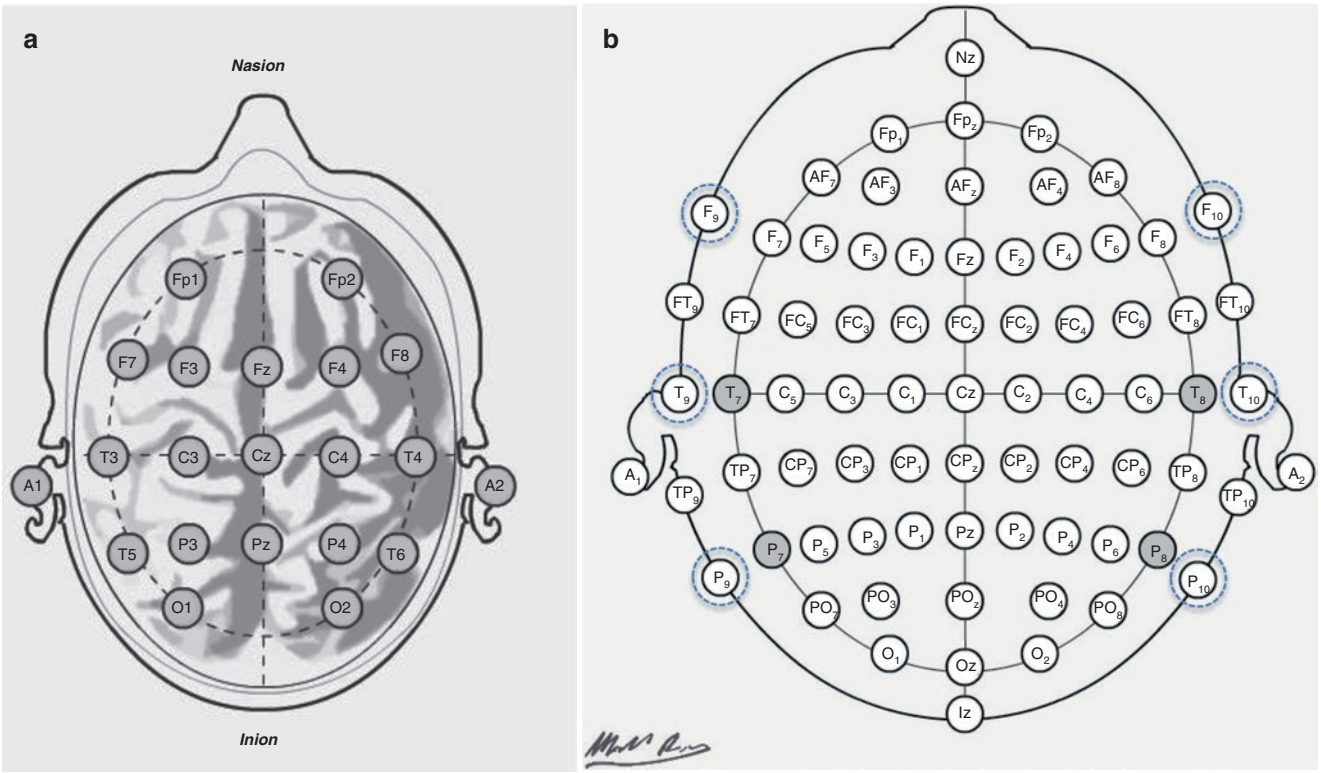

Fig. 4.2 (**a**) Standard positions of the 19 scalp electrodes and of the 2 ear reference electrodes, according to traditional 10-20 system; (**b**) modified 10-10 system, with 73 electrode positions on the scalp and 2 ear reference electrodes (note that the electrodes T8, P8, T7 and P7 replace the electrodes formerly named T4, T6, T3 and T5); the electrodes of the inferior temporal chain F10, T10, P10, F9, T9 and P9 (dotted circles) are actually recommended as new standard montage with 25 electrodes

4.2 Modification of 10-20 System (10-10 System)

Digital-EEG development and the introduction of high-density EEG and source localization methods made it necessary to increase the electrode arrays. Therefore, a modification of 10-20 nomenclature with the definition of 10-10 combinatorial nomenclature has been proposed and accepted by the American Clinical Neurophysiology Society (ACNS) and by the International Federation of Clinical Neurophysiology (IFCN) [3–7].

The modified combinatorial nomenclature is an extension of the 10-20 system and it entails the positioning on the scalp of more than 70 electrodes, placed along 11 sagittal chains and 9 coronal chains. The modified 10-10 terminology replaces the inconsistent T4/T3 and T6/T5 terms with the consistent T8/T7 and P8/P7 (Fig. 4.2b). The advantage of this new labelling is that all electrodes designated by the same letter are placed in the same coronal line and that all electrodes positioned along the same sagittal line have the same post-scripted number (except for Fp2/Fp1 and O2/O1); however, the disadvantage of the new nomenclature is represented by the fact that the letter "P" might suggest a *parietal* location, whereas P8/P7 are electrodes placed over the posterior temporal lobe. According to ACNS guidelines in the clinical context, it is still an acceptable alternative to continue to use T4/T5 and T6/T7 [6]. Electrodes between the frontal and central rows are named "FC", between the frontal and temporal rows "FT", between the central and parietal rows "CP" and between the parietal and occipital rows "PO". The electrodes between the frontopolar and frontal rows are named "AF", indicating "Anterior Frontal" placement [7].

The 10-10 system added also 10% contacts that are inferior to the standard frontotemporal and temporal-occipital chain. These electrodes are named F10/F9, FT10/FT9, T10/T9, TP10/TP9 and P10/P9. This inferior temporal chain may be completed with electrodes Fp10/Fp9, AF10/AF9, PO10/PO9 and O10/O9.

During the routine recordings with the traditional 10-20 system, the placement of the 19 standard scalp electrodes does not always detect the activity originating or propagating from mesial temporal structures. For this reason, the IFCN recommends a new standard array for clinical practice that includes the six electrodes of inferior temporal chain (F10/F9, 10% inferior to F8/F7; T10/T9, 10% inferior to T8/T7; P10/P9, 10% inferior to P8/P7): this results in a total of 25 electrodes placed on the scalp (Figs. 4.2b, 4.3 and 4.4) [7].

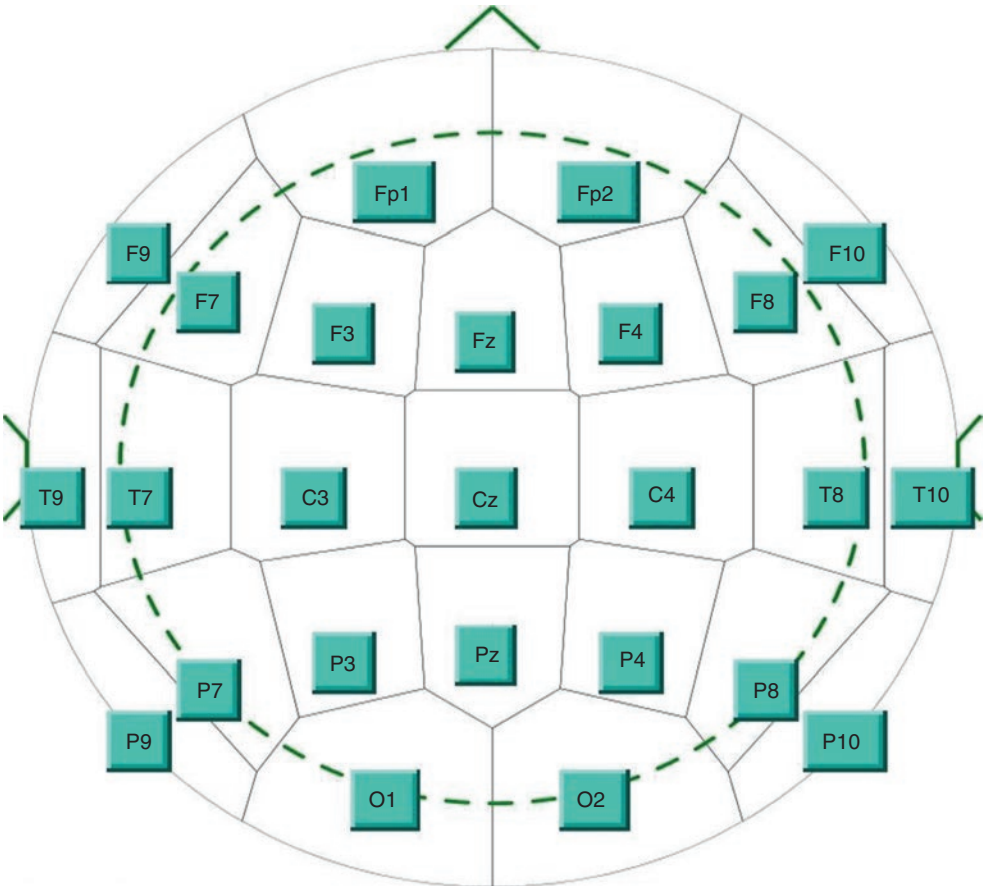

Fig. 4.3 New standard montage with additional coverage of the inferior and anterior brain regions, according to the recent recommendations of International Federation of Clinical Neurophysiology (from ref. [7], with permission)

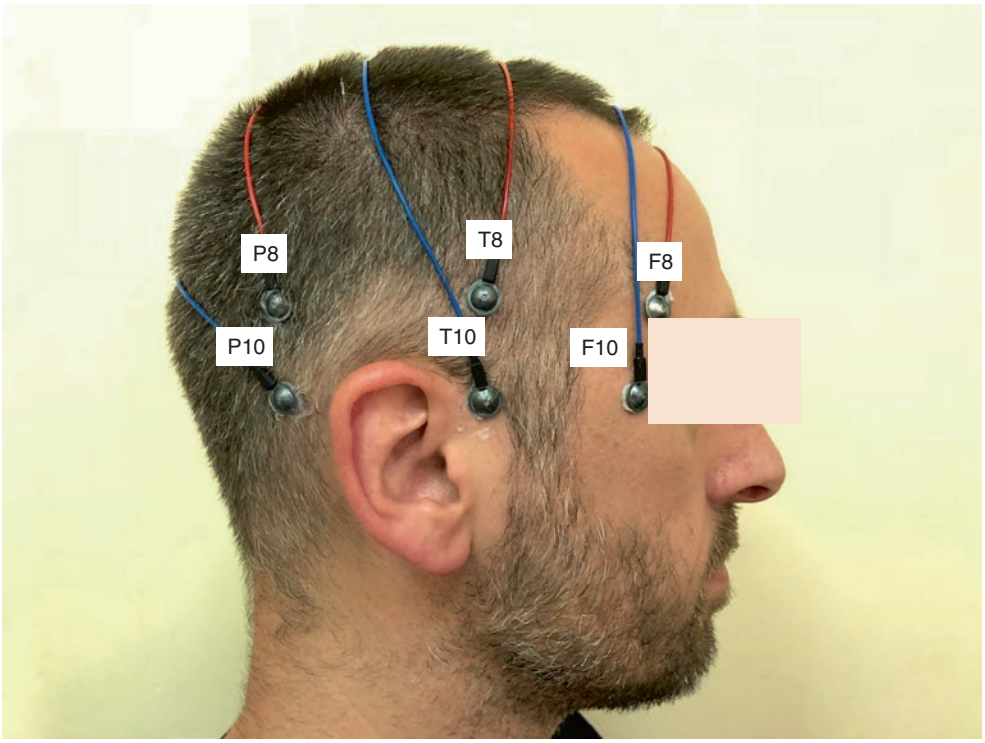

Fig. 4.4 Electrodes of the right inferior temporal chain according to new recommendations of IFCN (T8 = ex T4; P8 = ex T6)

Recently, it has been demonstrated that adding six electrodes in the inferior temporal chain to the traditional 10-20 system improves the identification of EEG abnormalities originating from the basal part of the temporal lobes [8].

4.3 Proposed 10-5 System for High-Resolution EEG

A further extension of 10-10 system, named 10-5 system, was proposed in 2001, but it has not yet been accepted by ACNS and IFCN [9]. The 10-5 proposed extension defines the position and nomenclature of 345 locations on the head and it can accommodate a homogeneous distribution of a subset containing, for example, 128 or 256 electrodes (Fig. 4.5a, b). The nomenclature of this system uses the combination of two letters to indicate the contours lying halfway between the original 10-20 system contours (the electrodes between the F and C contour were labelled FC and so on for others) [9]. In this way, the locations for the coronal contours from anterior to posterior were named: AF, AFF, F, FFC, FC, FCC, C, CCP, CP, P, PPO and PO. Electrodes for high-density EEG are applied by using expandable nets or caps with embedded electrodes and their localization is determined by digitization in three-dimensional space (Figs. 4.6 and 4.7).

4.4 Final Recommendations

Although in clinical practice the electrode placement method should be individualized on the basis of the clinical needs of the individual patient, the following recommendations should be considered, according to the guidelines of ACNS and IFCN: [6, 7].

- The 10-20 traditional system (21 electrodes) may be adequate for most of the patients, even for ambulatory or video-EEG long-term monitoring.
- In the suspicion of epilepsy or in epileptic patients without a clear visualization of the epileptic focus, supplementing the 10-20 EEG array with six electrodes for the inferior temporal chain (25 electrodes in total) is recommended.
- In children, except for special cases, the same number of electrodes as in adults is usually recommended.
- The 10-10 system should be used in epileptic patients undergoing pre-surgical evaluation and for source localization purpose.
- For the transition from the traditional system to the new larger arrays, the modification of EEG machine headboxes and a gradual process of educating operators on the new terminology are necessary.

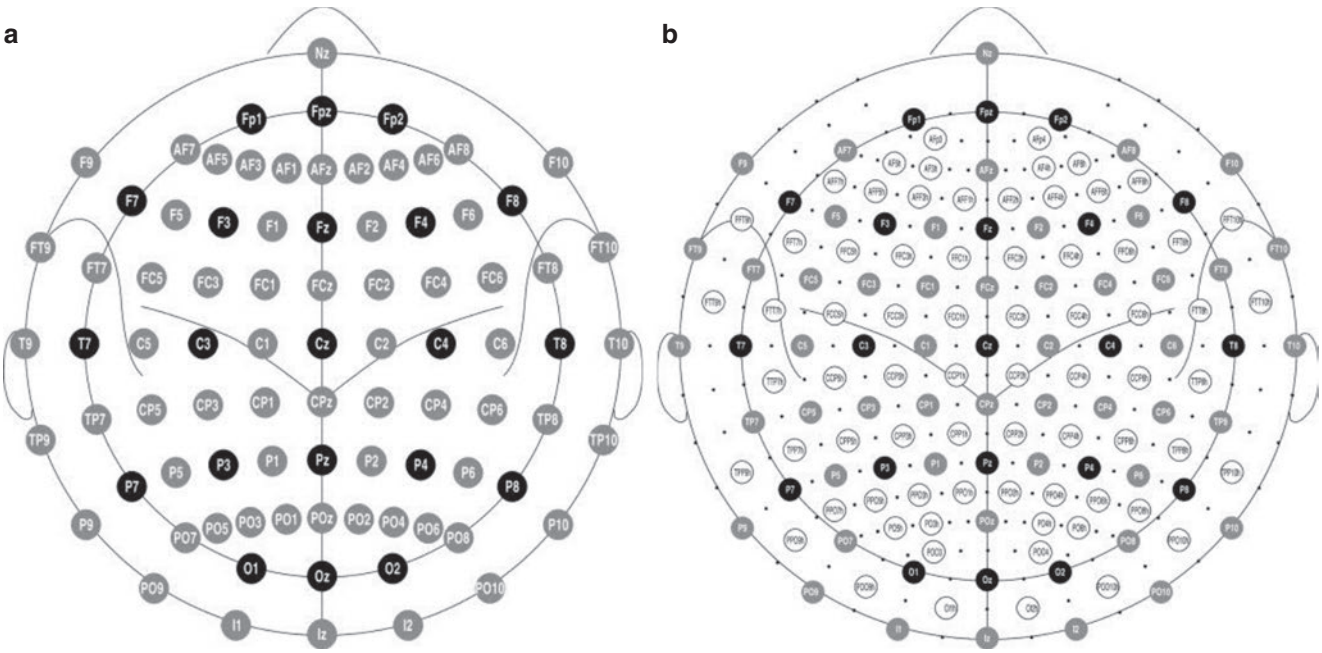

Fig. 4.5 The 10-10 and 10-5 extension of traditional 10-20 system. In (**a**) black circles indicate positions of the original 10-20 system and grey circles indicate additional positions introduced in the 10-10 extension. In (**b**) electrode positions in the proposed 10-5 system: additional positions to the 10-10 system are indicated with dots; a selection of additional positions useful for a 128 channel EEG system is indicated with open circles (from ref. [9], with permission)

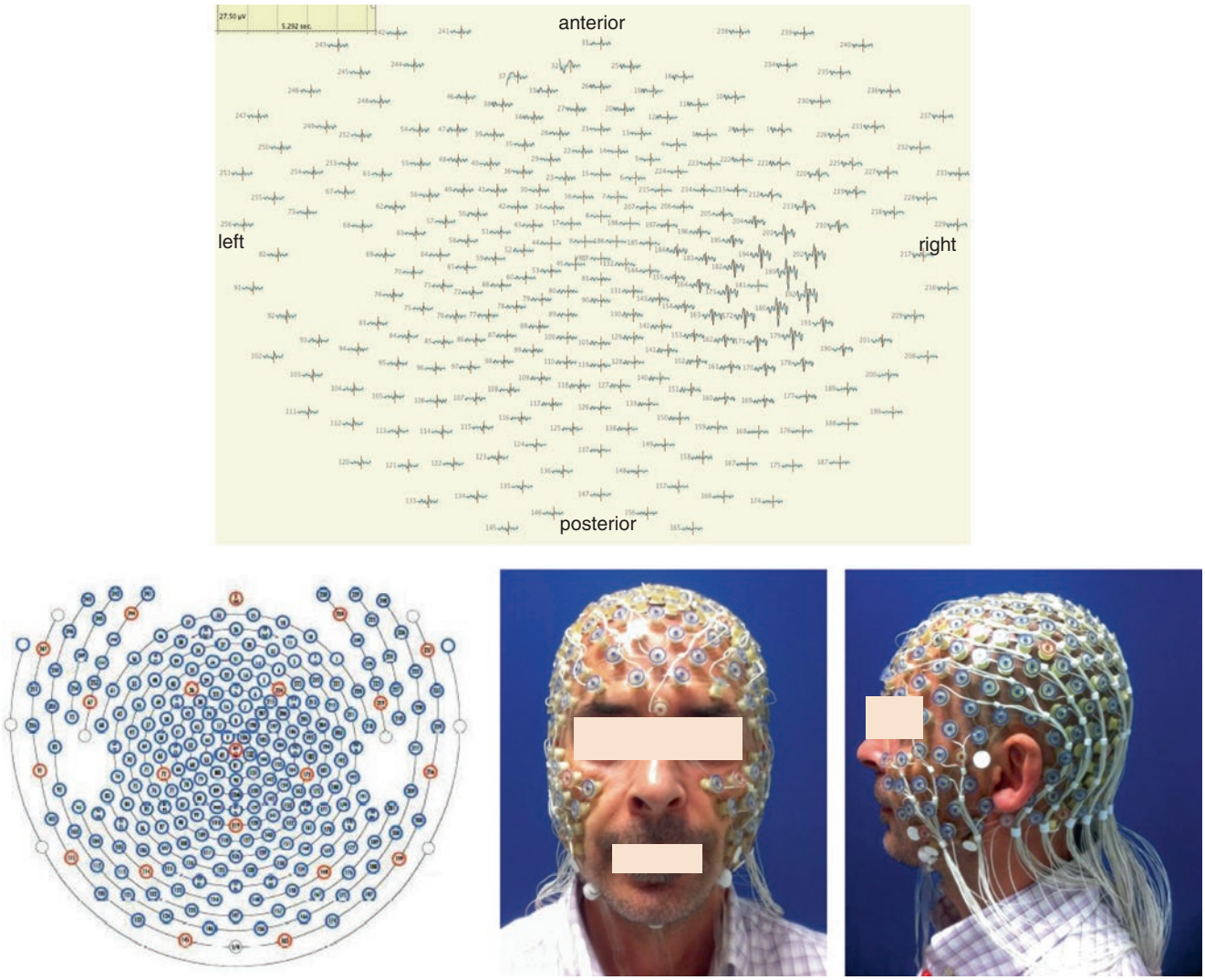

Fig. 4.6 An example of 256-channel high-density EEG, with projected locations of the electrodes on the scalp (courtesy from: Paolo Manganotti, Clinical Neurology Unit, University of Trieste—Italy)

4.5 Electrode Derivations and Montages

Brain electrical signals are displayed on the monitor depending on how the electrodes are connected to the amplifiers. Each amplifier has two electrode inputs (1 and 2) and the *potential measurement* represents the *potential difference* between these two points. From the electrical point of view, one of these points is called "common" or "ground" and its potential is deemed to be *zero*: unfortunately, ground points generate potentials and do not correspond to a real zero. This can be overcome by connecting two amplifiers together at the ground point and comparing the potential difference between their active inputs. Then, if two amplifier inputs (1 and 2) have the same polarity and voltage, the output will be zero (*in-phase rejection*) while, when these potentials are different, the recorded output value will be proportional to the difference between the two input values. Using differential amplifiers, only the difference between two inputs is known and not the absolute value of the potentials of electrodes attached to either inputs 1 or 2. Comparing a large number of electrode positions, EEG allows—with a good approximation—the localization of an abnormal activity on the scalp. In summary, on the monitor or recording paper, the signal is displayed with two fundamental characteristics: voltage and polarity. With regard to polarity, by convention, if the relative voltage difference is negative, the signal deflects upward and, if the voltage difference is positive, it goes downward. Therefore, if input 1 is more negative than input 2, the output signal will deflect upward, whereas if input 1 is more positive than input 2, the output signal will deflect downward. Finally, when inputs 1 and 2 have the same polarity and voltage, the output signal will be a flat line (Fig. 4.8).

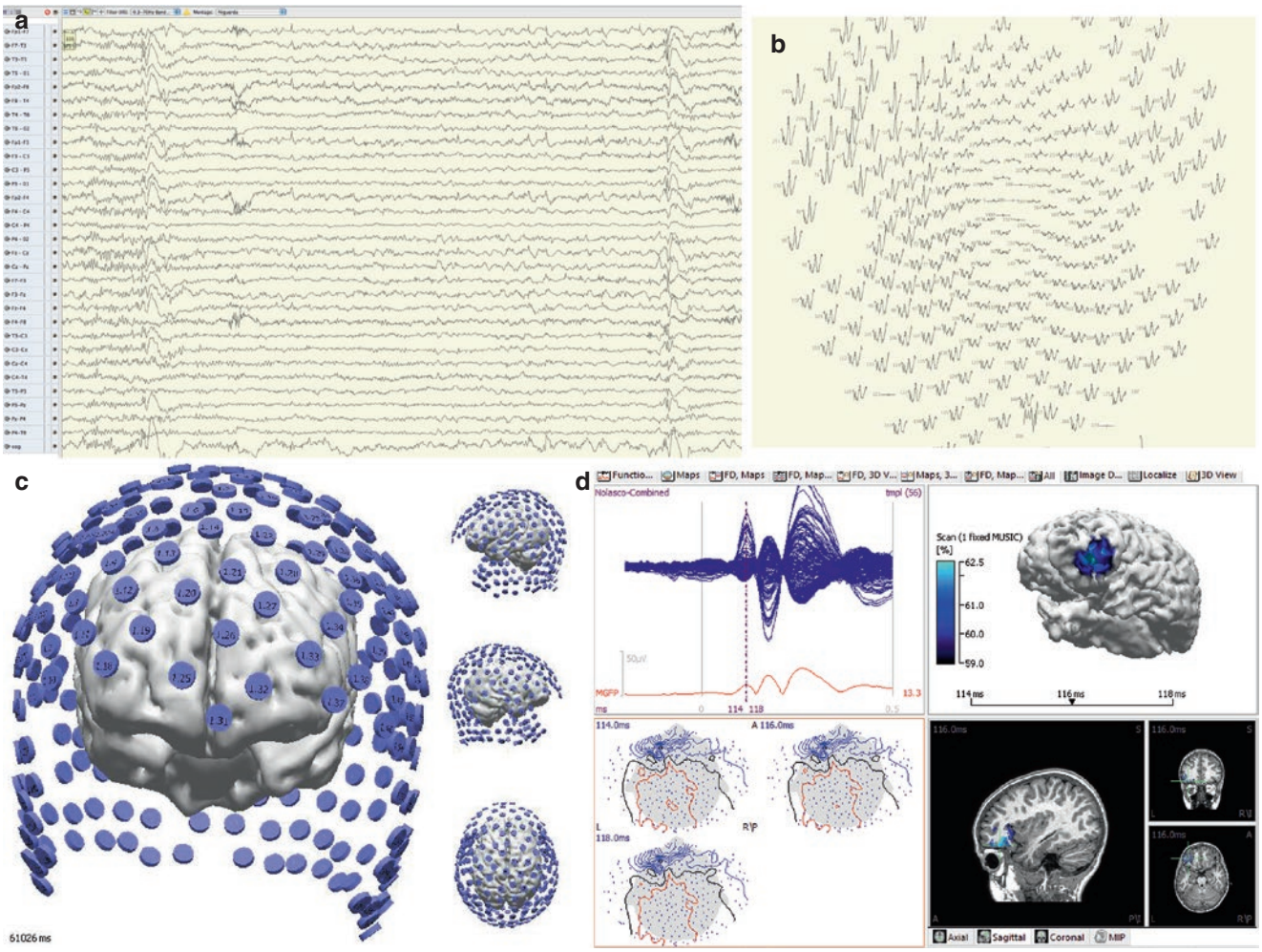

Fig. 4.7 Comparison of standard and high-density EEG in a patient with epileptic left temporal focus; (**a**) standard EEG recording with placement of electrodes according to 10-20 system; (**b**) recording of a single spike by 256 electrodes placed on the scalp; (**c**) the 256 placed electrodes projected onto a 3D image of the patient's brain, obtained by MRI; (**d**) source analysis of epileptic focus (56 spikes average) (courtesy from: Annalisa Rubino, Lino Nobili, Epilepsy Surgery Centre—Niguarda Hospital, Milan, and Child Neuropsychiatry, Department of Neurosciences, University of Genoa)

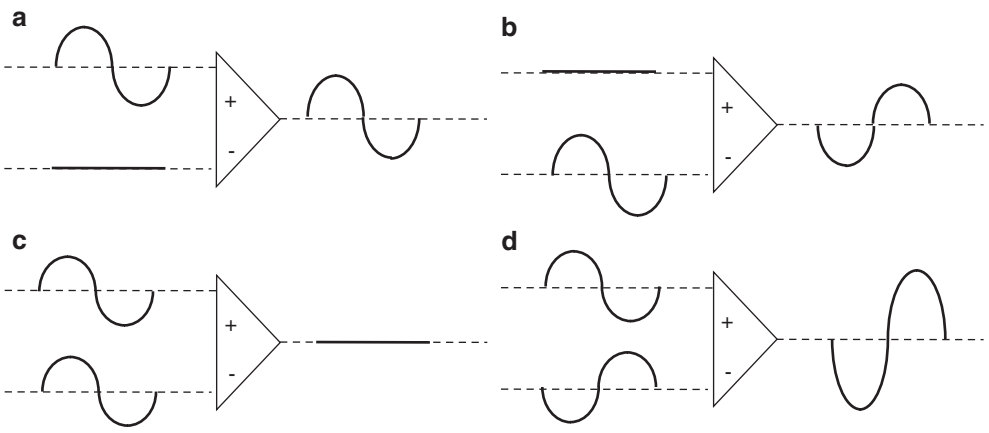

Fig. 4.8 Morphology and amplitude of different input signals of differential amplifiers and the respective output signals. The figure shows obviously ideal circumstances. If the signal is confined to a single channel (**a**, **b**), the output signal will have a different polarity, depending on the characteristics of input signal. If, instead, the two input signals are identical (with the same polarity), the output will be zero (**c**). Finally, if the two input signals have different polarity, the output signal will be the result of their summation (**d**)

Since there are endless input combinations that can generate the same output value, it is impossible to know the value of two inputs only knowing the output value of a differential amplifier. Back to EEG, if we imagine the electric fields on the surface of the scalp as the surface of the sea, rippled by waves of different sizes intersecting with each other, an EEG is rarely like a pond with almost imperceptible waves (when this happens, it means we are close to cortical activity suppression, characteristic of severe clinical conditions as brain death). Continuing with this analogy, electrodes are like corks, floating on the water, and the only thing we can do is to measure the height differences among them. This analogy would be perfect if the corks were correctly positioned, with regular distances, and if they were arranged in an orthogonal grid. A fixed point is then needed, as the shore to which all corks should refer.

In electroencephalography, aside from electrode positioning on the scalp (according to IS 10-20), a fundamental role is played by electrode combination (montage) and their type of connection to the amplifier (derivation). For historical and practical reasons, EEG is usually displayed as a set of traces showing how potential differences change over time. In a traditional EEG tracing (analog EEG), each trace is the result of the connection of two electrodes to the amplifiers and filters, with the signal sent to the galvanometer and to the writing device. With the introduction of digital EEG, the whole system has been replaced by computer software and hardware, but every trace continues to be called c*hannel*.

4.5.1 Reference Derivations

4.5.1.1 Common Reference

With this recording method, each electrode placed on the scalp is referred to as a common electrode, placed at a point x, on the scalp or elsewhere. The principle is similar to a geographical map, where the altitude of every location is measured in relation to the sea level. The common reference electrode should be as neutral as possible from the electrical point of view (not contaminated by cerebral electric potential nor by other biological electrical signals), which is a really rare occurrence. Fig. 4.9 shows the fundamental principles of the so-called "*inactive*" *common reference.* A potential with a negative voltage peak at the F3 electrode generates a surrounding electric field with gradient marked by the circular lines. The bilateral occipital and right parietotemporal areas are considered to have a uniform potential, which we can arbitrarily establish as zero. Therefore, the scalp electrodes T4, T6, P4, O2 and O1 and the A2 ear reference electrode have zero potential and they are consequently positive when compared to the other cerebral electrodes; they are also very different from F3 (which has the maximum negative peak). Starting from this situation, any point of the head can be chosen as a reference but, to better demonstrate the distribution of the potential generated under F3, the best option would be to choose an electrode not "contaminated" by this activity, like the A2 contralateral ear electrode or non-

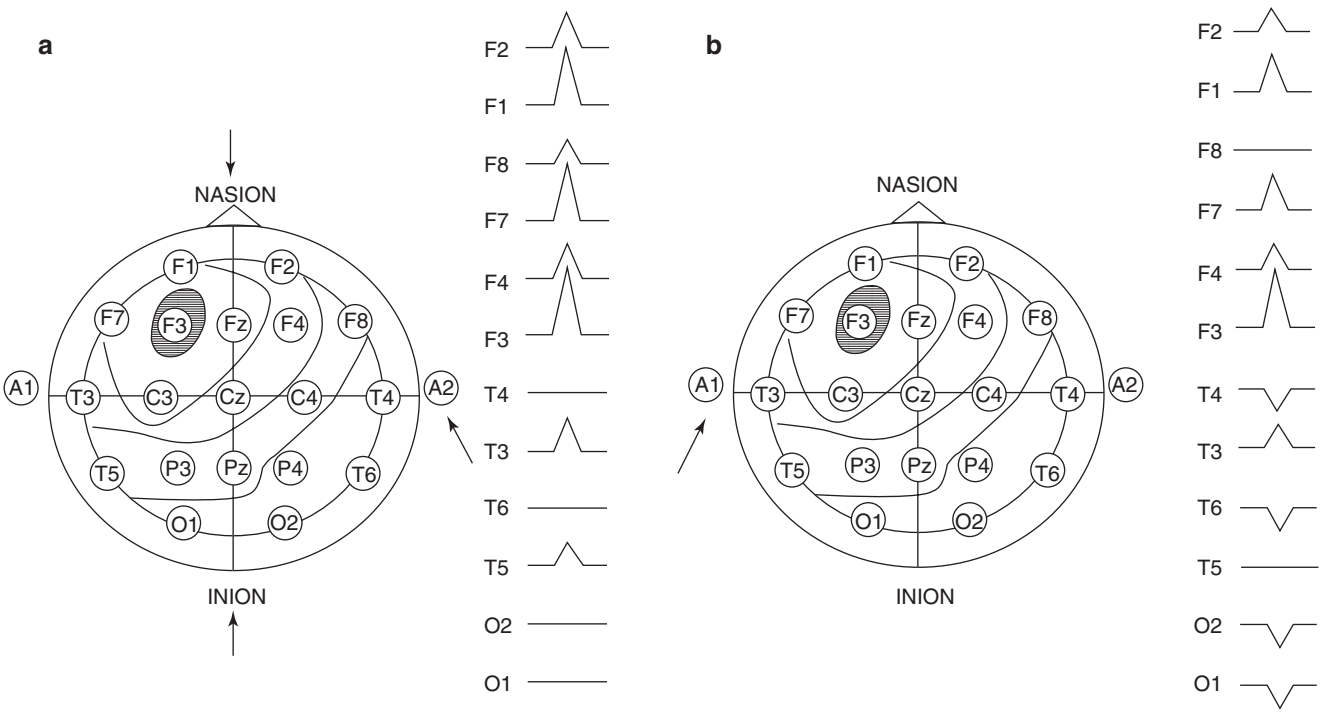

Fig. 4.9 Common reference recording (see text for explanation; F2 and F1 = Fp2 and Fp1). (**a**) reference electrode A2; (**b**) reference electrode A1

cephalic reference. Using A2 as a reference, the signals in this virtual situation would be displayed like in Fig. 4.9a.

Choosing the A1 left ear electrode as a reference, which is located inside the F3 electrical field and which has a low-amplitude negative potential when compared to the arbitrary zero (a common occurrence in normal practice), a very different pattern will be drawn: the channels showing lack of activity will be the ones with the same potential as the reference and, therefore, will be evened out; a downward deflection, caused by the relative negativity of the common reference, will be found instead on the electrodes placed in the area of zero potential (Fig. 4.9b).

An active scalp electrode can also be chosen as the *active common reference*. Figure 4.10 shows a virtual situation in which the electrode placed at F3 is chosen as the common reference. F3 is over the maximum electrical field on the scalp and it records the highest negative signal. Since, in this case, the reference is negative in comparison to other electrodes, all amplifiers will produce downward deflections. Moreover, since the electrodes surrounding the activity peak (F1, Fz, F7, C3) differ only slightly in potential from the reference, their corresponding channels will show smaller deflections than the ones farther away (the longer the distance from the reference, the higher the deflection).

The major drawback produced by active common reference is the *reference contamination*: when the reference electrode is placed close to a maximal peak potential, all the corresponding electrodes will be subjected to a change in voltage; all electrodes equipotential to the reference will be evened out, while the one least affected by the reference will show a pseudo-positivity. So, theoretically, given a known electric field (see Fig. 4.9), it would not be hard to estimate the shape of the wave that will appear on the EEG channel, depending on the reference. In practice, the concept must be reversed as we need to understand the distribution of the potentials on the scalp without knowing *a priori* - in a better way - the precise localization and the origin of the signal nor its positive or negative polarity.

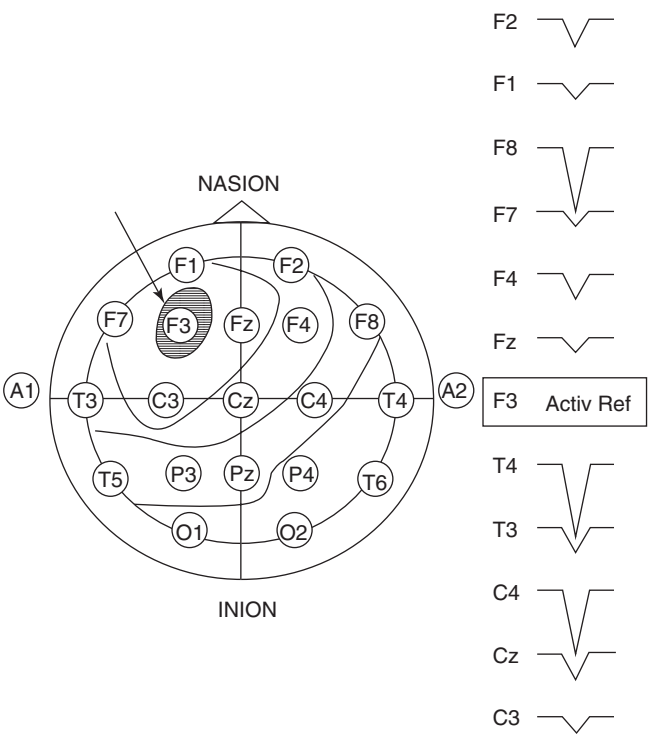

Fig. 4.10 Active common reference recording (see text for explanation; F2 and F1 = Fp2 and Fp1)

There are, however, more complex conditions than those mentioned above. For example, when it is necessary to analyse multiple events, localized to various electrodes, both synchronous and asynchronous, it could be difficult to interpret the resulting patterns.

All the problems analysed so far could be overcome by choosing an acceptable inactive reference electrode, placed in non-cephalic areas, named *physical* reference (neck-chest reference). Auricular or nuchal electrodes can be also chosen as the reference, but they cannot be considered completely "inactive". For example, electrical events generated from the temporal lobes can be recorded with auricular or mastoid electrodes; also nasal or mental electrodes can record activities originating from the orbital surfaces of the frontal lobes. On the other hand, when using a non-cranial reference, there is the risk of recording many artifacts: when they are in-phase in all channels, there is no problem for the interpretation, but when this does not occur, the EEG tracings can be completely obscured. Vertical eye movements produce high potential differences between scalp electrodes and the nasal or mental reference. Equally important are interferences produced by muscles and the ECG.

In conclusion, common reference tends to "contaminate" differential amplifiers, reducing in-phase rejection and increasing interferences; for this reason, depending on the particular situation, a specific reference should be chosen: auricular lobe or mastoid, omolateral or contralateral to the analysed activity (not recommended in the case of bilateral activity); electrodes placed along the mesial line in frontal region or at the vertex (not recommended in case of drowsiness or sleep because arousal phenomena mostly affect the reference electrode); nasal or mental electrodes (not recommended for alert patients because they produce larger artifacts).

Current digital EEG systems always refer the cerebral bioelectric signal to a common reference electrode, which typically has an input in patient headbox named G2 and which can be positioned on the scalp or elsewhere (usually, it is placed medially on the scalp, anterior to Fz or between Fz and Cz). The G2 common electrode is the common point referring to which all potentials of the single electrodes are measured (Fig. 4.11).

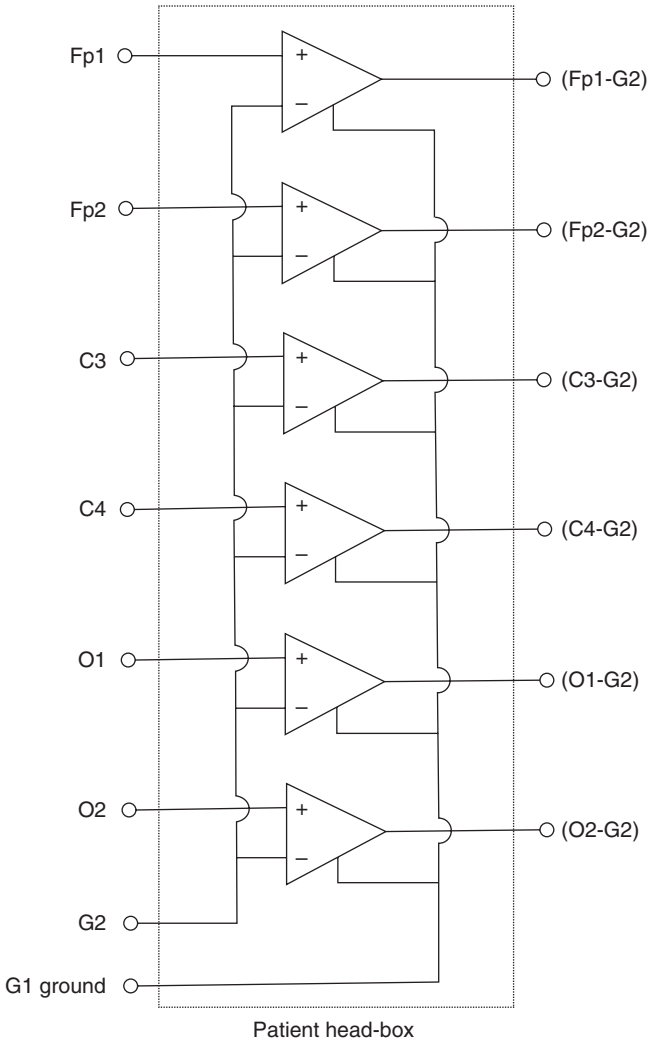

Fig. 4.11 G2—common reference recording. G2 electrode is connected to the inverting input (negative) of all amplifiers, while the electrode to be measured is connected to the non-inverting input. What the machine physically measures is the potential difference between each electrode and G2 (Fp1–G2, etc.)

4.5.1.2 Common Average Reference

Many of the problems encountered with the use of common reference can be overcome by average reference (AVG), a mathematical reference, introduced in electroencephalography by Goldman and Offner in 1950 [10, 11]. In this case, the potentials of single electrodes are referred to an instant average value obtained by adding together the potentials of all applied electrodes. The higher the number of electrodes, the closer to zero the reference average potential will be. In fact, one of the properties of the mathematical average of a series of numerical values is that the sum of the average differences equals zero. Regarding the results on the EEG tracings, this means that we will always have positive or negative deflections, with respect to the zero value of the reference.

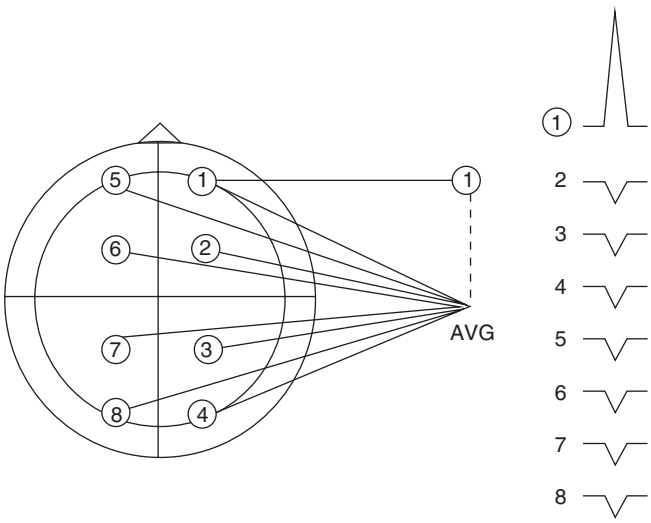

Fig. 4.12 Average reference (AVG) recording (see text for explanation)

In analog systems, this derivation method is achieved by joining all electrodes to a high resistor placed in a common place inside the device. Modern digital systems calculate the mathematical average of the potential differences of all the electrodes used at the same time, and moment by moment. Figure 4.12 exemplifies how AVG reference works. In this case, an ideal situation is presented with only eight electrodes applied to the scalp; electrode 1 has a more significant potential difference than the others (−80 μV), while the other electrodes remain at arbitral values of *zero*. The average of all electrodes will be:

$$\frac{-80+0+0+0+0+0+0+0}{8}=-10\mu V$$

As a result, electrode 1 will have a negative potential equal to:

$$-70\mu V \rightarrow \left[-80-\left(-10\right)=-70\mu V\right],$$

other electrodes will have a small positive potential equal to:

$$10\mu V \rightarrow \left[0-\left(-10\right)=10\mu V\right]$$

Therefore, the first electrode will have an upward deflection equal to −70 μV, while other electrodes will have a downward deflection equal to 10 μV.

More generally, when an electrode has a potential of value P, the AVG reference of that electrode will record a potential difference P_1 equal to:

$$\frac{P\left(n-1\right)}{n}$$

The higher the value of n, the closer P_1 will get to the value of P and the lower the deflections on the other channels will be. This means that the number of electrodes which contribute to average calculation should be as high as possible.

In digital electroencephalography, calculation of the average reference is achieved as follows (in this case, with application of 19 standard electrodes):

$$\frac{\left[\left(\text{Fp1}-\text{G2}\right)+\text{Fp2}-\text{G2})+\ldots+(\text{O1}-\text{G2}\right)}{19}$$
$$=\frac{\left[\text{Fp1}+\text{Fp2}+\ldots+\text{O1}+\text{O2}\right]}{19}-\frac{19\times\text{G2}}{19}=\frac{[0]}{19}-\text{G2}=-\text{G2}$$

All above described is valid assuming that the average value of the 19 electrodes is 0. In this case, AVG value constitutes the absolute value of point G2. The AVG reference trace tells us that:

$$\left(\text{Fp1}-\text{AVG}\right)=\left(\text{Fp1}-\text{G2}\right)-\left(-\text{G2}\right)=\text{Fp1}-\text{G2}+\text{G2}=\text{Fp1}$$

The recorded potential should then be the absolute potential of the Fp1 electrode.

Some systems are equipped to eliminate some of the electrodes from the total summation, but this can cause reviewing errors. Every average common derivation, whose deflections summation is other than zero, should be carefully and cautiously evaluated.

When we use an AVG reference, a localized event affects multiple channels, though the electrodes directly above the focal fields can usually be identified as the ones with higher amplitude deflections and of opposite polarity, compared to the majority of the other electrodes.

An accurate localization of a specific event is not easy in the case of multifocal and not in-phase potentials recorded by various electrodes, which will lead to activity resets.

Furthermore, the problem of contamination exists also in this case and it is accentuated in the case of high-amplitude localized activities on the scalp, including artifactual activity. To avoid this, the *correct average reference* can be calculated by excluding, from the average, the electrodes in which an excessively high-voltage or artifactual activity is recorded.

4.5.1.3 Source Derivation

Finally, a particular type of average reference is source derivation, introduced for the first time by Hjorth in 1975 [12] to improve the localization of focal activity on the scalp.

In this case, each electrode potential is referred to a reference making the weighted average of the electrodes around it. Its basic principle is that each cerebral generator causes a wave, which is much wider than the starting focal point. Source derivation tries to view focal generators as radial currents, travelling along the scalp, starting from the generator itself. This method is based on the application of Laplace's equation, according to which the radial current of a given point can be calculated by the second derivative of the electric field potential of that point. Basically, the radial current is calculated by the summation of the potential differences of the dipole created by the electrode in question and by the four surrounding electrodes. The resulting currents are called Laplacian. In the ideal situation where the focal point is located underneath the electrodes that are being observed, the Laplacian current will be the only visible one, while the value of the currents underneath the neighbouring electrodes will be zero. Source derivation, then, is nothing more than the visualization of a single electrode potential, compared to the weighted average of its neighbouring electrodes and the average weightings are inversely proportional to the distance between the electrode in question and its neighbours, from which the reference is calculated.

However, this technique has considerable limitations, including alteration of the real width of a potential and the generation of false opposition of polarity.

Figure 4.13a shows the differences that can be encountered using source derivation, starting from an "ideal" situation in which a high potential, placed under the F3 electrode and transmitted to the neighbouring electrodes in a variable manner, is recorded on the scalp with common reference (the F3 absolute potential is of 100 μV). With the source derivation method, considering the potential of F3 with respect to the weighted average of the four surrounding electrodes (Fp1, F7, C3, Fz), the resulting potential will be of 20 μV, significantly lower than the one we started from.

$$\text{F3}=100-\frac{80+80+80+80}{4}=20\mu V$$

Conversely, if the electrode F8 has an absolute potential of 0 (as in Fig. 4.13b), with source derivation method an opposite polarity (−40 μV) will be obtained, in comparison to the weighted average of the surrounding electrodes Fp2, F4, C4 and T4.

$$\text{F8}=0-\frac{40+80+40+0}{4}=-40\mu V$$

4.5.1.4 Bipolar Derivations

In bipolar derivations, the potential difference is calculated between electrode pairs, placed along chains (longitudinal or transversal) in which an electrode is shared with two following channels.

In this way, an event localized underneath a specific electrode will generate a deflection with the same voltage, but opposite polarity, in the two adjacent points in the chain of the electrode.

Figure 4.14a shows how the previously described theoretical example of common reference (maximum negative potential at F3 electrode) appears using bipolar derivation. The phenomenon known as *phase-reversal*, typical of bipo-

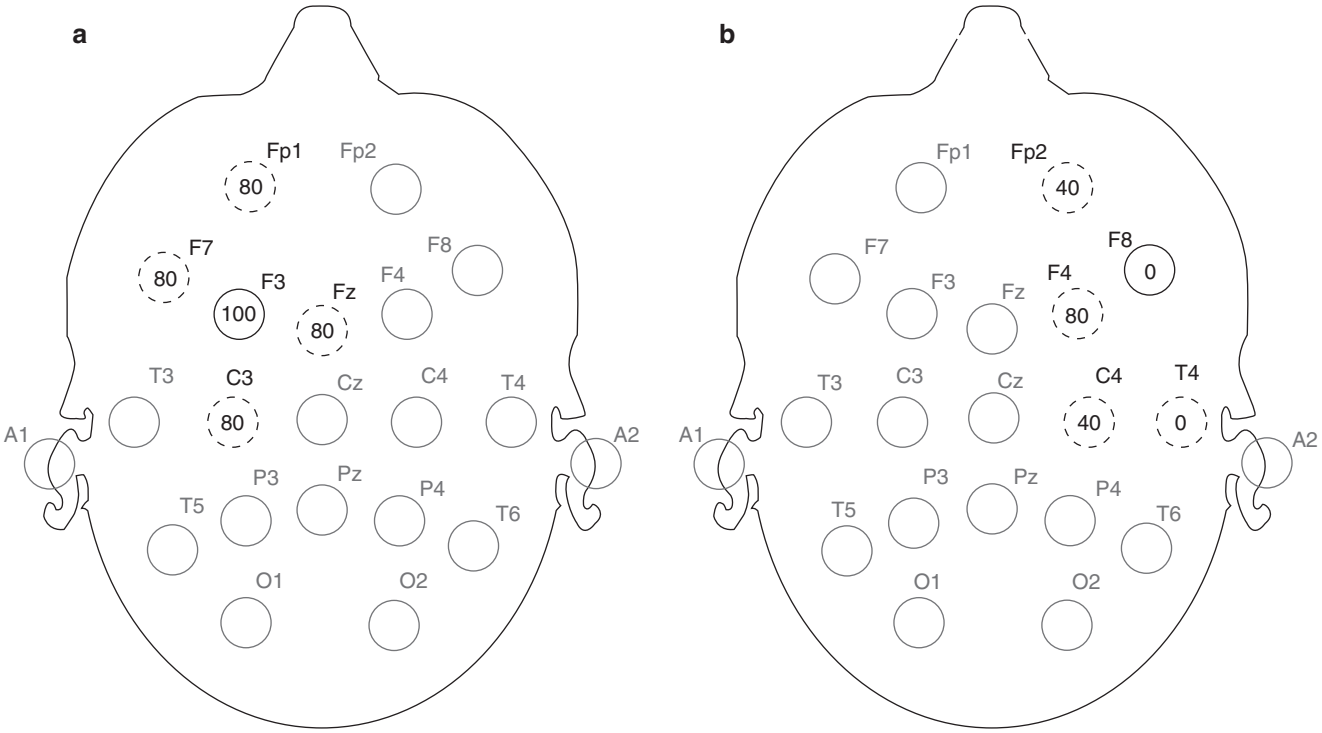

Fig. 4.13 Comparison between the absolute potential of F3 and F8 obtained with "inactive" common reference (CR) and that deriving from source derivation (SD) method. The dotted circles indicate the electrodes used for the source derivation. In (**a**) the absolute potential of F3. In (**a**) the absolute potential of F3 with CR is 100 μV and with SD 20 μV. In (**b**) the absolute potential of F8 is 0 μV with CR and—40 μV with SD

lar montages and caused by the fact that an electric event affects the electrode in the middle of the chain, occurs between channels 1 and 2. In this case, F3 localizes the maximum field and the reverse phase is due to the fact that it is a common electrode to the first and second channel. This is an *instrumental phase reversal,* because it is the instrument that causes the phase reversal; it must be distinguished from a *true phase reversal*, due to two different polarities simultaneously present in adjacent cortical areas.

When the maximum potential field is equally distant from the F3 and C3 electrodes (Fig. 4.14b), the second channel will not record any potential difference (zone of isopotentiality), while the phase reversal will be observed between the first and the third channel. Finally, if the maximum potential field takes place at the end of the chain (Fig. 4.14c), the only positive deflection will be detected in the channel connecting C3 with P3, possibly causing a wrong interpretation of the phenomenon. The phenomenon of phase reversal is shown also in Fig. 4.15.

Using bipolar derivations for a correct focal localization of the bioelectrical events, it is necessary to simultaneously display two electrode chains, placed perpendicular to each other: an accurate and exact localization is possible only when the phase reversal occurs at the point where the two lines intersect. In Fig. 4.16, the maximum focal field is localized in the quadrangle enclosed between the Fz, F4, C4 and Cz electrodes, with its relating isoelectric line on the channels connecting orthogonally the F4–C4 and C4–Cz electrodes. In conclusion, bipolar derivations have a remarkable localization ability but, in order to achieve this, it is essential that the various interelectrode chains are displayed simultaneously (anteroposterior and transversal).

With the bipolar montage, it is harder to compare the asynchrony between two homologous regions and it is difficult to map the voltage of a specifically localized event. It is also important to remember that in-phase activities affecting both inputs of the differential amplifier are evened out: therefore, spikes generating a fairly extensive area can be completely obscured or only partially shown. The opposite can also happen though: if a spike is positive in F4 and negative in C4, by pairing F4–C4 we will see a "false" spike of higher amplitude (addition-out-of-phase).

As already pointed out, recent digital EEG systems always use a reference derivation in signal acquisition, measuring the potential of each electrode with reference to a common electrode (G2).

With these systems it is possible, both online and offline, to reformat any type of montage and, thus, to display the tracing both in reference (common or AVG) and in bipolar derivation. To reformat a bipolar derivation starting from the one using G2 as a common electrode, the computer executes the following process:

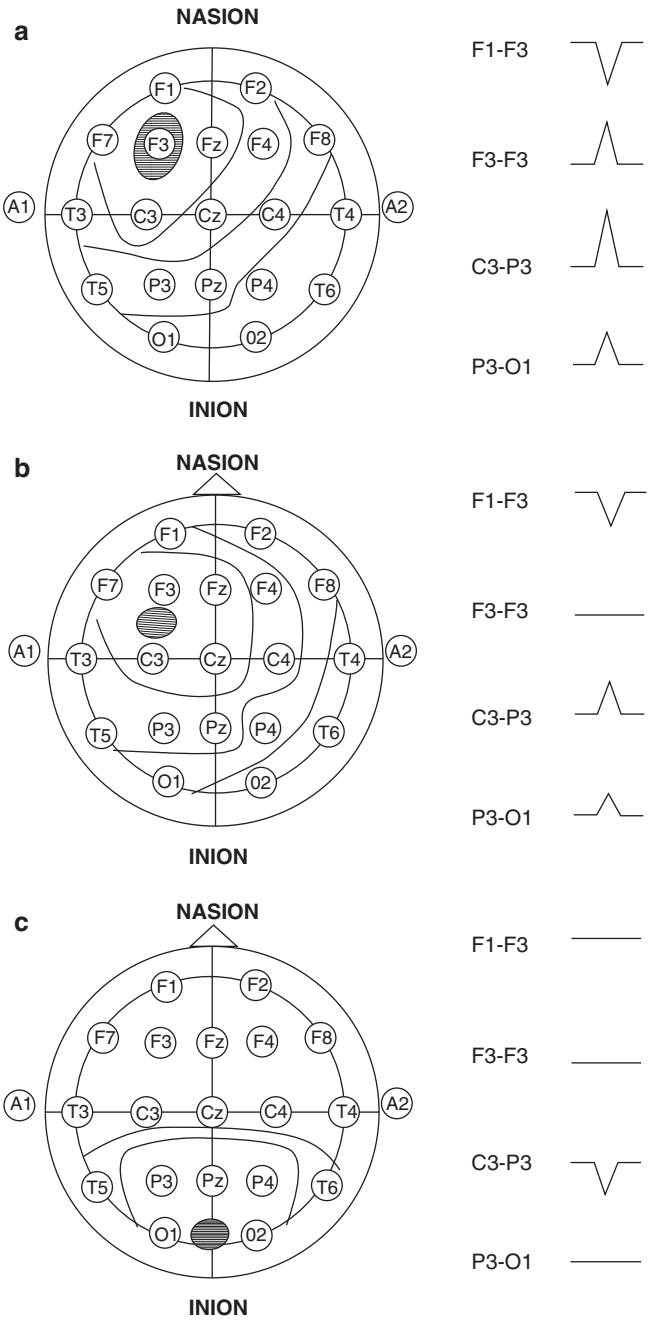

Fig. 4.14 Bipolar derivation recording (see text for explanation). (**a**) maximum negative potential at F3 electrode, phase reversal phenomenon; (**b**) zone of isoipotentiality when maximum potential field is equally distant from F3 and C3; (**c**) maximum potential field at the end of the chain: only positive deflection will be detected in the channel connecting C3 with P3

$$\left(\mathrm{Fp2}-\mathrm{G2}\right)=\mathrm{A}$$

$$\left(\mathrm{F4}-\mathrm{G2}\right)=\mathrm{B}$$

$$\mathrm{A}-\mathrm{B}=\left(\mathrm{Fp2}-\mathrm{G2}\right)-\left(\mathrm{F4}-\mathrm{G2}\right)=\mathrm{Fp2}-\mathrm{G2}-\mathrm{F4}+\mathrm{G2}=\mathrm{F2}-\mathrm{F4}$$

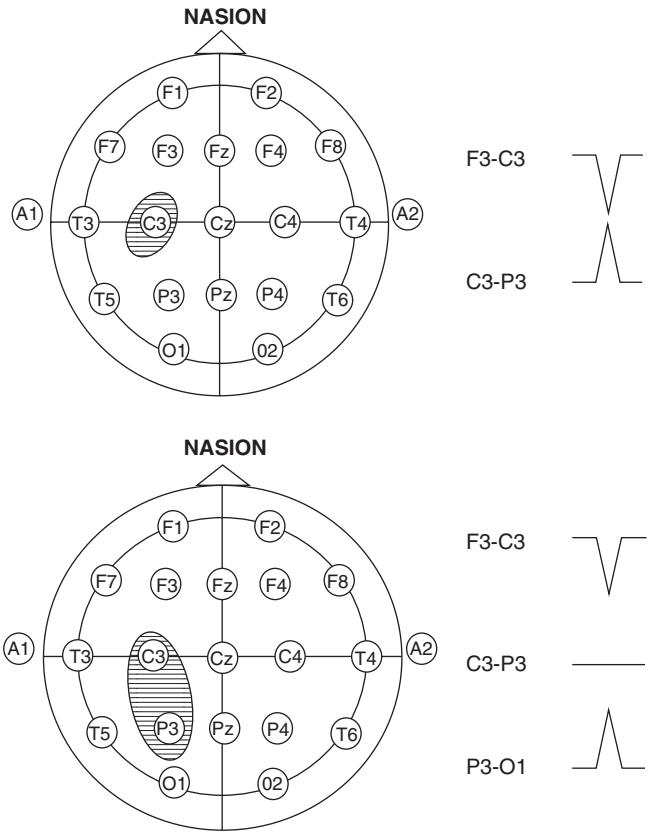

Fig. 4.15 Schematic representation of an instrumental phase reversal phenomenon between F3–C3 and C3–P3 channels. A maximum field potential underneath C3 will be observed in phase reversal on the two channels having C3 in common (*above*) while, if the event equally affects the two adjacent electrodes C3 and P3, the potential will be cancelled on the channel connecting these two electrodes (*below*)

Through this simplified mathematical calculation, the computer is able to reformat the montage and show it as bipolar, subtracting the value of G2 electrode, used as reference.

4.5.1.5 Choice of Derivation in Clinical Practice

Since EEG patterns are variable (focal or diffuse, transient or persistent), there is not one single ideal derivation to highlight all cerebral activities. A first important factor to take into account in the choice of derivation is the *interelectrode distance*, and this is particularly valid for active common references and bipolar derivations. In bipolar derivations, distances between the paired electrodes are small and equal, favouring the detection of the fast EEG activities; in active common reference, distances are bigger and unequal, facilitating the amplification of the signal, thus better showing the slower activities.

Focal epileptic activity is a phenomenon that provokes a change in the potential, limited to a small part of the scalp. In order to accurately localize a strictly isolated focal potential with bipolar derivations, it is necessary to demonstrate the simultaneous phase reversal at the point of intersection between two electrode chains placed perpendicular to each

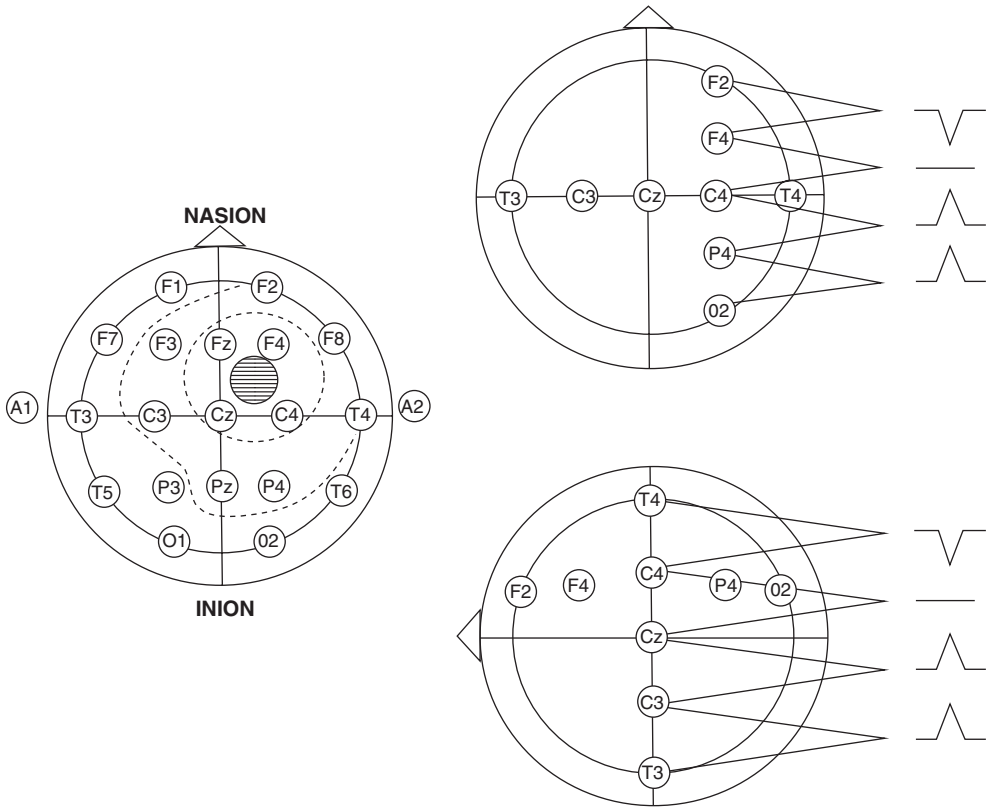

Fig. 4.16 In bipolar derivations the correlation between longitudinal and transversal interelectrodic chains allows a more accurate localization of focal event with the identification of phase reversal and isopotentiality phenomena (see text for further explanation)

other: therefore, it is necessary to use a suitable montage and, sometimes, to also apply additional electrodes.

Common reference does not present such limitations and it has some advantages, especially for the detection of an epileptic activity with a not very good localized focus; it is important, though, to be sure that the chosen reference is not contaminated by the activity of the phenomenon itself (e.g., in case of a focus with centrotemporal spikes, the ideal common reference is placed on the contralateral auricular lobe).

Average reference seems to be the preferable technique, even if the problem of contamination still exists for all channels (it is thus advisable to calculate the correct average reference, obtained by excluding the most active electrodes from the average calculation). When the focus is recorded by multiple electrodes, the phenomenon is better showed using common reference (preferably inactive), which provides a better definition of the potential distribution and of the shape of the wave.

In order to correctly identify and localize any focal activity, it should always be best to use more than one derivation. Generally, it is important to bear in mind some important considerations:

- Common reference allows to locate focal activity with higher voltage and with the same polarity.
- Average reference shows a wider signal underneath one or more electrodes, but of opposite polarity than the majority of other electrodes.
- Bipolar derivation localizes focal activity highlighting the phase reversal or cancellation of the signal (zone of isopotentiality).

Figure 4.17 shows how visualization of a real right temporal epileptic focus, recorded with a digital system, which varies depending on the displayed derivations.

Most of EEG diffuse activities are correctly evidenced by bipolar derivations, while average reference (AVG) can be misleading, possibly showing a localized phenomenon as a diffuse one. However, with bipolar derivation, the potential differences between adjacent electrodes are recorded and there are no indications regarding the activity of each electrode with respect to a distant reference point; in addition, bipolar derivation can show a reduction in signal amplitude or, within a widespread pattern, it can underestimate focal amplitude reductions, which has the same localization value as spikes. Generally, EEG diffuse activities are better evidenced by a common reference derivation, but the reference electrode should not be affected by the studied activity and so, when this is not possible, it should be placed in a way that allows equal recording of both hemispheres. An extracranial medial reference, for example, can be used. Fig. 4.18 shows a widespread spike-wave discharge, predominant anteriorly, with the three recording methods.

To summarize, the main advantages and disadvantages of the derivation systems are the following:

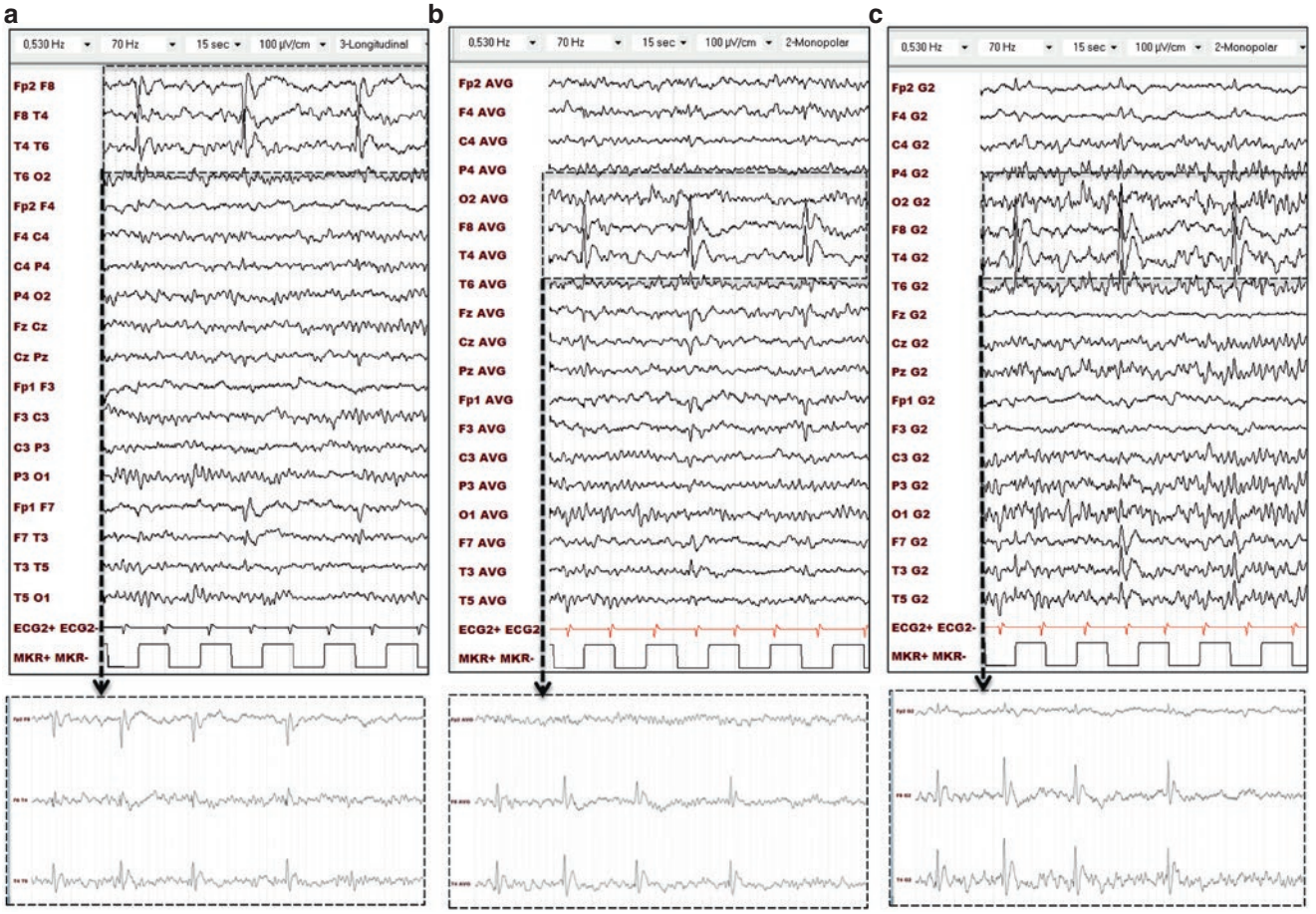

Fig. 4.17 The same EEG epoch of 5 s shows a right temporal epileptic focus in bipolar, AVG reference and common active reference derivations. In (**a**) (bipolar derivation) the phase reversal phenomenon in the first and third channel is evident, with almost total cancellation of the spikes in the intervening channel F8–T4 (these electrodes are placed over the focus and their potentials presumably have the same polarity and voltage as input to the differential amplifiers); note the poor spread of spikes to the homologous contralateral areas. The AVG reference derivation (**b**) confirms the higher negative signals at F8 and T4 electrodes; note, however, that positive signals are present also in Fz, Cz, Fp1 and F3, and negative in F7 and T3. When a common active electrode of reference is used (**c**) (G2, placed on midline in Fpz), the signal shows the same negative higher voltage in F8 and T4, with the evidence of synchronous lower negative signals contralaterally in F7, T3 and T5. However, in this practical example, all three derivations allow to localize the epileptogenic focus with good reliability (T4, T6, T3, T5 = T8, P8, T7, P7 according to the new nomenclature)

1. Common reference derivation.
   (a) Good localization of any kind of focal activity (including low-voltage or flat activity).
   (b) Good wave-shape definition.
   (c) Acceptable localization of the most common artefacts.
   (d) Good mapping of diffuse activity.
   (e) Acceptable evaluation of bilateral synchrony of homologous areas.
   (f) If the reference is not inactive, its activity will "contaminate" the related electrodes, compromising the above-listed advantages.
2. Average reference derivation.
   (a) Acceptable localization of transient focal graphoelements
   (b) Poor wave-shape definition (except for sharp focal potentials on a low-voltage background activity)
   (c) Unsatisfactory highlighting of areas with low-voltage activity
   (d) Poor artifact localization
   (e) Unreliable in cases with high-voltage asynchronous diffuse activity
   (f) Unreliable when one or several electrodes record high-amplitude activity, influencing the calculation of the average too much
3. Bipolar derivation
   (a) Good localization of transient focal activity
   (b) Good definition of bilateral synchrony-symmetry of homologous areas
   (c) Good localization of the most common artefacts

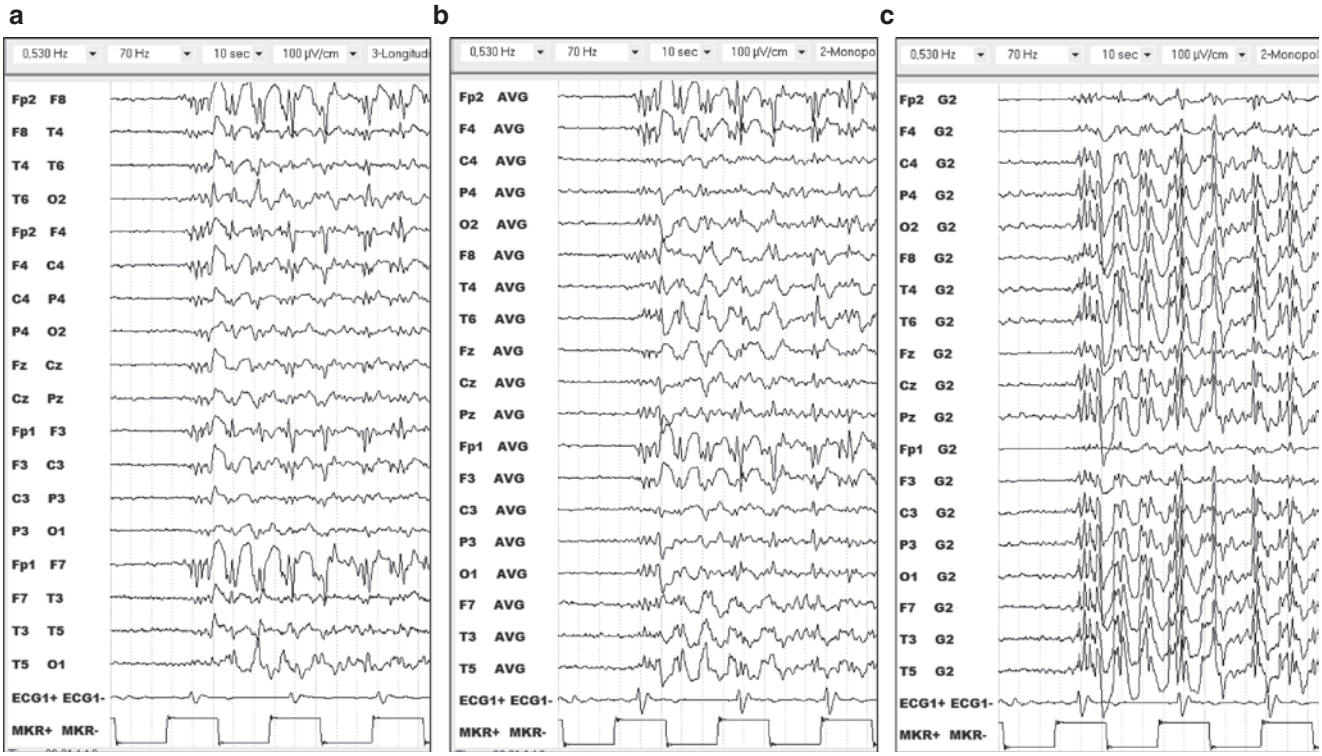

Fig. 4.18 Diffuse discharge of polyspikes and spike-and-wave complexes, predominantly in anterior areas. The bipolar (**a**) and AVG reference derivation (**b**) show the real characteristic of discharge, while the common active reference derivation (with G2-reference electrode placed in Fpz) is misleading (**c**). In (**c**) the contamination reference is very evident and the electrodes with larger signals are precisely those closest to the reference electrode; in them, therefore, the recorded activity is significantly reduced in voltage (T4, T6, T3, T5 = T8, P8, T7, P7 according to the new nomenclature)

(d) Poor mapping of diffuse activity
(e) Poor or non-existent emphasizing of areas with absence or reduction in signal voltage
(f) Suppression or reduction in amplitude of in-phase activity on a pair of electrodes (isopotentiality areas)
(g) Not always good wave-shape definition

4.5.2 Montages

A montage is the specific method of electrode connection to the recording channel of the electroencephalograph. With 21 electrode positions in the 10-20 system and 16 channels on display, the number of possible montages is 21. The 10-10 system, with more than 70 electrode positions, allows the creation of an even higher number of montages and the modern digital EEG machines allow the display of up to 256 channels.

A wide range of montages, many of which are complex and inadequate, is used in EEG laboratories for routine recordings. This dissimilarity prevents the correct exchange of information between experts in the field. To counteract this, both the International Federation of Clinical Neurophysiology (IFCN) and the American Clinical Neurophysiology Society (ACNS) have published some guidelines which include ad hoc recommendations [7, 13].

The montages for routine EEG recording are designated as Longitudinal Bipolar (LB), Transverse Bipolar (TB), or Referential (R). Montages are designed for 18, 20, 26 and more channels. Here we report a list of the main recommendations drawn from the above-mentioned guidelines:

- Not less than 16 channels of simultaneous recording should be used (a larger number of channels would be encouraged).
- At least 21 electrodes should be placed following the 10-20 system (the IFCN recommend at least 25 electrodes, including the inferior temporal chain) [7].
- Both bipolar and referential montages should be used for clinical interpretation.
- The electrode derivations of each channel should be clearly identified at the beginning of each montage, so that the pattern of electrode connection is made as simple as possible and easily comprehensible.
- In bipolar derivations, electrode pairs should run in straight lines and their interelectrode distance should be kept equal.
- Channel progression must be anterior-posterior.

Guidelines also recommend that a single channel Electro Cardio Gram (ECG) should be included on one EEG channel.

According to IFCN and ACNS, channels obtained by connecting the left-side electrodes should be above the right-sided ones. This recommendation coincides with the prevailing practice of the vast majority of EEG laboratories in North America and in other areas, but it is not followed in Italy and in many other European countries. In this book, according to the tradition of the Italian and European neurophysiological academic school and the totality of clinical practice in our country, the right-sided leads are placed above the left-sided leads for either blocks of derivations.

Regarding referential montages, the choice of reference is critically important. For the ACNS, a midline electrode (as Cz) would be a better choice of reference than A1 or A2. However, the referential suggested montages by ACNS establish the right auricular electrode (A2) as reference for the electrodes on the right side and the left auricular electrode (A1) for the ones on the left side.

Currently, in digital electroencephalography, the G2 reference electrode can be used as an "active" reference, placing it on the midline, anteriorly to Fz.

Figures 4.19 and 4.20 show suggested bipolar longitudinal and transverse montages with the extended standard array. Table 4.1 shows bipolar (old and new) and referential suggested montages. According to 10-10 position nomenclature, T4, T6, T3 and T5 should be changed to T8, P8, T7 and P7.

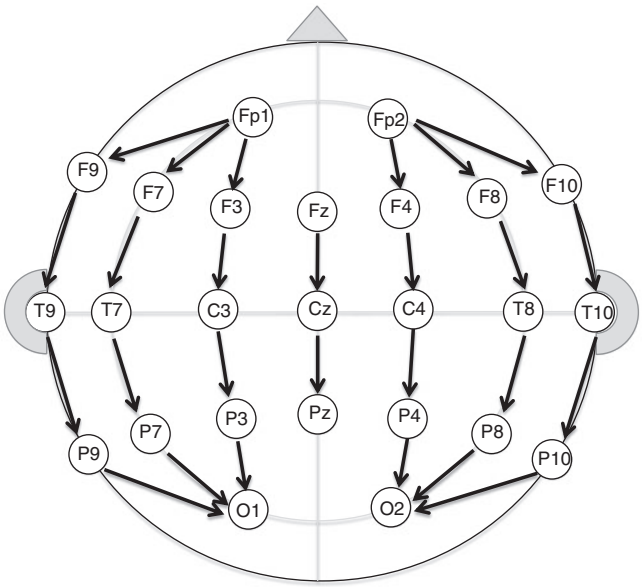

Fig. 4.19 New longitudinal bipolar montage proposed by International Federation of Clinical Neurophysiology (IFCN) [7]

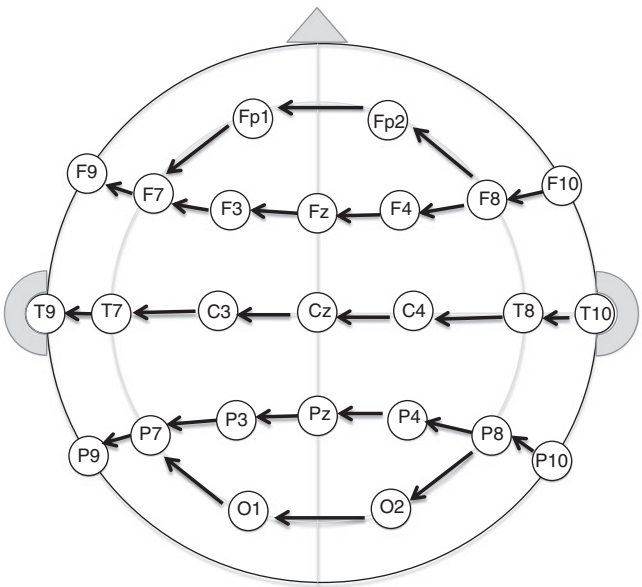

Fig. 4.20 New transverse bipolar montage proposed by International Federation of Clinical Neurophysiology (IFCN) [7]. Note that the interelectrode distance between the inferior and superior temporal electrodes is shorter (10%) compared to the other interelectrode distances (20%)

Table 4.1 Suggested old/new Longitudinal Bipolar (LB) and Transverse Bipolar (TB) and referential montages with the extended standard array [7]

No. channel	LB montage (old)	No. channel	LB montage (new)	No. channel	TB montage (old)	No. channel	TB montage (new)
1	Fp2—F8	1	Fp2—F10	1	F8—Fp2	1	F8—Fp2
2	F8—T8 (F8–T4)	2	F10—T10	2	Fp2—Fp1	2	Fp2—Fp1
3	T8—P8 (T4–T6)	3	T10—P10	3	Fp1—F7	3	Fp1—F7
4	P8—O2(T6–O2)	4	P10—O2	4	F8—F4	4	F10—F8
5	Fp2—F4	5	Fp2—F8	5	F4—Fz	5	F8—F4
6	F4—C4	6	F8—T8	6	Fz—F3	6	F4—Fz
7	C4—P4	7	T8—P8	7	F3—F7	7	Fz—F3
8	P4—O2	8	P8—O2	8	T8—C4 (T4–C4)	8	F3—F7
9	Fz—Cz	9	Fp2—F4	9	C4—Cz	9	F7—F9
10	Cz—Pz	10	F4—C4	10	Cz—C3	10	T10—T8
11	Fp1—F3	11	C4—P4	11	C3—T7 (C3–T3)	11	T8—C4
12	F3—C3	12	P4—O2	12	P8—P4 (T6–P4)	12	C4—Cz
13	C3—P3	13	Fz—Cz	13	P4—Pz	13	Cz—C3
14	P3—O1	14	Cz—Pz	14	Pz—P3	14	C3—T7
15	Fp1—F7	15	Fp1—F3	15	P3—P7 (P3–T5)	15	T7—T9
16	F7—T7 (F7–T3)	26	F3—C3	16	P8—O2 (T6–O2)	16	P10—P8
17	T7—P7 (T3–T5)	27	C3—P3	17	O2—O1	17	P8—P4
18	P7—O1 (T5–O1)	18	P3—O1	18	O1—P7 (O1–T5)	18	P4—Pz
19	ECG	19	Fp1—F7	19	ECG	19	Pz—P3
		20	F7—T7			20	P3—P7
		21	T7—P7			21	P7—P9
		22	P7—O1			22	P8—O2
		23	Fp1—F9			23	O2—O1
		24	F9—T9			24	O1—P7
		25	T9—P9			25	ECG
		26	P9—O1				
		27	ECG				

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EEG Signal Acquisition

5

Cristiano Rizzo

5.1 Introduction

Electroencephalography (EEG) signal acquisition originated in the 1930s, but not until the development of digital systems in the 1980s was there a significant impact on the technology, particularly with respect to EEG signal analysis.

Before digital technology, EEG systems were analogues, recording signals using pens directly onto paper that didn't allow any further modifications or processing. It was only possible to inspect or "read" the ink tracing and add some handwritten comments or observations.

The adoption of digital technologies allowed the data to be stored into a computer and subsequently processed and displayed. This has opened new opportunities for the user to analyse and display the data which has changed the way EEG data is "read". Not only is the EEG now read on a high-resolution PC screen and manipulated, but the screen can display additional information that is of added value to the reporting process.

In order to appreciate the significance of digital electroencephalograph, this chapter will explore the structure of a modern data collection system to identify the different components and understand their function. The next chapter describes some of the ways data can be processed and/or analysed.

This chapter presents information that is essential for the overall understanding of a digital electroencephalograph system. Other information that is not essential will be found as notes or in the appendix and can be read only if deemed necessary. This is to simplify the text for those who want an overview of the topic but also provides more detailed information for those who wish to understand more.

5.1.1 Digital EEG System Structure

A digital electroencephalograph (Fig. 5.1) is a system composed of the following main elements:

Fig. 5.1 Digital electroencephalograph

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1. Data acquisition devices
   (a) EEG "headbox" - Amplifier
   (b) Video camera
2. Manual input devices
   (a) Keyboard
   (b) Mouse
3. Stimulation devices
   (a) Photic stimulator
4. Output devices
   (a) Monitor
   (b) Printer
5. Processing devices
   (a) Computer
6. Recording accessories
   (a) Electrodes
   (b) Caps
   (c) Conductive gel
7. Supports
   (a) Carts
   (b) Arms/stands

The *data acquisition devices* are the core of the system and convert the analogue signals and visual images collected from the patient to a digital representation that can be stored in a computer. The main component of the entire EEG system is the *headbox* and collects the EEG data from the patient and will be the subject of most of this chapter. The *video camera* is the device that records the continuous image (video) of the patient and is closely synchronized with the electrical (EEG) information. Section 5.5 describes the Video in more detail.

The *input devices*, usually a *keyboard* and *mouse*, allow the user to enter additional information into the system and to control the system functionality.

The *stimulation devices* are used to deliver controlled stimuli to the patient with the objective of stimulating a controlled response, for example, to induce an epileptic seizure. The most common example of a *stimulation device* is the *photic stimulator* that emits a powerful flash (up to 2 J/stimuli) at a given frequency and intensity and for a selectable duration. The first photic stimulators used a xenon lamp to generate the light. These lamps had the ability to deliver very powerful bursts of light for very short durations. However, they have now been replaced with high-power LED (light-emitting diode) systems which have similar, or even better, characteristics. For additional information on the use of the photic stimulator, see Chap. 13.

The *output devices* provide the user with feedback and output from the system. This includes the *monitor*, where the EEG and additional information is displayed (see Sect. 5.4.3), and the *printer*, where information and results can be printed for a permanent record (see also Sect. 5.4.4).

The *processing devices* include the *computer*, which always hosts a *processor*, that performs all the basic analysis, an internal *RAM—random access memory*—to temporarily store the data (typical values are 4–8 Gb) and programmes necessary to run the analysis, at least one *hard disk* to permanently store the data (typical values are 500 Gb to 1 Tb) and usually a *CD/DVD reader/writer* to read and/or write data onto external media that can be read on any PC. The computer will have several interfaces or *communication ports* (i.e. network,[1] serial port,[2] USB port[3]), allowing the computer to communicate with the various peripherals including the *input and output devices*. One particular type of interface are the *synchronization devices* commonly referred to as *trigger IN* and *trigger OUT*; these are communication ports that allow the user to send and receive very simple signals (typically TTL[4]) used to synchronize devices. The trigger IN port of an EEG system receives synchronization signals from external devices (e.g. a photic stimulator), while the trigger OUT port of an EEG system can send synchronization signals to peripheral devices that need to be driven or controlled. In general, the role of the computer is to process all the data coming from input devices and data acquisition devices and provide the user with feedback and control through the output devices.

The *recording accessories* are the *electrodes*, *caps*, *conductive gel* and other transducers that interface or connect the patient to the headbox. Information about these accessories can be found in Chap. 3 of this book.

The *supports* consolidate the system into a single unit for ease of use and functionality. They are typically the *cart* and the various arms and support frames that hold the amplifiers, computer and other devices.

5.2 Analogue Components

5.2.1 EEG Signal Detection: The Electrodes

The electrodes, which include all the signal detection devices like the caps, wire electrodes, belts and other transducers, connect directly to the patient and play a fundamental role in

[1] The *network* interface supports very fast communication between PCs. The kind of interface depends on the communication standard, but currently all PCs use the Ethernet standard 10/100 or Gigabit Ethernet. Wireless networks are also common, often called WiFi (technical name of IEEE 802.11) which support speeds from 11 to 54 Mbps or even higher with the new standards.

[2] The *serial port* is a standard serial communication that transmits data at low speeds between different devices. This has been replaced with the USB Port (see next note).

[3] The *USB port* (*Universal Serial Bus*) is a standard serial communication protocol for high speed communication between different devices. It is now the most common standard and is available on almost any PC or device with multiple different connector types.

[4] The *standard TTL* (transistor-transistor logic) is a binary standard, using just 0 and 1, where "0" is associated with a voltage between 0 and 0.8 V and "1" is associated with a voltage between 2 and 5 V. This is why it is often referred to as the 0–5 V standard.

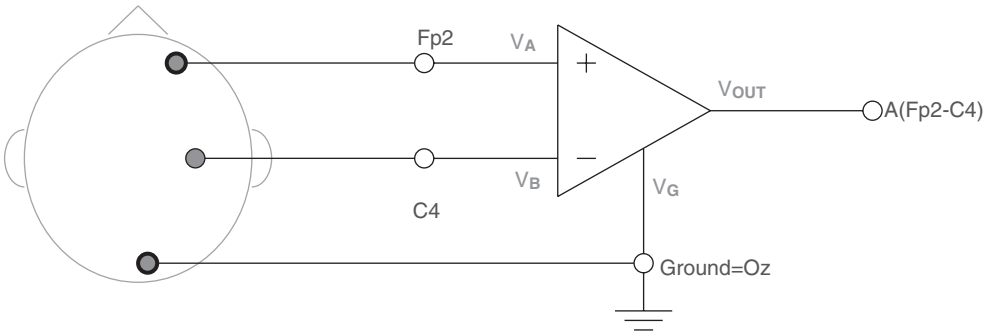

Fig. 5.2 Differential amplifier

the EEG signal acquisition. They represent the connection between the location where the signal is measured and the amplifier. Given their fundamental importance and the number of different electrodes available on the market, this book has a dedicated chapter on this topic (Chap. 3).

5.2.2 EEG Acquisition System: The Differential Amplifier

EEG signals are normally acquired using a differential amplifier. This is a component that measures small electrical potential difference between two points and then amplifies several times that potential for recording.The general design of a differential amplifier, connected to two points on the scalp, can be represented by Fig. 5.2.

The amplifier has two inputs, normally referred to as inverting input and non-inverting input. The amplifier then measures and amplifies the difference of potential between these two inputs, that is[5]:

$$V_{OUT} = A\left(V_A - V_B\right)$$

where V_{OUT} is the measured voltage, V_A the voltage at the inverting input, V_B the voltage at the non-inverting input and A is the amplification factor. In the case of an EEG signal, the amplification factor is in the range of 10,000 and increases the measured voltage, normally in the range of 500 μV, to become compatible with the voltage normally used in electronic circuits that are in the range of a few volts. The exact value of this amplification factor is not relevant for the user because it is made redundant by the signal processing, and for the sake of simplicity, it will be omitted, and a simplified version of the formula will be used:

$$V_{OUT} = \left(V_A - V_B\right)$$

The measured voltage V_{OUT} is theoretically referenced to a potential normally called "ground"[6] and highlighted in Fig. 5.2 as V_G, so that:

$$V_{OUT}=(V_A-V_G)-(V_B-V_G)=V_A-\cancel{V_G}-V_B+\cancel{V_G}=V_A-V_B$$

The formula shows that the value of the measured voltage is independent of the ground potential. However, this is only true if the amplifier can effectively measure the voltages $(V_A - V_G)$ and $(V_B - V_G)$; if not, the amplifier could "saturate" and measure V_{OUT} incorrectly. As a result, although the electrode that detects the ground potential could, theoretically, be placed in any location on the patient, its position must actually consider the possible saturation effect and should always be positioned close to all the other electrodes to minimize the difference of potential between them.

In reality, signal amplification is not perfect and cannot be simplified to the extent shown in the formula. As a result, several parameters have been defined to evaluate the ability of an amplifier to amplify the signal. The most common parameters for this evaluation are the CMRR (Common Mode Rejection Ratio), the *internal noise* of the amplifier, its *input impedance* and its *bandwidth*.

CMRR is an index of the rejection of common noise between two inputs of the amplifier (inverting and non-inverting). If the same noise is present at the two inputs (very common in practice), this noise should be completely cancelled by the amplifier because of its "differential" nature. In other words, because the amplifier is only detecting the difference of potentials between the two inputs, any common

[5]Note that, according to the electronic naming convention, the non-inverting input should be highlighted with the symbol "+" that, in the above example, corresponds to Fp2, and the inverting input should be highlighted with the symbol "−" that, in the above example, corresponds to C4. Consequently, the signal Fp2-C4 should have positive signals going up and negative signals going down. However, in the EEG naming convention, for historical reasons, all signals are drawn in reverse, and the notation Fp2-C4 implies that a positive Fp2 signal will go down (i.e. an eye blink). This inversion is commonly done by the display system together with inverting the amplifier input. For the sake of simplicity, the electronic naming convention is used in this text, assuming that the inversion is performed by the display system.

[6]The name "ground" for the reference potential is misleading because it is not in contact with the real ground or earth of the power supply but is in fact just a "common" potential for the measurement. Despite "common" being a more appropriate term, "ground" is used in this text following the common terminology used in the EEG field.

noise should be eliminated. In practice, the common noise is not perfectly cancelled but is significantly attenuated. For example, a common noise of 1 V will not be cancelled entirely but will result in a component of noise typically about 1 μV. The value of the CMRR is measured in dB to highlight the attenuation factor and is calculated as follows[7]:

$$\mathrm{CMRR} = 20\log_{10}\left(V_{\mathbf{IN}} / V_{\mathbf{OUT}}\right)$$

Using the values of the example this becomes:

$$\mathrm{CMRR} = 20\log_{10}\left(1\,\mathrm{V}/1\,\mu V\right) = 20\log_{10}\left(1{,}000{,}000\right) = 20\times 6 = 120\,\mathrm{dB}$$

The value recommended by [1] is 110 dB, and amplifiers currently on the market have values around 100 dB or higher.

The *internal noise* of the amplifier is the value of the output when all inputs are set to zero. Theoretically according to the formula, the output should be zero, but, in practice, the circuits that compose the amplifier produce some noise that by design should be minimized. Normal values for this noise[8] are a few μV, if measured peak to peak (indicated as $\mu V_{\mathbf{PP}}$), or below 1 μV, if measured as effective value (indicated as $\mu V_{\mathbf{RMS}}$).[9]

The *input impedance* of the amplifier is a parameter that indicates the resistance to current flow through the amplifier as a function of the applied voltage. Its value should be as high as possible and is typically in the range of hundreds of MΩ or higher.

The *bandwidth* of the amplifier defines the operating frequency range of the amplifier. If the lower limit of the bandwidth is 0 Hz, the amplifier is called a DC-amplifier (direct current) and can record very slow potentials.[10] In all other cases, the amplifier is called an AC-amplifier (alternating current) and will have a cut-off frequency below which all potentials will be significantly attenuated.[11] The lower limit of the amplifier bandwidth should be selected based on the signal to be recorded, typically in the range of a tenth of a Hertz (i.e. 0.1 Hz). Values for this limit are shown in Table 5.1 and in Sect. 5.3.4 where the upper limit of the bandwidth is shown and which is always correlated to the anti-aliasing filter that is necessary for sampling.

5.2.3 EEG Acquisition Technique: Common Reference and Bipolar Electrodes

One of the biggest advantages offered by digital EEG is that the signals are no longer recorded in an unmodifiable way on paper but acquired and stored in a format capable of post-processing and display. This big advantage is used by digital systems to record not the potential differences between only two electrodes, as on paper EEG, but to record the potential difference between each electrode and, through a common electrode, any other electrode. For this reason the common electrode is called a common reference. A common reference amplifier design is shown in Fig. 5.3.

Figure 5.3 only shows four electrodes with common references, but this can be extended to any number of channels in a recording system. The common reference electrode is connected internally to the inverting input of each differential amplifier, and the ground electrode is connected internally to each differential amplifier. Consequently in order to record, for example, a 19-channel EEG, it is necessary to apply 21 electrodes to the patient, 19 so-called active electrodes plus the common reference and the ground. Generally speaking, to record N channels, N + 2 electrodes have to be applied.

Once all the active electrode potentials are recorded with respect to a common reference, any specific signal between any two electrodes can be calculated using simple subtraction[12] for example:

$$(\mathrm{Fp2\text{-}Ref})\text{-}(\mathrm{C4\text{-}Ref}) = \mathrm{Fp2}\text{-}\cancel{\mathrm{Ref}}\text{-}\mathrm{C4}+\cancel{\mathrm{Ref}}=\mathrm{Fp2\text{-}C4}$$

The formula illustrates that the result does not depend on the position of the common reference electrode, at the condi-

[7] Note that the CMRR value can vary as a function of the frequency of the signal. As a result, when a CMRR value is specified, it should always be accompanied by the frequency, or the bandwidth, of the signals.

[8] Note that the internal noise of the amplifier can vary as a function of the bandwidth of the signal so that when an internal noise value is specified, it should always be accompanied by the frequency, or the bandwidth, of the signals used for the measurement.

[9] The approximate value of the internal noise, measured as peak to peak, can be obtained from the internal noise measured as the effective value (or RMS—Root Mean Squared) using the following formula:

$$V_{\mathrm{PP}} = 2\times\sqrt{2}\times V_{\mathrm{RMS}}$$

The approximation is that this formula is valid only for sinusoidal signals.

[10] With respect to DC amplifiers, see Chap. 3 where the problems generated by the coupling with the recording electrodes are discussed.

[11] Note that below the *cut-off frequency* of a *high-pass filter*, the signal is not completely cancelled but only attenuated, and its attenuation becomes higher and the signal approaches zero the further the signal is away from the cut-off frequency. The same applies for the low-pass *filter*: above the cut-off frequency, the signal is not completely attenuated, and its attenuation becomes higher the further the signal is away from the cut-off frequency. Note that, by definition, at the cut-off frequency, the signal has an attenuation of 70% meaning that a signal of 100 μV is attenuated to 70.7 μV.

[12] This assumption depends on the fact that the EEG fields have been demonstrated to be *conservative fields*, which means that given three points A, B and C and measuring $V_A - V_C$ and $V_B - V_C$, the potential $V_A - V_B$ can be obtained as the difference of the first two.

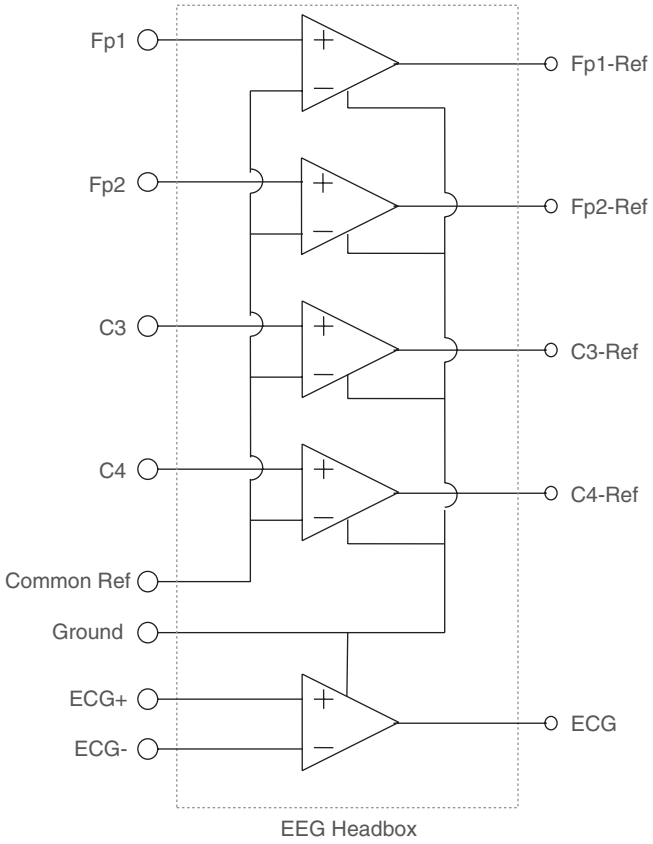

Fig. 5.3 Common reference acquisition

tion to avoid any saturation of the recorded signal. Saturation can occur in two different ways:

1. Both recorded potentials (Fp2-Ref) and (C4-Ref) saturate: in this case, the display of Fp2-C4 will be a flat line because the difference between two saturated signals (which implies they are both at the maximum value) is zero. This situation is typical in cases where the potential of the common reference electrode increases due to artefact. In a unipolar montage, this artefact will be seen easily, while in any bipolar montage, only a short flat line will be seen.
2. Only one of the two recorded potentials (Fp2-Ref) or (C4-Ref) saturates: in this case, the display of Fp2-C4 will be the signal from the electrode that does not saturate; thus, this problem is very difficult to detect.

Note that in Fig. 5.3, there are a couple of bipolar electrodes (ECG), to show examples of polygraphy electrodes (ECG, respiration and others) that are recorded in bipolar mode and only share the ground electrodes with the EEG channels.[13]

Note that the physical bi-auricular reference is a common reference where two earlobe electrodes are shorted and used as a common reference as shown in Fig. 5.4:

5.2.4 EEG Acquisition System: Noise

What has been described for the differential amplifier is valid under ideal circumstances; however, we must consider the "true" characteristics of the amplifier operating under non-ideal circumstances. The main problem is that the contact between the electrodes and the scalp is never perfect. This imperfect contact is defined as the *contact impedances* and is measured on all the electrodes, including the common reference and ground electrodes, and leads to the susceptibility of unwanted noise detected through the electrodes and the connecting cables. The complete analysis of this interference is very complex and depends on a large number of variables; however, a simplified analysis can be made using the following diagram (Fig. 5.5):

In the diagram, I_P indicates the micro-current that can flow through the patient due to electromagnetic induction (the patient acts as an antenna for the electromagnetic noise) and that reaches the ground. I_C indicates the micro-current that can flow through the cables again caused by electromagnetic induction (the cables form a loop, and an electromagnetic force is induced in the cables following Faraday's Law). Z_A, Z_B and Z_G represent the contact impedances at input A, B and ground respectively, while Z_{IN} represents the input impedance of the differential amplifier. By applying the law of electronic circuits,[14] the output voltage, V_{OUT}, can be calculated as:

$$V_{OUT} = \left[V_A - V_B\right] + \left[I_P \times Z_G \left(Z_B - Z_A\right) / Z_{IN}\right] + \left[I_C \left(Z_A - Z_B\right)\right] = \text{Signal} + \text{Noise}$$

It is clear that the output is two components: the desired signal $V_A - V_B$[15] plus an undesired noise component. To understand the origin of this noise component, representative values can be used for the variables: if it is assumed that the induced micro-current caused by the patient and cable is, respectively, I_P = 0.2 μA and I_C = 10 nA and the contact impedances are Z_A = 10 kΩ, Z_B = 5 kΩ and Z_G = 20 kΩ (which are representative of values seen in practice) and the input impedance of the differential amplifier Z_{IN} = 100 MΩ. The result is:

$$V_{OUT} = \left[V_A - V_B\right] + \left[0.2\,\mu A \times Z_G \left(Z_B - Z_A\right) / Z_{IN}\right] + \left[10\,\text{nA}\left(Z_A - Z_B\right)\right]$$

[13] Note that to record polygraphy channels, it is necessary to always have a ground electrode applied to the patient; otherwise the differential amplifier of these bipolar channels will not have a reference potential and may not work correctly.

[14] Consider the current I_P flows through Z_A and Z_B and then Z_G. Then consider the current I_C in the loop $Z_A - Z_B$, and apply Ohm's Law.

[15] Note that for simplicity, the amplification factor has been omitted.

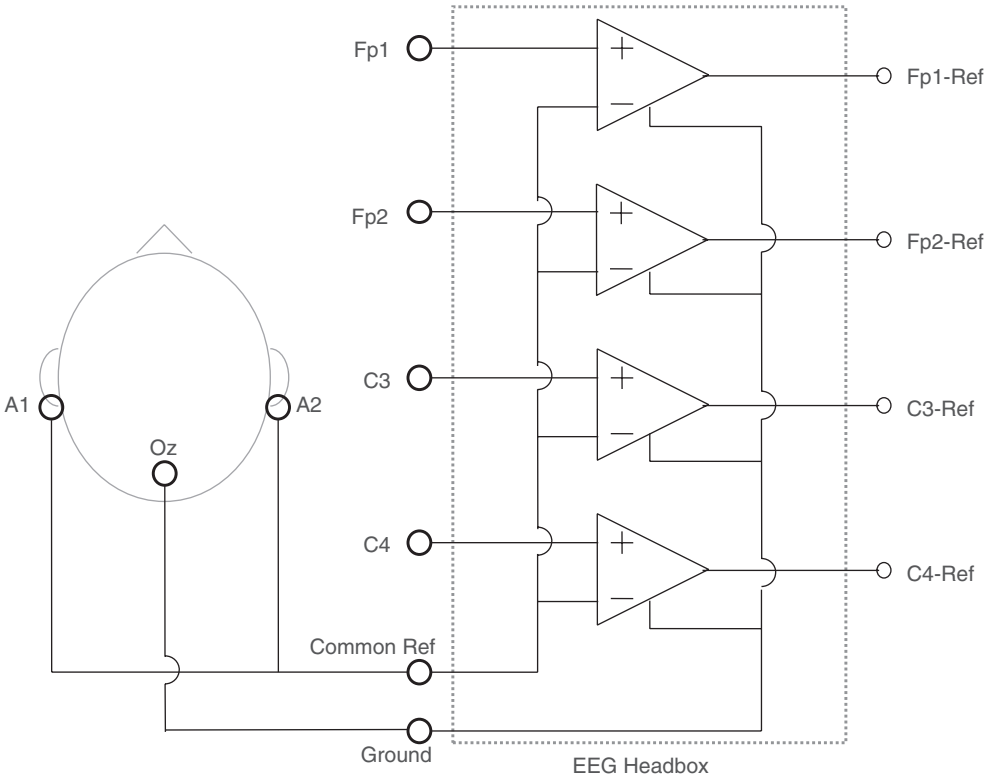

Fig. 5.4 Physical bi-auricular common reference acquisition

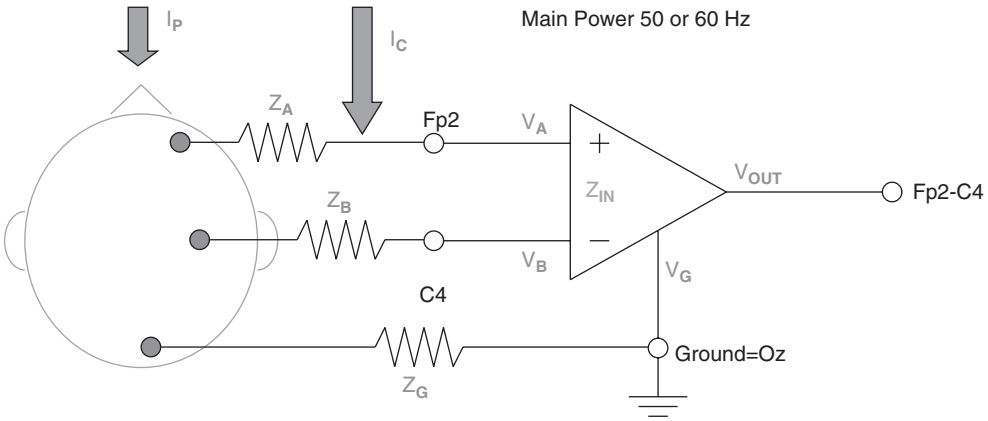

Fig. 5.5 Diagram of noise detected by a differential amplifier

$$V_{OUT} = [V_A - V_B] + [0.2\,\mu V] + [50\,\mu V]$$

Clearly, the majority of the noise is generated by the induction through the cables and can have significant values that are in the same range, or even greater, than the signal. Typical EEG signals are normally in the range of hundreds of μV, so it is clear that a component in the range of 50 μV can significantly impact the recording. The most common noise detected by the electrode cables is induced by the mains power (in Europe 220 V at 50 Hz, in the US 110 V at 60 Hz) and is generated by almost every electronic device. Typically, the induced noise has a frequency of 50 Hz (or 60 Hz in the US).[16] This is the reason why all EEG systems feature a stop-band filter, centred at 50 Hz. This filter, commonly called a *notch filter*,[17] is designed to eliminate the undesired component (i.e. 50 Hz) and is often called *50 Hz Filter*.[18] The transfer function of the filter is shown in Fig. 5.6.

Unfortunately, given the growing number of electronic devices that are present in a hospital environment, plus old or poorly installed main lines, the noise is not only a sinusoidal component at 50 Hz but 50 Hz signal contaminated by other components which quite often create harmonics of the mains

[16]Note that several other countries than the USA have a mains frequency of 60 Hz, so the notch filter needs to be centred appropriately depending on the country.

[17]The notch filter (or multi-notch) is usually a digital filter that is run during the signal display process so that it can be activated or deactivated as the signal is displayed to the user.

[18]Note that the term *50 Hz* should only be used to indicate just the 50 Hz noise component and not all the other noise components discussed. Often, *50 Hz* is used improperly to refer to any kind of noise visible on the EEG.

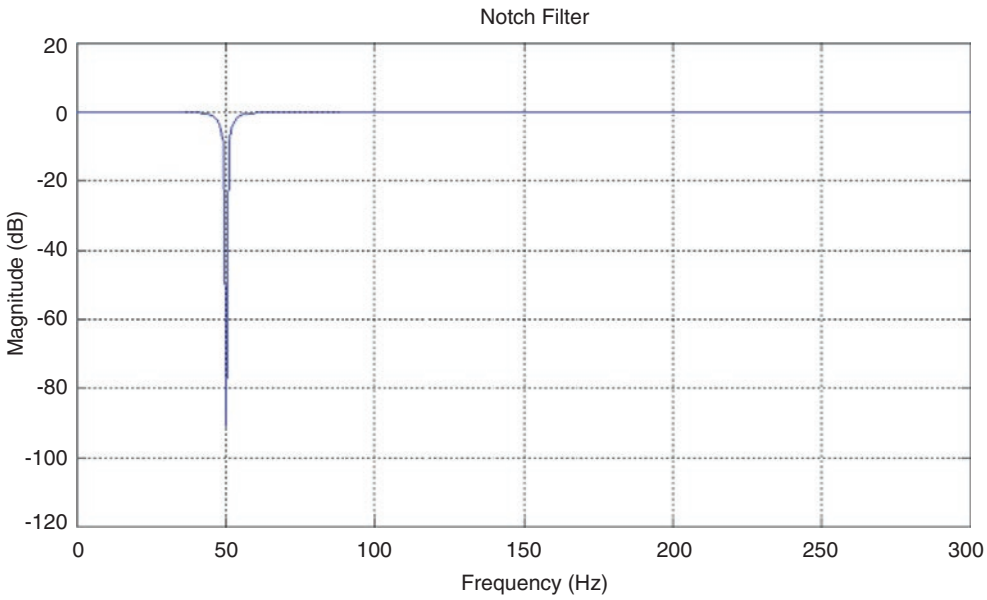

Fig. 5.6 Notch filter transfer function

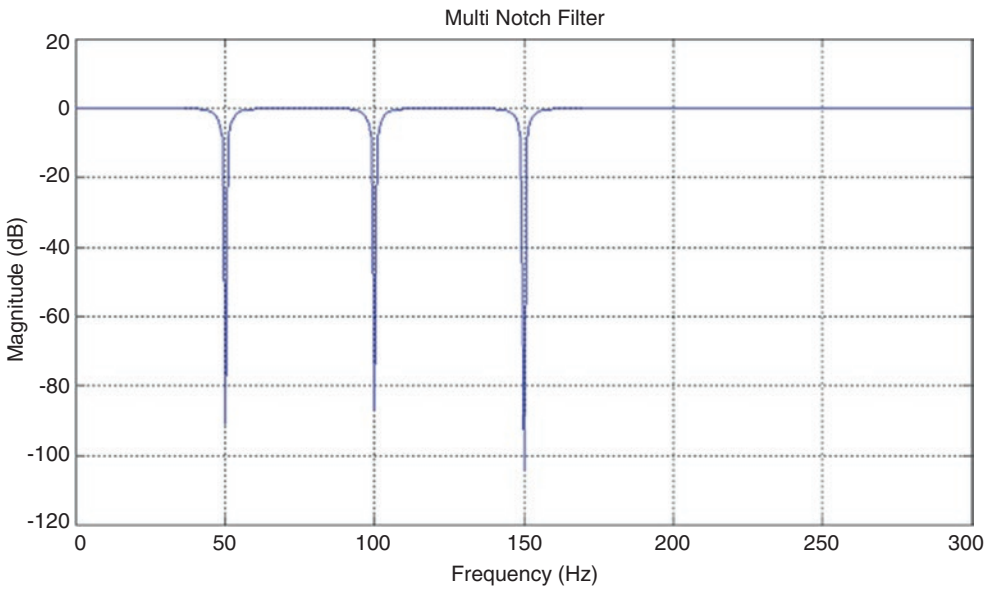

Fig. 5.7 Multi-notch filter transfer function

frequencies, or multiple frequencies, each a multiple of the original mains frequency. The most typical example of this is the 50 Hz sinusoidal signal with multiple peaks associated with its cycles that are caused by switching systems. The notch filter eliminates the 50 Hz component, but all the peaks remain, contaminating the signal. These problems have resulted in the design of *multi-notch filters* that can be set to eliminate several frequency components of the original signal, starting from 50 Hz and moving forward with each main harmonic, for example, 100 Hz, 150 Hz, 200 Hz and further if necessary. The transfer function of such a filter is shown in Fig. 5.7:

Another important reason to consider the formula for the noise with respect to the output voltage is that both additional noise terms are functions of $(Z_A - Z_B)$. This means that noise does not depend on the "value" of the impedance of a single electrode but on the "difference" between the values of two electrodes. As a result, to minimize the noise, it is necessary to make the two impedances equal to each other. Clearly, this is not possible so the only available strategy to minimise noise is to *reduce all the contact impedances as much as possible*, including those of the common reference and the ground electrodes, so that their difference will be minimal.

5.3 Analogue-To-Digital Conversion

The analogue-to-digital conversion of a signal is a process that converts an analogue signal waveform to a sequence of numbers that can be processed and stored in a PC. The analogue-to-digital conversion is very common in our daily

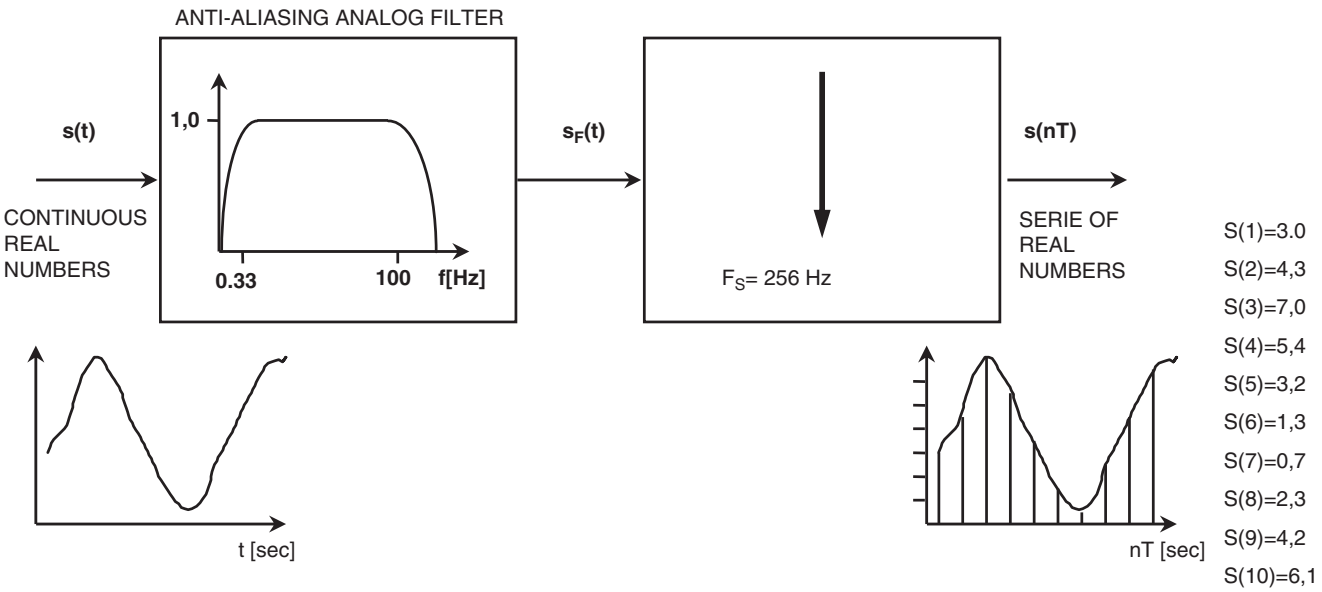

Fig. 5.8 Sampling process equivalent scheme

life, used for music, telephones, televisions and many other applications. This is discussed in Sect. 5.3.5.

5.3.1 Sampling

Sampling is a very simple process that, given an analogue signal properly amplified, consists of "measuring" the signal a given number of time per second and then storing the measured values instead of the entire analogue signal. An example of an analogue-to-digital conversion is shown in Fig. 5.8.

As shown in the diagram, the analogue signal is measured at regular periodic intervals. The frequency of this measurement is defined as the *sampling frequency*, indicated as F_S. Sampling is a no-loss process, which means that no information is lost, if and only if the sampling frequency is at least twice F_{MAX}, the maximum frequency that occurs in the signal.

This is known as the sampling theorem[19] and can be written as a formula:

$$F_S > 2 \times F_{MAX}$$

If the sampling theorem is not followed, the resulting digital signal can be corrupted, so all sampling systems filter the analogue signal at least at half the sampling frequency before sampling. This is usually called an anti-aliasing filter, where the name aliasing is taken from the typical error that can appear if the sampling is not performed correctly.[20] For example, if we assume that the bandwidth of the EEG does not exceed 100 Hz, an adequate sampling rate, in agreement with [1], is 256 Hz,[21] which means that the low-pass anti-aliasing filter should have a cut-off frequency of approximately 100 Hz as shown in the diagram. Note that the cut-off frequency of the anti-aliasing filter is never exactly half the sampling frequency. This is because at the cut-off frequency, the signal is not completely cancelled but only attenuated to about 70% of its value. Normal cut-off frequencies are in the range of 1/3 or even 1/4 of the sampling frequency to ensure that frequencies above half of the sampling frequency are properly cancelled.

Note that with the sampling process, we represent a set of continuous real numbers (the signal to measure) with a set of real numbers (the sampled signal).

5.3.2 Quantization

The objective of the quantization process is to complete the analogue-to-digital conversion process by reducing the measured samples to a set of finite numbers. It is important to note that the values measured by the sampling process are

[19] The mathematician and electric engineer Claude Elwood Shannon, known as "the father of information theory," formulated the sampling theorem in 1948. It was the first step toward the "digitization" of communications and started the revolution in digital technology.

[20] Aliasing is the phenomenon that represents signals associated with frequencies that exceed half of the sampling frequency appearing in the reconstructed signal as "duplicates" of the original signal. This means they will appear at frequencies that are specular to the original pivoting on the sampling frequency. For a better understanding, see Appendix 1—The Aliasing

[21] Note that for the sampling rates, most of the time a power of 2 value is selected (i.e. 256, 512, 1024 and so on) as this makes data processing by a PC more time efficient.

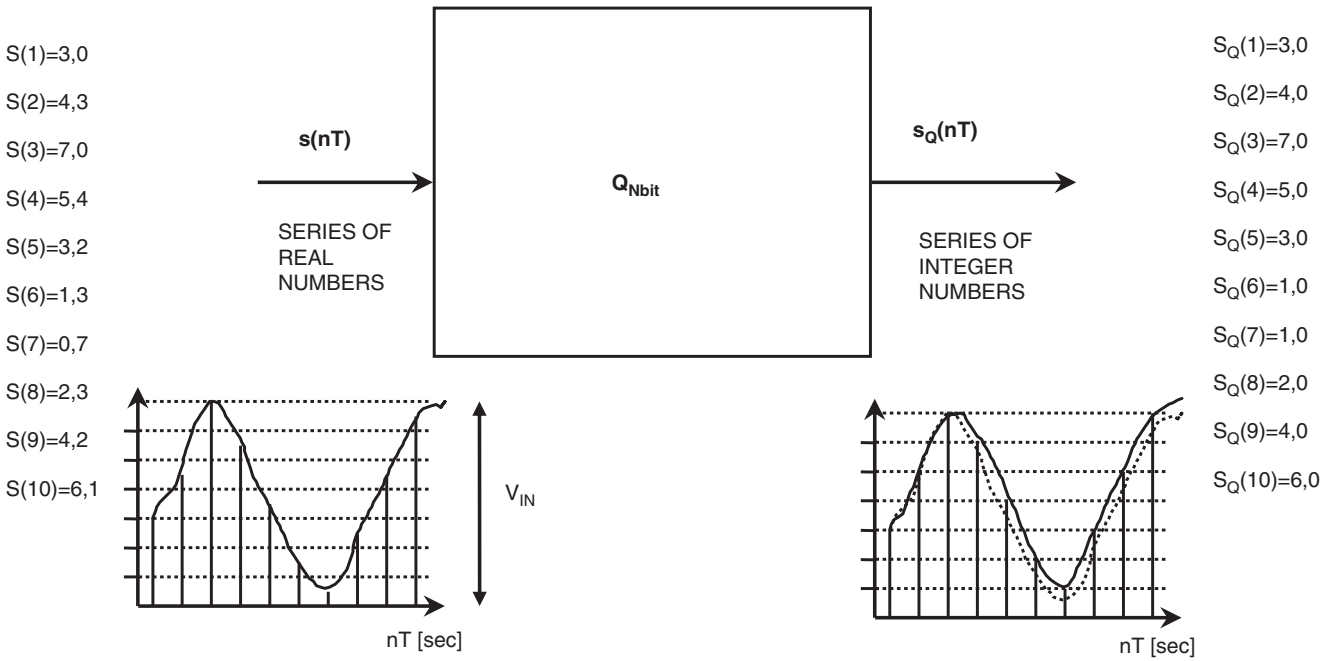

Fig. 5.9 Quantization process equivalent diagram

real numbers, so they have practically infinite resolution. This makes it impossible to store them in a simple form like a byte. Quantization approximates the real measured value to a close integer value.

A diagram of such a process could be that of Fig. 5.9

As the diagram highlights, quantization happens in a finite range of amplitudes, often referred to as the *maximum signal input* (indicated in Fig. 5.9 as V_{IN}), which defines an upper and lower limit for the signal to be converted. This parameter plays a very important role in the EEG signal acquisition process, because it needs to encompass the signal to be converted to avoid the *saturation* phenomenon. This happens when the measured signal exceeds the maximum signal input with the result that the value above the maximum signal input appears as the maximum signal input instead of the real signal, "cutting" the signal at the upper or lower value.[22] This saturation phenomenon should not be confused with the saturation of the amplifier, even though the result is very similar (as described in Sect. 5.2.3).[23] An example of saturation is shown in Fig. 5.10.

Another very important parameter for the quantization process is the precision of the measurement. In a digital system, this is determined by the *number of bits* used for the quantization of the signal (indicated in Fig. 5.9 as Nbit). The number of bits used is directly proportional to the *number of intervals* (or more correctly *number of digits*) in which the maximum input signal is split. The relation is the following:

Nbit = 8 → 2^8 digit = 256 digit
Nbit = 12 → 2^{12} digit = 4,096 digit
Nbit = 16 → 2^{16} digit = 65,536 digit
Nbit = 22 → 2^{22} digit = 4,194,304 digit
Nbit = 24 → 2^{24} digit = 16,777,216 digit

We can define the *precision of the measurement* or *resolution* as the ratio between the maximum input signal and the number of intervals in which such a range is split:

$$\text{Resolution} = \frac{\text{Maximum input signal}}{\text{Number of intervals}}$$

This value identifies the precision of the measurement of the quantization process and is expressed in [V/digit]. Note that the precision of the process is not uniquely identified by the number of bits, as often specified, but by a well-defined ratio between two values where only the denominator is proportional to the number of bits.[24]

[22] This phenomenon is similar to what happened with paper EEG systems when the pens reached their maximum excursion. In those systems, the limit was set by the physical limit of the excursion of the pens; in the digital systems, the limit is defined by the maximum signal that can be quantified.

[23] The main difference is that the saturation of the amplifier has a minimum recovery time before it functions correctly (the ability to amplify properly), while the saturation of the maximum signal input is a reversible problem, and the correct signal is shown as soon as the signal returns to within limits.

[24] The number of bits is quite often used as an indicator of the precision in those systems that can use several different values of maximum input signals, having multiple precision values (one for each different maximum signal input value).

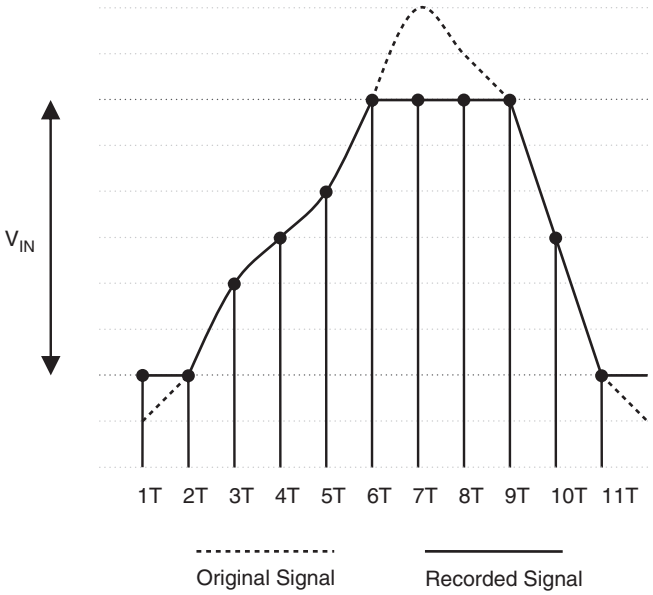

Fig. 5.10 Example of saturation of the input signal

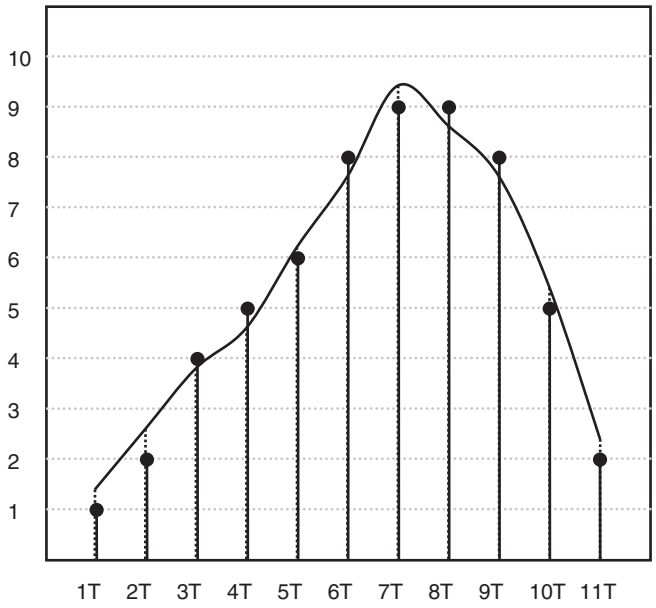

Fig. 5.11 Example of approximation of the signal due to quantization

As the quantization process induces an error in the measurement, it is necessary to quantify the magnitude of such an error to evaluate its importance. Considering how the process is performed, by "measuring" the signal using the closest interval, it is evident that the average quantization error is half the interval into which the maximum input signal is divided, as shown in Fig. 5.11.

As shown in Fig. 5.11, a signal is represented by the closest quantization level either above it (samples 3 T, 4 T, 6 T, 8 T, 9 T of Fig. 5.11) or below it (samples 1 T, 2 T, 5 T, 7 T, 10 T, 11 T of Fig. 5.11).

More precisely this can be written as:

$$\text{Average measurement error} = \frac{\text{Quantization interval amplitude}}{2}$$

In systems on the market, the number of bits normally used for quantization is typically 16 (with a minimum value recommended by [1] of 12) combined with a maximum input signal of at least 1 mV for EEG (±500 μV), which leads to the following values:

$$\text{Resolution} = \frac{1000[\mu V]}{65536[\text{digit}]} = 0.015[\mu V/\text{digit}] = 15[\text{nV}/\text{digit}]$$

Because this resolution is more than sufficient for most applications, quite often systems use maximum input signals higher than 1 mV to handle intracranial signals and various polygraphic signals (i.e. ElectroCardioGram, ElectroOculoGram and others).

5.3.3 Decimation

Decimation is an advanced technique that is not essential for the comprehension of the EEG signal acquisition process. This paragraph describes some of the more sophisticated aspects of the process. *Decimation* is basically a digital process which reduces the number of samples collected. For example, sampling a signal at 512 Hz and then keeping one sample for every two (which means one sample is kept and one sample discarded) results in a signal sampled at half the original sampling rate or 256 Hz. This operation is often referred to as *downsampling*, as it leads to a reduction of the original sampling rate.

In order to obtain the correct result from decimation, the sampling theorem (seen in Sect. 5.3.1) must be honoured. This means that the signal to be decimated must not contain any frequencies higher than half of the new sampling frequency resulting from the decimation. As a result an additional anti-aliasing filter should be applied to the signal before decimation. The advantage is that this filter operates on a sampled signal and is therefore a *digital filter*. This is the main reason over-sampling techniques are used. The original signal is sampled at very high frequencies (i.e. 8 kHz) and then decimated to obtain the desired sampling rate with a digital anti-aliasing filter, which has a much better performance than a similar analogue filter. A second advantage, which is more complicated and will not be addressed in this book, is the reduction of background noise (minimal) that results using this technique.

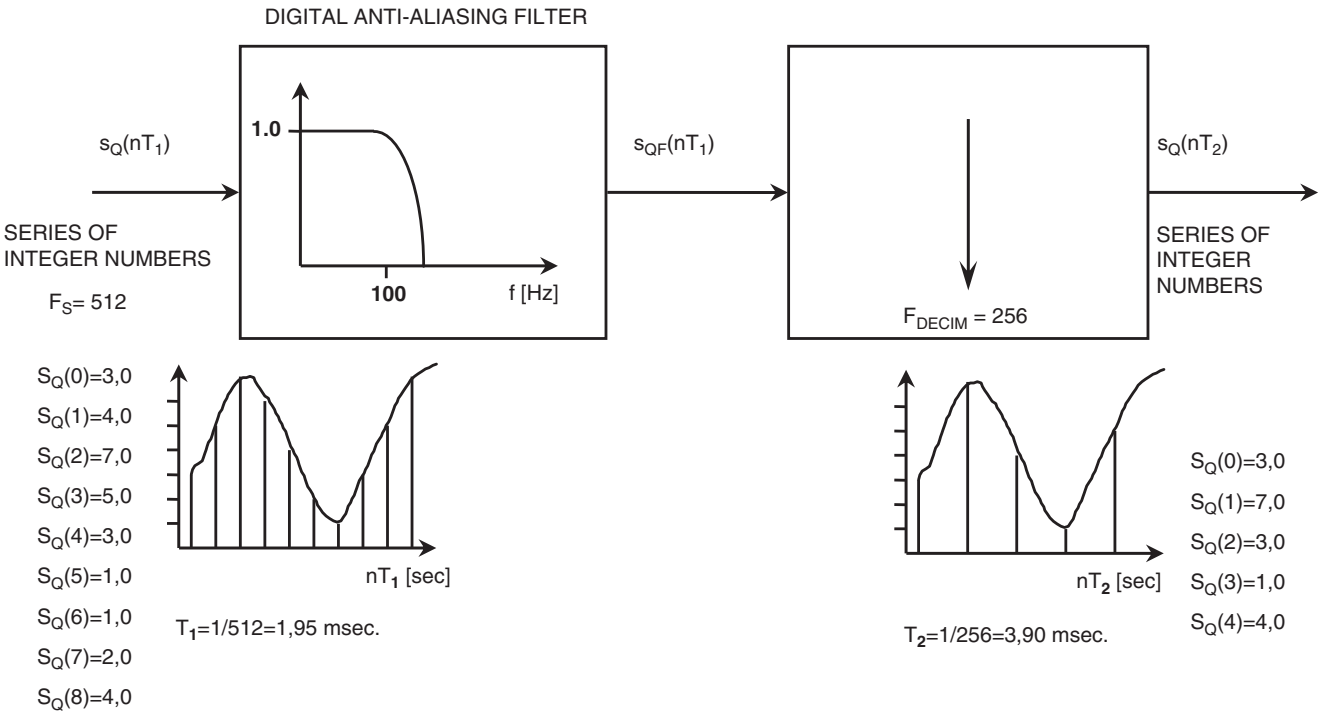

Fig. 5.12 Decimation equivalent scheme

A possible scheme for the decimation process is shown in Fig. 5.12:

As shown in Fig. 5.12, assuming an input signal $S_Q(nT_1)$ sampled at 512 Hz, to perform a decimation of 2 to 1 (which means moving from a sampling rate of 512 Hz–256 Hz), the first process is to apply an anti-aliasing filter with a cut-off frequency that is at least half of the resulting sampling rate (i.e. lower than 256/2 = 128 Hz). In the example this frequency has been chosen to be 100 Hz. The decimation process of keeping just one sample for every two can only be completed after the filtering, obtaining the desired output signal $S_Q(nT_2)$.

In reality the decimation process is often used to convert a signal from very high sampling rates (e.g. 8192 Hz) to much smaller values (e.g. 256 Hz) to take advantage of having a single analogue anti-aliasing filter in the circuits and the rest of the process performed by the software (or firmware) with digital filters to allow the selection of the desired sampling rate.

5.3.4 Summary of the Parameters of EEG Signal Acquisition

As discussed in the previous paragraphs, the parameters that must be known to sample EEG signals correctly are:

B = *signal bandwidth*[25]
A_{MAX} = *maximum signal amplitude*

Consequently, the following parameters must be set in the recording system:

F_S = *sampling frequency*, which must be at least twice the maximum frequency composing the signal (i.e. the upper limit of the bandwidth)
V_{IN} = *maximum signal input*, which must be larger than the maximum signal amplitude to guarantee correct signal recording

The most common parameters for typical EEG signals are shown in Table 5.1, derived from recommended standards [1], and calculated with a 16 bit quantization:

[25] For the sampling process, the upper limit of the bandwidth is the important parameter, while the lower limit of the bandwidth is more important for the selection of the high-pass filter.

Table 5.1 Recording parameters for EEG and polygraphic signals

Signal type	A_{MAX}	V_{IN} (μV)	Resolution (nV/digit)	Bandwidth (Hz)	F_S (Hz)
EEG—adult	50–400 μV	800	12.2	0.3–70	256
EEG—children	100–1000 μV	1600	24.4	0.3–70	256
EEG—intracranial	1–2 mV	3200	48.8	0.3–150	512
ElectroCardioGram	0.5–3 mV	3200	48.8	1.6–70	256
Muscle	10 μV to –10 mV	12,800	0.19	50–500	1024
ElectroOculoGram	50–400 μV	800	12.2	0.3–70	256

Table 5.2 Example parameters for analogue-to-digital conversion of common signals

	Signal type	Band	FC	N_{BIT}	Channels	Data throughput (kbytes/s)
	EEG	120 Hz	256 Hz/channel	16	20	10
	Acoustic EP	8 kHz	16 kHz/channel	16	2	32
	Telephone	4 kHz	8 kHz	8	1	8
	Audio	20 kHz	44.1 kHz/channel	16	2	172

5.3.5 Examples of Other Analogue-To-Digital Conversion Processes

The analogue-to-digital conversion process described for EEG signals is common to many other applications of daily life such as telephones, music and others. For example, voice transmitted by our mobile phones is sampled at 8 KHz with a quantization at 8 bit, with a resulting bandwidth of less than 4 KHz, which works correctly for a normal conversation. However, when we consider high-fidelity audio, because the audible signal that can be heard by humans is in the range of 20 KHz, the music must be sampled at 44.1 KHz and 16 bit to sound correct. Examples of analogue-to-digital conversion of signals are shown in Table 5.2:

5.4 The Digital Component

Once the analogue EEG signal is converted to digital, the signal goes through additional processes such as *storing*, *display*, *printing* and other manipulations for further analysis. The following paragraphs describe these processes.

5.4.1 EEG Signal Storage

Once the EEG signal is converted to a digital format, most EEG systems immediately store it. The first destination for data is the *hard disk* of the recording PC or another disk over the network. Subsequently the data is normally transferred to a disk over the network which provides reading station access for viewing, analysis and reporting. Once the signal has been displayed, analysed and reported, the signal (or just a part of it[26]) is transferred to a permanent storage media, which could be another disk or a non-rewritable media like *CD-R*[27] or *DVD-R,*[28] through an application that is normally part on the reporting system. These media allow the data to be permanently stored (or at least for several years) in an unmodifiable way, as required by some national laws. It's important to remember that in modern systems, the EEG is normally stored as "raw" data, that is, exactly as the signal was acquired by the amplifier. This means that all EEG channels are stored with a common reference, with only the filters performed by the hardware system and without any additional filter (including the notch filter), and these processes are performed when displaying the signal on the screen, as described in the next paragraphs.

[26] It's a common practice to select only parts of the EEG and video to be permanently stored. This is necessary to reduce the amount of data stored while keeping all the relevant information (e.g. seizures) for subsequent review and/or analysis.

[27] CD-R is a non-rewritable optical media (not the same as rewritable CD, which should not be used for this purpose) with a capacity of 650 or 700 Mb.

[28] DVD-R is a non-rewritable optical media (once again, not to be confused with rewritable DVD which should not be used for this purpose) with a capacity of 4700 Mb, often referred as 4.7 Gb even if in the informatics standard 4.7 Gb should be 4.7 × 1024 Mb = 4812 Mb.

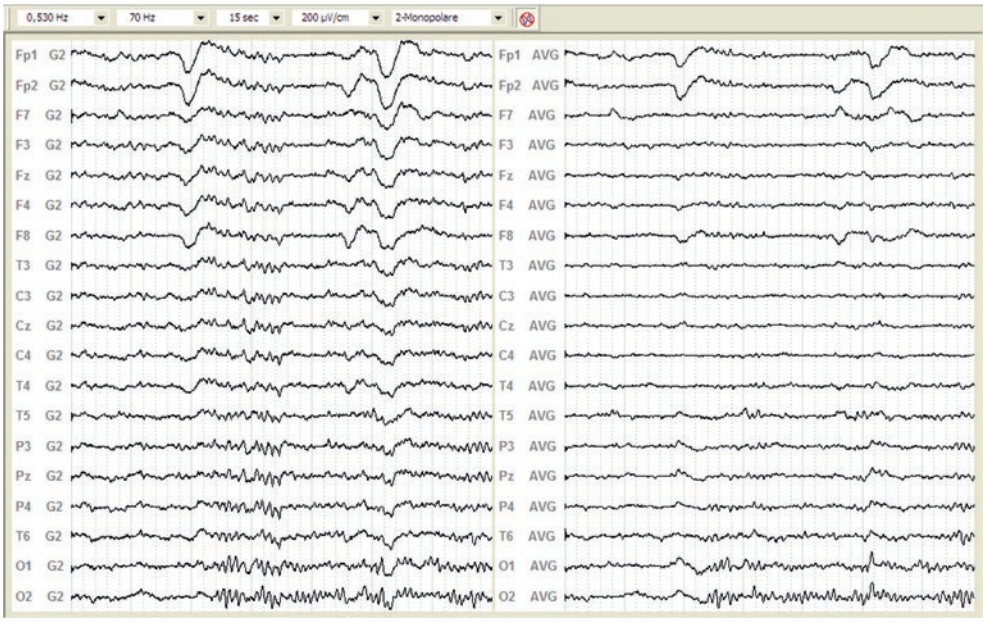

Fig. 5.13 Example of EEG signal with a common reference and average reference

5.4.2 EEG Signal Digital Processing

Before being displayed, the EEG signal goes through various processes, which include some or all of the following:

1. The original signal, where all channels are recorded in Common Reference, can be re-referenced, that is, calculating for each signal the *Average Reference* or the *Source Reference.*
   - *Average Reference* yields the absolute potential of each recorded electrode, as discussed in Sect. 5.2.3. For example, for the electrode C3 recorded as (C3-Ref), the average reference yields $C3_{ABS}$. This is obtained by calculating the average of all the common reference electrodes (which should ideally be the absolute potential of the common reference electrode—named AVG) and subtracting this value from the signal of each channel. Written as a formula, this is:

$$AVG = \frac{(Fp1\text{-}Ref)+(Fp2\text{-}Ref)+..+(O2\text{-}Ref)}{19} = \frac{(Fp1+Fp2+....+O2)\ -19\cdot Ref}{19}$$

$$= \frac{(Fp1+Fp2+....+O2)}{19} - \frac{19\cdot Ref}{19} = -Ref_{ABS}$$

The first term of the formula should tend to zero as the arithmetic average of a large number of uncorrelated signals, so the result will be the real "absolute" potential of the common reference electrode Ref_{ABS}. By simply re-montaging the signals with this newly calculated reference, the result is:

$$C3_{ABS} = (C3\text{-}Ref)\text{-}AVG = C3\text{-}Ref+Ref = C3_{ABS}$$

The disadvantage of this process is that the number of averaged signals is normally not as large as required (should be infinite), so the AVG potential obtained is not the "real" potential of the common reference electrode but is contaminated by all the high-amplitude signals that are present in the various electrodes (e.g. eye blink artefact). When this signal is subtracted from each electrode, the contaminated signal spreads to all the electrodes.[29] This phenomenon, known as *average reference contamination*, can be avoided by increasing the number of electrodes to be recorded (which in most cases is not possible) or by excluding those electrodes where artefacts are most often present (e.g. Fp1, Fp2 for Eye Blinks) from the calculation of the AVG potential.

Figure 5.13 shows two set of signals displayed in unipolar montage. The signals on the left are shown in common reference and the signals on the right in average reference, including the fronto-polar electrodes in the average calculation.

As the figure shows, the artefact due to eye blinks that is present in the common reference display, mainly in the frontal area (i.e. Fp1 and Fp2), contaminates other electrodes (i.e. O1, O2 with reverse polarity) with the average reference display.

The average reference is rarely used for the visual interpretation of EEG, but it is often necessary for processing that requires an absolute value for the potentials, such as mapping.

Also, note that the average reference does not affect the display with a bipolar montage because the same potential is

[29] The signal is spread into any other channel attenuated by a factor that is the number of channels used for the calculation, with reverse polarity (inverted) due to the subtraction performed by the re-montaging.

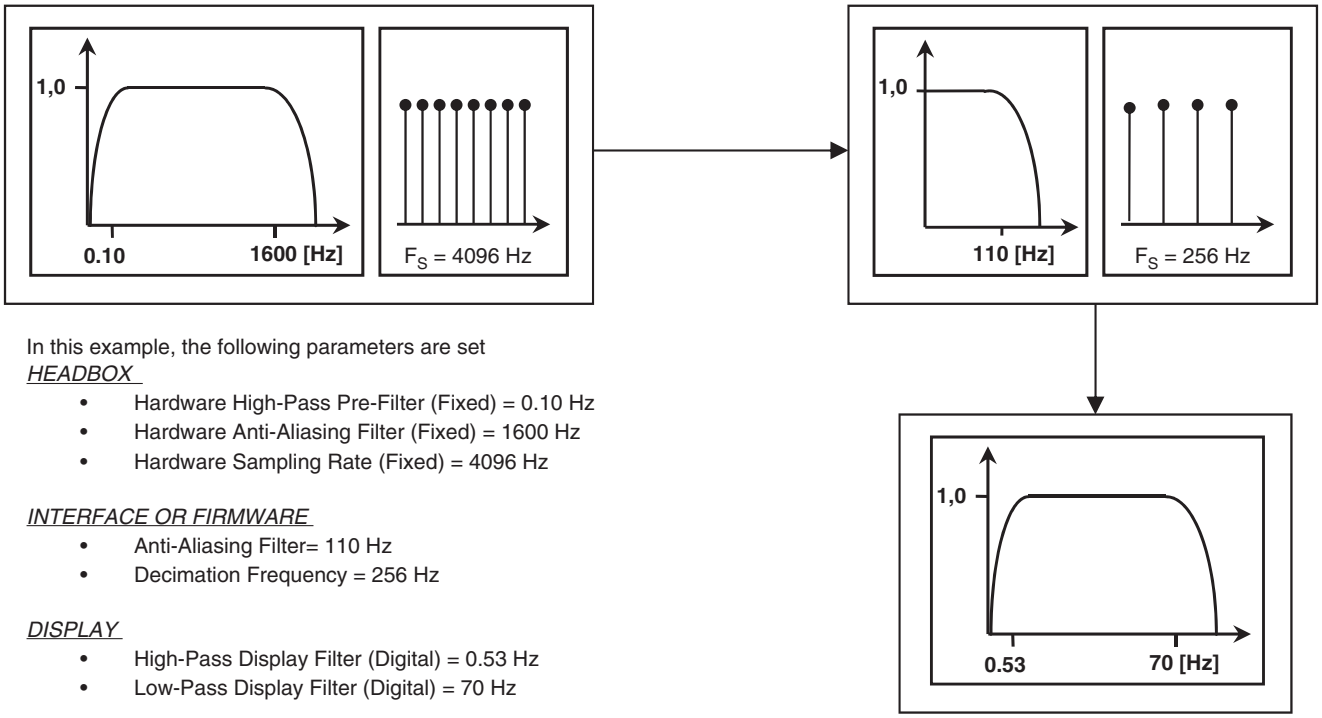

Fig. 5.14 Example of a complete filtering chain for an EEG signal

subtracted from all the electrodes so that the difference of potentials between two electrodes remains the same.

- *Source Reference* is a signal processing technique that aims to highlight the "source" of the potentials. In other words, the potential will be higher in the electrode that is closest to the source of the potentials. A complete analysis of this technique is complicated and described in Appendix 2—Source Reference.

2. The *Montage* defines how signals are recombined and selected for display. This could be *unipolar* (each signal with the reference selected at the previous point) or *bipolar* (the difference between two channels recorded with the same reference). Refer to Sect. 5.2.3: Common Reference and Bipolar Electrodes—for further details.
3. Signals are *filtered* (using correctly designed digital filter) to reduce the recorded bandwidth for the display and to cut noise (e.g. a digital notch filter). These filters represent additional processing over and above the filters already applied by the hardware as seen in the previous paragraphs. For example, Fig. 5.14 shows a diagram of the complete filtering chain for a typical acquisition and display process.

As Fig. 5.14 shows, the system works to progressively narrow the bandwidth of the signal until it is compatible with the display.

These three processes are all digital and allow any of their parameters to be modified to prepare the signal for display on the screen and/or for printing.

5.4.3 EEG Signal Display

Signal display is a very important process, often under evaluated, because it defines the quality of the final "presentation" of the recorded EEG to the user and can therefore influence correct data interpretation.

Data are drawn on a matrix of points, called *pixels*, that compose the LCD[30] screen. The size of the pixel matrix is a characteristic of the graphic card of the PC and the screen that is connected to the graphic card. In fact, to display an image on the screen, the matrix must exist in the memory of the graphic card, and the screen has to be capable of displaying the matrix of pixels, or interpolations have to occur. Typical matrix is 1440 × 900, 1680 × 1050 (mainly used on laptops) and 1920 × 1080 (Full HD). It is worth noting that the size of the pixel depends on the resolution and the size of

[30] *LCD* is the acronyms of liquid crystal display and is the most common display type. Depending on the brand and model, its size ranges typically from a minimum of 15″ up to 24″, 27″ or even 30″. The screen proportions are always 16:9 or 16:10, or in other words, the horizontal size is 16/9 of the vertical size. The resolution again depends on the brand and model but is often 1920 × 1080 as this is a common TV standard (full HD resolution), but there are also even higher resolutions.

Table 5.3 Typical pixel sizes

Monitor	Proportion	Resolution	Monitor size	Pixel size
17″	16:9	1440 × 900	37.6 × 21.2 cm	0.29 × 0.29 mm
19″	16:9	1600 × 900	42.1 × 23.7 cm	0.26 × 0.26 mm
21″	16:9	1920 × 1080	46.5 × 26.2 cm	0.24 × 0.24 mm

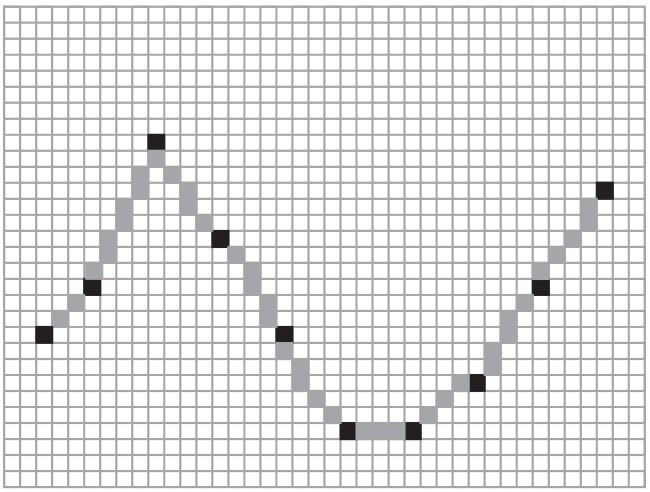

Fig. 5.15 EEG signal drawn on a pixel matrix 40 × 30

the screen. Typical values for pixel size are shown in Table 5.3.

The display of the EEG signal is presented by drawing on the pixel matrix of the graphic card the sequence of signal samples connecting each point, in the simpler hypothesis, with a line identified by "on" pixels. The result, on a different scale, is shown in Fig. 5.15, where the digital signal $S_Q(i)$ = [3.0; 4.0; 7.0; 5.0; 3.0; 1.0; 1.0; 2.0; 4.0; 6.0] is drawn.

As Fig. 5.15 shows, the value of a signal sample is associated with a specific pixel (drawn in black in Fig. 5.15). The vertical coordinate is proportional to the value of the sample, while the horizontal coordinate is time (in Fig. 5.15 the proportion factor is 4 pixel/digit). These pixels are then linked by additional pixels (drawn in grey in Fig. 5.15).

The vertical scaling factor determines the *video gain*, often improperly called its *sensitivity*, that is calibrated by the EEG system manufacturer with proportions that are, for example, 100 μV/cm, 200 μV/cm, 400 μV/cm, 800 μV/cm for the EEG and other values for other signal types.[31] It is worth noting that typically a signal that is quantized at 16 bit, that is 65,536 digits, is then drawn in about 200 vertical pixels[32]; this means that all the efforts made to increase the precision of the quantization vanish when the signal is displayed.

The horizontal scaling factor determines the so-called *base time*, that is, the number of seconds of EEG drawn on the screen. This factor is also calibrated by the EEG system manufacturer to display an integer number of seconds on the screen (typically 10, 15 or 20 s) or to represent a proportion, for example, 1.5 cm/s or 3.0 cm/s. It is worth noting again that a signal, for example, sampled at 256 Hz is then drawn in about 96 horizontal pixels.[33] This quite often contaminates the signal (most of the time unperceivably) due to the number of samples that are drawn on the same horizontal position.

It is clear that for an optimal display of EEG signals, both the horizontal and vertical resolution of the screen must be chosen as high as possible. For the screen of an EEG reporting station, a minimum resolution of 1920 × 1080 pixel is recommended.

5.4.4 EEG Signal Printout

Signal printout is also a very important process but is less and less common as the display interpretation is now preferred. Printouts still occur, for example, to give patients a few pages of EEG together with the report and/or for medical-legal reasons. Printouts are normally done in two ways:

Single sheet printout, typically on A4 paper format (or "Letter" in the US) and with laser technology on standard paper. The process is very much the same as the display described in the previous paragraph: the paper is divided into a matrix of points that can be switched "on" or "off." In the case of a printer, the number of points is determined by the resolution of the printer that is often at least 600 dpi,[34] which is four times larger than the video, minimizing the resolution issue described for the screen. This is also the reason why EEG signals printed on paper look "thinner" than the same signals on the screen: they are plotted on a matrix of much smaller points and consequently the lines are thinner.

Continuous module printout is rarely used. This was done on thermal paper that, by heating, became darker. The reso-

[31] Values range from 1, 2, 5, 10 μV/cm plus all their multiples 20, 50, 100 μV/cm up to 1, 2, 5 mV/cm for polygraphic signals which have typically higher amplitudes.

[32] The calculation is done assuming a vertical resolution of 1080 pixel with 10 EEG signals on the screen. Every signal will occupy at maximum the space between the signal above and the signal below. So, considering a space between lines of 1080/10 = approx. 100 pixel, the space occupied by a signal will be 2 × 100 = 200 pixel.

[33] The calculation is done with a horizontal resolution of 1920 and 20 s of EEG signals drawn on the screen, that is, 1920/20 = 96 pixels per second of signal.

[34] DPI is the acronym for "dots per inch" and is the number of dots per inch of the matrix. One inch corresponds to 2.54 cm, so 600 dpi corresponds to 600/2.54 = 236 points/cm. As an A4 sheet size is 29.7 × 21 cm, assuming a border of 1 cm, the matrix of points on an A4 sheet is (29.7–2) × 236 = 6537 and (21–2) × 236 = 4484 or 6537 × 4484 points.

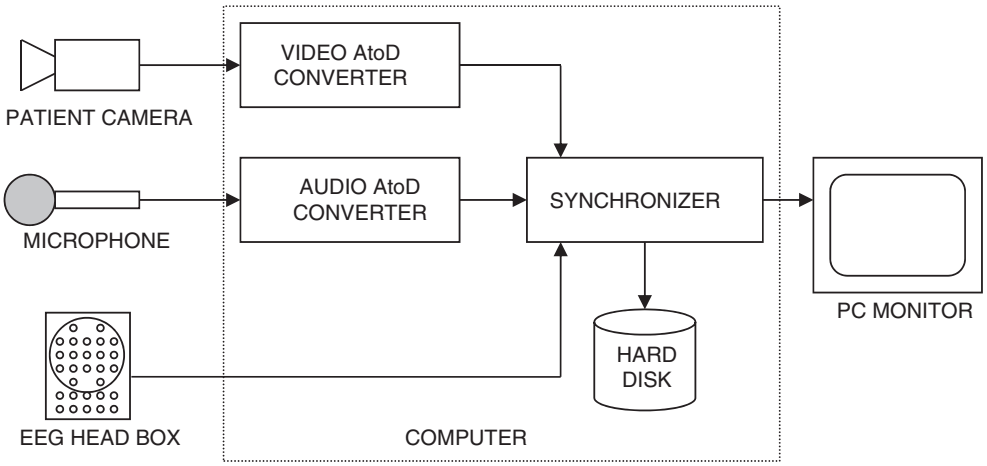

Fig. 5.16 Block diagram of a digital video EEG acquisition system

lution of these printers, typically 16 points/mm, was not as high as the laser printers but still better than the screen resolution.

In both printout cases, vertical and horizontal scaling factors are properly calibrated by the EEG system manufacturer to reach the desired *gain on paper* and *base time*.

5.5 Synchronized Digital Video

Recording the patient video synchronously with the EEG is a technique used for many years and has evolved to its current form of synchronized digital video.

The first systems were composed of a camera filming the pens writing the EEG data onto the scrolling paper, while a second camera filmed the patient; the two signals were then mixed together and the video EEG was obtained.

With the first digital EEG, recording of the video started on videotape and the synchronization signal was encoded into the video tape. This kind of system is often referred to as the *analogue video* option for digital EEG.

In the middle 1990s, the first *digital video* systems were developed, which involved recording the video into a file, together with the EEG; the recording PC and its software performed the synchronization. It is worth noting that in many of these systems, analogue or digital, audio was always recorded.

Main advantages of digital video over analogue are:

- Digital video is easier to store and transfer as both EEG and video can be written on the same media (hard disk, CD or DVD or any other).
- Digital video offers direct access to any time instant of the video, without the need to rewind or fast forward the tape as with the analogue video.

However, it is worth noting that digital video has introduced new variables such as the resolution of the image, the codec used for the compression and the codec used to play the video on a PC. The following paragraphs describe these parameters in detail and how the digital video is recorded and stored.

5.5.1 Digital Video EEG Acquisition

A digital video EEG acquisition system is basically a PC that performs three digitizing processes simultaneously: analogue-to-digital conversion of the EEG, the video and the audio. Figure 5.16 shows a diagram for such a video EEG acquisition system:

Analogue-to-digital conversion of the EEG has already been reviewed in Sect. 5.3. The analogue to digital conversion of the audio, as discussed in Sect. 5.3.5, is the same as EEG, just with different parameters; the next paragraph will analyse the digitizing process for the video.

5.5.2 Video Signal Digitalization

The video signal normally acquired by a standard camera is composed of 25 images per second,[35] captured by the camera itself.[36] The complete analogue to digital conversion consist of digitizing every image and storing the entire sequence of

[35]The 25 images/s. Comes from the PAL video standard adopted in Europe for all TV signals. In the USA the TV standard is NTSC which uses 30 images/s (originally 29.97 fps but now adapted to digital cameras using 30 fps).

[36]Note that the video signal has already been sampled in the time domain by acquiring 25 images per second. This means that, according to the sampling theorem discussed previously, there should not be any movement in the signal faster than 12.5 movements/s. In reality there's no way to apply an anti-aliasing filter to this signal, so if a movement is faster than 12.5 times/s, it will be displayed incorrectly. A typical example is the wheels shown in older western movie that appear to turn backward.

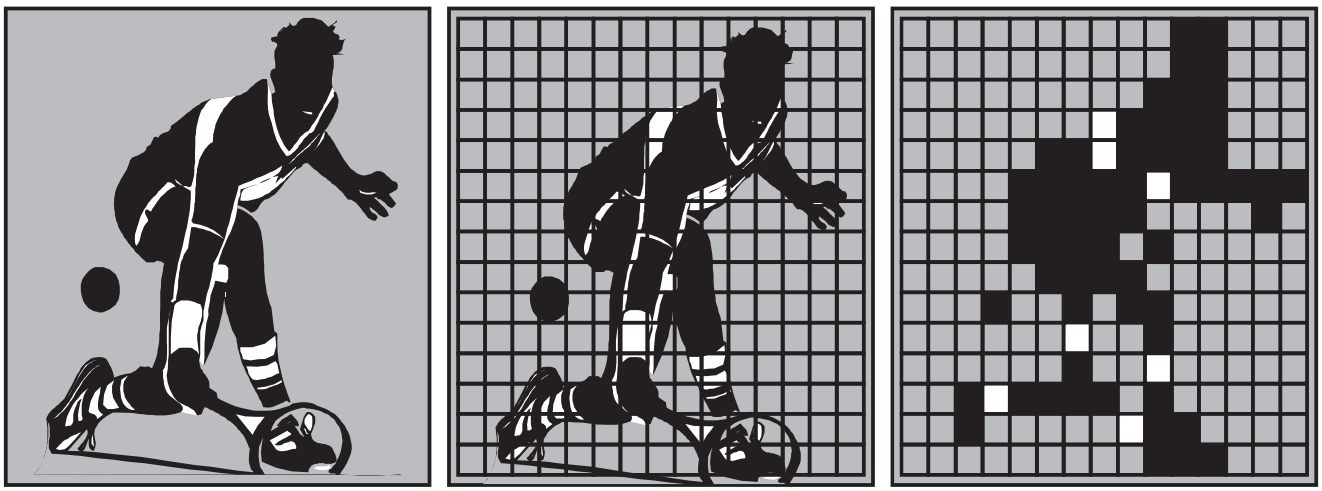

Fig. 5.17 Digitalization of an image

Table 5.4 Video resolution

Name	Image resolution
Full HD—1080i/p	1920 × 1080
HD—720p	1280 × 720
CIF[a]	384 × 288

[a]CIF is the acronym of Common Interchange Format that was a common format representing a good compromise between quality and size

25 images per second, or less if necessary,[37] into a file. The *number of images* or *frames per second (fps)* is the number of images per second that is recorded into the file. The *resolution* of the video is the number of pixels used for the digitization of each image, which defines the quality of the images and of the video, as shown in Fig. 5.17.

As shown in Fig. 5.17—if the resolution of the image is too small, there is the "pixelisation" effect where the border of the original image is no longer visible in the digitized image. In practice resolution is much better than this, and typical values are shown in Table 5.4:

Once the video signal has been digitized, it is never stored in its original form because its size would be too large and not practical to manage. To solve this problem, a process of *compression of the video signal* is performed to obtain more acceptable file sizes. Compression is a very complex process that is reviewed in the next paragraph.

5.5.3 Digital Video Compression

Digital video compression is a widely used process that is performed on all digital video signals currently used.

The first compression used in digital video was called *MJPEG* (Motion JPEG[38]), in which every single image was compressed into a JPEG format and the sequence of images stored. This technique, despite being intuitive, didn't exploit the fact that the difference between one image and the next could be minimal, so that new techniques have been developed, all of them named *MPEG* (Motion Picture Experts Group), that exploit this concept of only storing the difference between sequential images.

It is simple to understand that several different algorithms can be developed for this type of compression, so the MPEG standard has evolved enormously over time taking advantage of the increasing computational power of digital systems and optimizing the results. As a result, from the initial *MPEG-1* standard, the *MPEG-2* was developed (used by DVDs) up to the most recent *MPEG-4*. All these standards have their own peculiar characteristics but, as far as video EEG is concerned, their differences stand out in the fact that a similar quality result can be obtained with smaller file sizes, as shown in the following table:

The calculation in Table 5.5 was performed on a CIF resolution video and using a similar image quality factor. By changing these parameters, it is possible to get very different results that make any comparison looking at the file size, very difficult to identify the compression.

[37] In some applications, like sleep, it is not always necessary to record at 25 frames/s. As most of the time there's no need to monitor detailed movement and a lower number of frames/second is sufficient, typically 12.5 or 5 or 1, reducing the file size proportionally.

[38] JPEG is the acronym of Joint Photographic Experts Group and is the most used standard for the picture compression, allowing high-compression factor that can be selected according to the desired image quality.

Table 5.5 Video file sizes

Codec	File size	
MJPEG	28.1 Mb/min	1.65 Gb/h
MPEG-1	8.2 Mb/min	495 Mb/h
MPEG-2	5.2 Mb/min	315 Mb/h
MPEG-4	4.3 Mb/min	260 Mb/h

5.5.4 Digital Video File Display

As discussed in the previous paragraph, digital video files are always compressed, and there are several different compression standards. As each compression standard corresponds to a different compression algorithm, to display the video on a PC, it is necessary to have the complementary decompressor algorithm. The union of the two words (COmpressor–DECompressor) has created the word *codec* that identifies the software and algorithm that a computer should use for the compression of a video and which to use to display a compressed video. According to the compression type and the operating system used, it is possible to have different problems displaying a video, so it's strongly recommended to always have the codec software available when moving a video to a different PC (i.e. for a presentation at a conference or simply on another PC).

It is worth noting that the file extension does not automatically identify the compression. Files with the same extension (typically .AVI) can have very different codecs.

Acknowledgments Thanks to Raffaele Orsato MEng, PhD for Figs. 5.6 and 5.7, Marco Cursi MEng for Fig. 5.17, Arianna, Laura and Piergiorgio for revising this chapter and most of all to David and Kristen for revising the entire English text.

Appendix 1: The Aliasing

Aliasing is the phenomenon that "replicates" signal components that exceed half of the sampling rate into the part of the spectrum below half the sampling rate. The replication happens specular to the sampling rate. For a better comprehension of this phenomenon, one can think of taking the spectrum of the analogue signal and replicating it specular starting from the selected sampling rate. The resulting spectrum after the sampling will be the sum of the two spectrums: the original one and the replicated one. It is evident that if the two spectrums don't overlap, there's no error in the sampling. Vice versa, if the two spectrums overlap, some "unwanted" component will be generated on the signal and called "aliasing."

As an example, consider the EEG signal spectrum of Fig. 5.18 that is an EEG contaminated by 50 Hz. The signal has a main Theta component, a good Alpha peak and another peak at 50 Hz created by the noise. If the signal is sampled at 128 Hz, the original spectrum is replicated (symmetrically) starting from 128 Hz.

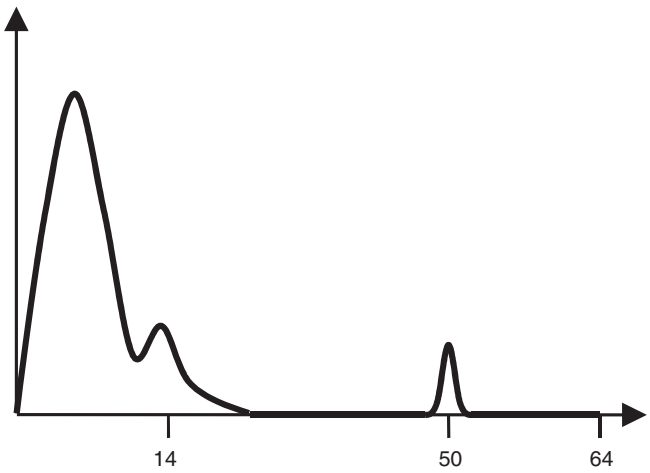

Fig. 5.18 Original spectrum of the analog signal

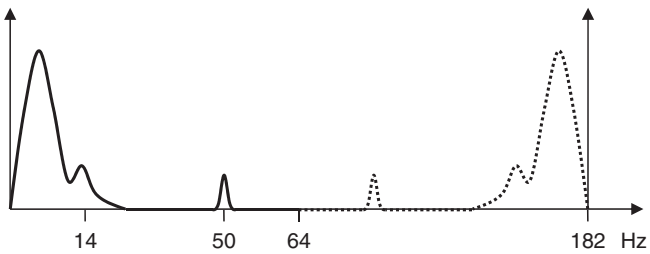

Fig. 5.19 Overlapped spectrum F_S = 128 Hz

In this case the "replicated" spectrum does not overlap with the original thus there's no aliasing effect, as shown in Fig. 5.19. The maximum frequency that composes the original signal is around 50 Hz, which is lower than half the sampling rate used.

However, if the signal is sampled at 64 Hz without a proper anti-aliasing filter, the replicate of the spectrum (symmetrically) starts at 64 Hz as shown in Fig. 5.20 with the dashed line and in this case, the overlap is clear and their sum would lead to the spectrum of Fig. 5.21 which does not represent the original signal.

As shown in Fig. 5.21, the 14 Hz peak is increased by the replication of the 50 Hz component (that replicates exactly at 64–50 = 14 Hz) and the result on the signal would be a "pseudo" alpha over all the EEG.

Appendix 2: Source Reference

Source reference is a signal processing technique that aims to identify where (in terms of which electrode) the signal originates or finding the "source" of the signal. In practice, the

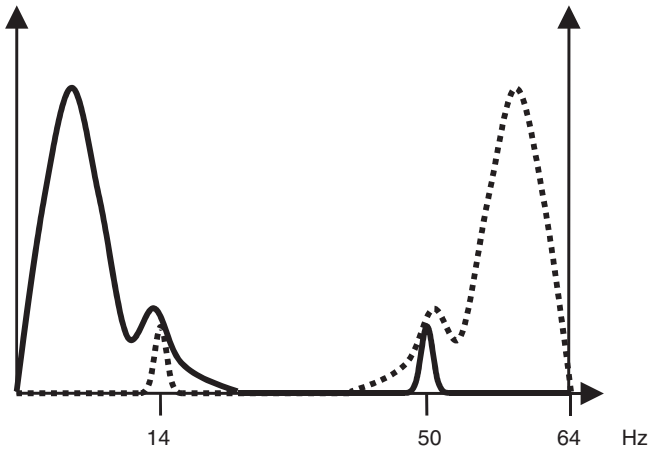

Fig. 5.20 Overlapped spectrum $F_S = 64$ Hz

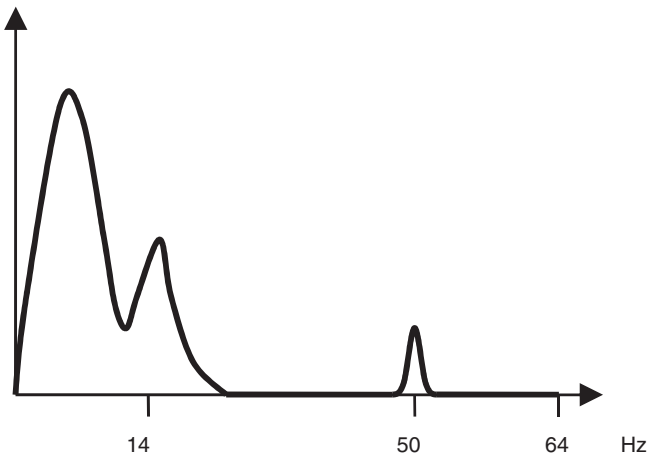

Fig. 5.21 Resulting spectrum $F_S = 64$ Hz

potential of an electrode will be higher if the source of the potential is located close to the electrode.

The fundamental concept of this principle is that the surface electrical fields are the expression of currents originating in points of the scalp that correspond to perpendicular field lines and there exists an equation that links the *source current* to the measured potentials, known as *Laplace's equation* (an alternative name for this technique is *Laplacian*). Such a current multiplied by a constant resistance becomes a potential, known as the *source potential* that can be calculated for every electrode. Using this technique the spatial dependent information is embedded into a new potential, i.e. $C3_{SRC}$, that highlights the topographic origin of the observed potentials. This results in the higher source potentials being located where the difference between the nearest potential is highest, thus localizing the source.

From a purely mathematical standpoint, the analysis is far too complex for this text, but the result is simple: The source potential of an electrode is the average of the difference of potentials between the electrode and its neighbouring electrodes. Consider, for example, the Cz electrode, recorded as (Cz-Ref), the source potential of Cz, will be indicated as Cz_{SRC} and can be calculated, under the hypothesis of using only four neighbouring electrodes, by the following formula:

$$Cz_{SRC} = \frac{(Cz - Fz) + (Cz - Pz) + (Cz - C3) + (Cz - C4)}{4}$$

Visually, the impact of calculating the source potentials for all the electrodes on the scalp is shown in Fig. 5.22:

As can be seen from Fig. 5.22, the potential of the Cz electrode, that is, the source of the signal, is the only location that the source potential calculation has increased, which highlights the source of the signal itself.

It is worth noting that the source reference can be seen as an average reference where the term to subtract *SRC* varies from electrode to electrode instead of being the same for each electrode. If we write this in formulas, we get

$$Cz_{SRC} = \frac{(Cz - Fz) + (Cz - Pz) + (Cz - C3) + (Cz - C4)}{4} = \frac{4(Cz - Ref) - \left[(Fz - Ref) + (Pz - Ref) + (C3 - Ref) + (C4 - Ref)\right]}{4}$$
$$= (Cz - Ref) - \left[0.25(Fz - Ref) + 0.25(Pz - Ref + 0.25)(C3 - Ref + 0.25))(C4 - Ref\right] = (Cz - Ref) - SRC$$

It becomes then a problem of calculating the weights that every neighbouring channel should have for the calculation of the SRC potential and to define how many neighbouring electrodes one wants to consider, typically 4 or 8. On a real EEG signal, the effect of the calculation of the source reference is shown in Fig. 5.23:

The figure shows clearly that the eye movement becomes visible only on the Fp1 and Fp2 electrodes (that are close to where they generate) and does not contaminate other electrodes as was the case with the average reference. Similarly the alpha-rhythm is only seen on the occipital electrodes O1 and O2.

Note that, unlike the average reference, the potential of the electrodes varies in a non-uniform way so that the source reference changes the display of the signals in all bipolar montages, not only in the unipolar montages.

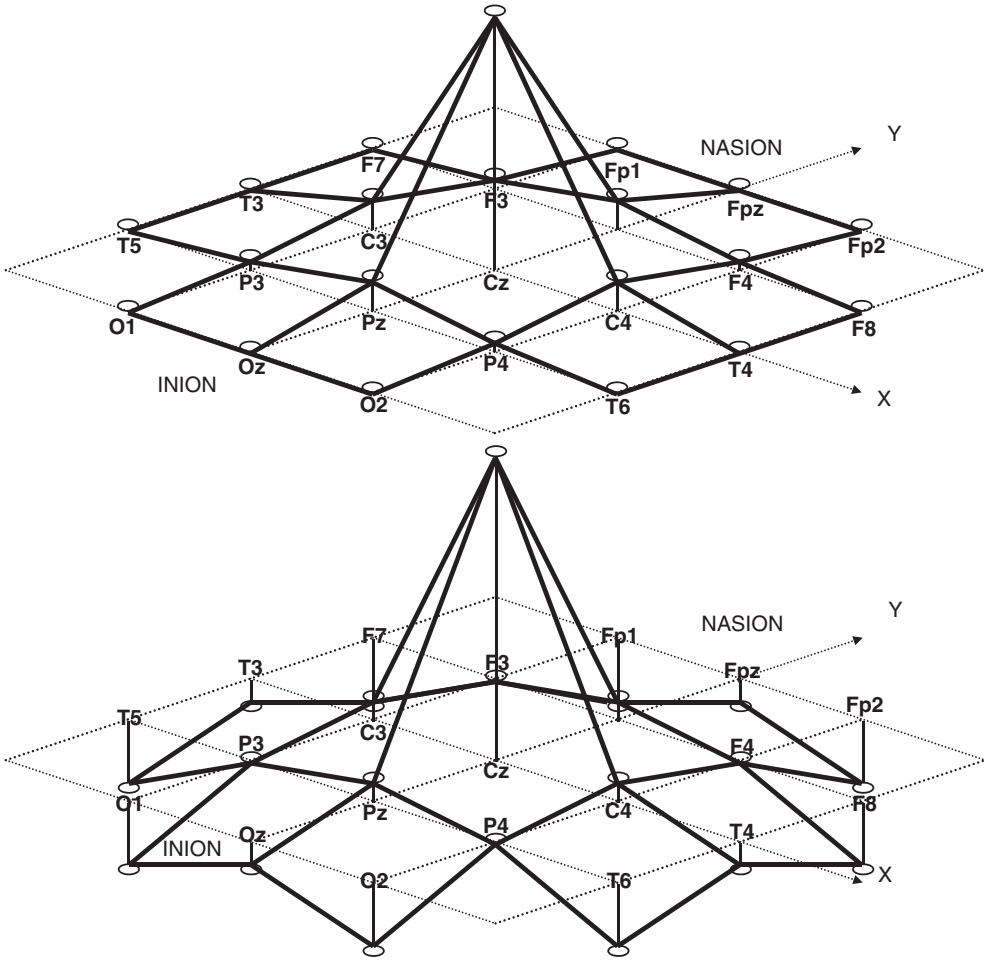

Fig. 5.22 Example of calculation of source potentials

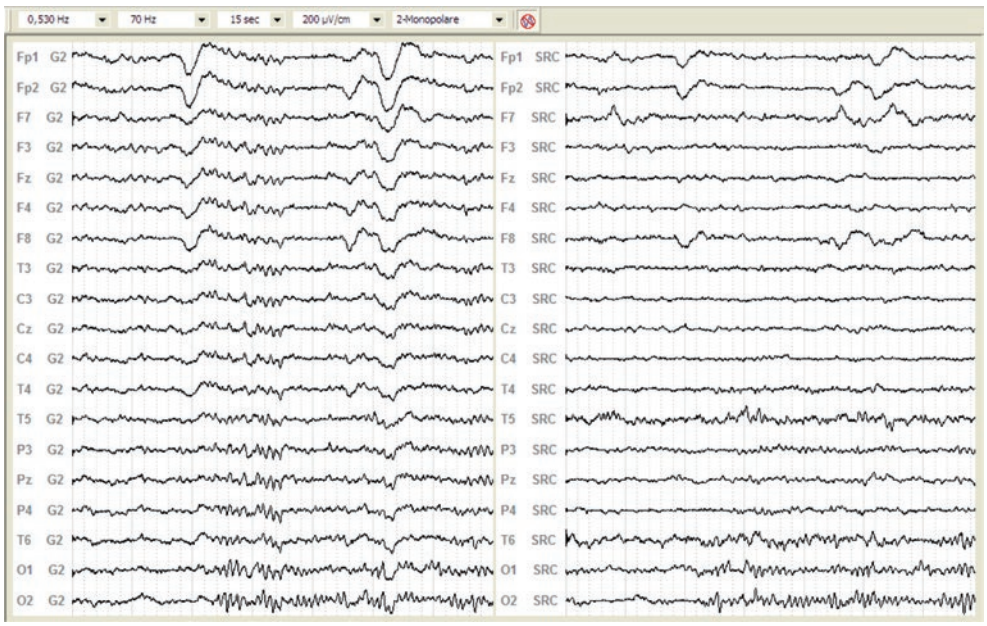

Fig. 5.23 Effect of the source reference on an EEG signal

Reference

1. Recommendation for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl. 1999;52:1–304.

EEG Signal Analysis

6

Cristiano Rizzo

6.1 Introduction

The analysis process of the EEG signal is to obtain values that can highlight a particular property of the signal itself, thus characterizing it. Any value obtained also needs to be displayed correctly through an accurate drawing technique in order to make the value useful and clearly legible to the user.

Given the definition, it is clear that there are many different EEG signal analyses and display techniques, so to list them would not be useful.

As such, given the objective of this section, we have chosen to list only some of the most diffused techniques of signal analysis and possible display techniques. We have selected the classic *spectral analysis*, the calculation of *parameters in the time domain* and their main display techniques as *cerebral mapping*, *trending over time* and *time-frequency graphics.*

6.2 EEG Signal Analysis in the Frequency Domain

Signal analysis in the frequency domain, or *spectral analysis*, is a technique widely used in several scientific fields and is the basis of many common processes such as MRI. By definition, spectral analysis is a statistical analysis of data, and its complete technical description is far too complicated for the purposes of this section, so it will not be included here. We will instead try to highlight its importance without getting too much into theory. The terminology used will not be the most precise from an engineering point of view, but hopefully this would allow a better understanding of the point.

We can start by stating that spectral analysis is based on the transformation of the EEG signal from the time domain (a series of samples in time) into the frequency domain (a series of samples for each frequency). The greatest advantage of this operation is the condensation into a few values of the information contained in some seconds to some hours. As this is by definition a statistical analysis, the result will be an average information on the structure of the EEG signal and will not highlight any very short signal patterns or any signal that has a weak power.

The basic principle is that any signal can be obtained as sum of pure sinusoidal components, with different amplitudes and phases as shown in Fig. 6.1.

In this example the 2 seconds of EEG signal are obtained as the sum of just four components at 4, 10, 11 and 20 Hz, each of them with different amplitudes (10 μV the 4 Hz component, 50 μV the 10 Hz component, 30 μV the 11 Hz component, 14 μV the 20 Hz component). The signal in the frequency domain in Fig. 6.1 shows, for each frequency, the amplitude of the component (to be exact, half of the peak to peak amplitude).

The display of the signal as a *spectrum*, as in Fig. 6.2, is a graphic that shows, for each pure component in the frequency domain, the power of the signal at that frequency and is called power spectral density (PSD). This graphic should be represented as a bar graphic, but, in reality, it is always drawn as a continuous graphic where the *X*-axis is the frequency (measured in Hz or cycle/s) and the *Y*-axis is the power density of each frequency quantum (measured in μV^2/Hz). The calculation of this decomposition is obtained by means of the Discrete Fourier Transform (DFT) that in the version that allows a very fast calculation, introduced in 1970 [1], takes the name of Fast Fourier transform (FFT).

Please note that Fourier analysis is just one of the possible spectral estimation techniques; other techniques like autoregressive modelling can be found in the literature [2].

Spectral analysis consists of cutting the EEG signal into epochs of 2 s or more and then transforming, according to the Fourier technique, every epoch to obtain the PSD. Finally, an average of all the spectrum is performed and the result is displayed as a graphic.

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O. Mecarelli (ed.), *Clinical Electroencephalography*, https://doi.org/10.1007/978-3-030-04573-9_6

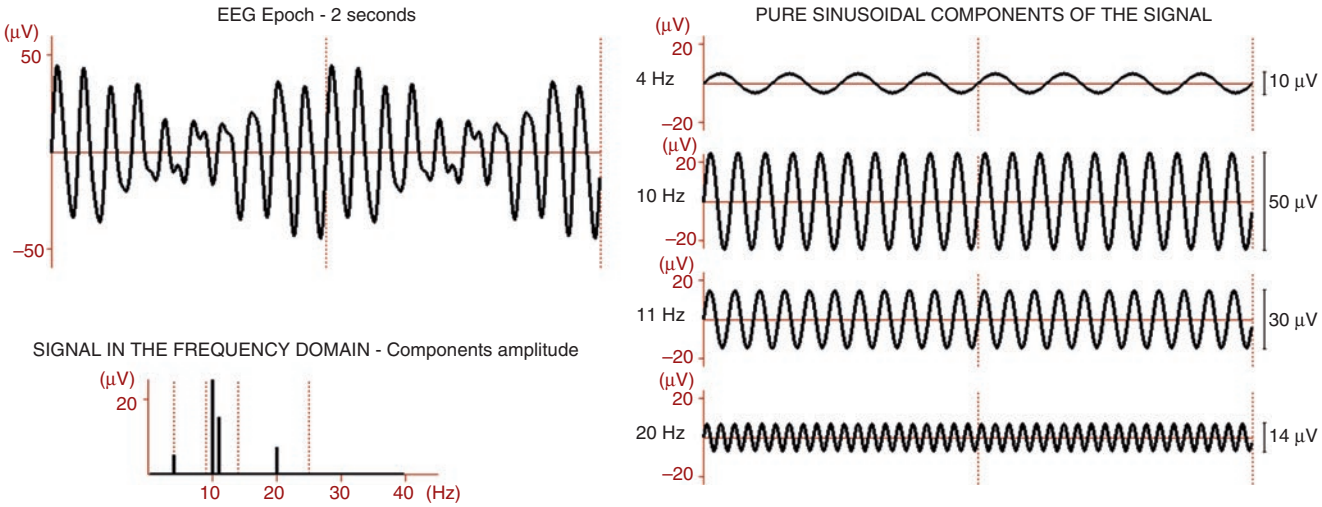

Fig. 6.1 Decomposition of an EEG signal into pure sinusoidal components

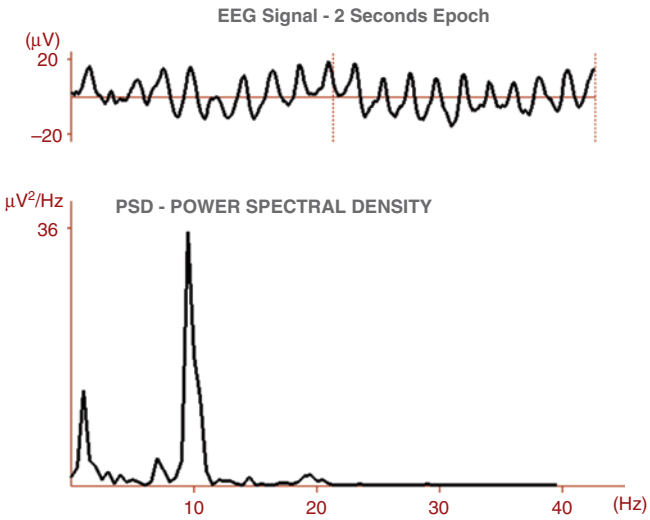

Fig. 6.2 Spectrum, or PSD, of an EEG signal characterized by alpha rhythm

As already discussed, spectral analysis is not a precise method but an average method as it highlights the harmonic content of the signal in predefined epochs; adding to the fact that several spectrums are averaged, it is clear that this technique cannot highlight short signal transient or very low-power signals.

In order to improve the performance of the spectral analysis, several techniques are often used, such as *overlapping*, *detrending* and *tapering*.

Overlapping consists of running the analysis on epochs that are overlapped, that is, analysing fixed epochs of 2 s, starting every second as shown in Fig. 6.3. This allows the analysis of every element of the signal in a way that in one epoch, or in the next one, the element is centred.

Detrending consists of removing continuous components or slopes from each epoch. Technically this means removing from the EEG signal the "line" that best approximates the evolution of the signal in the given epoch, as shown in Fig. 6.4:

Figure 6.4 shows the line that best interpolates the EEG signal and the signal resulting after the subtraction of this line. The resulting spectrum highlights a modification of the power in a way that best represents what an EEG expert could see in the signal itself. The "slow" components of the signal that are removed are rarely of interest for the analysis, while the faster components are highlighted, and they are quite often most important for the analysis.

Tapering, or windowing of the signal, aims to reduce the spectral leakage phenomenon that, spreading the power of a signal among the spectrum, tends to hide important components of the signal that might have a weaker power. The improvement obtained with this technique is important especially in those cases where a dominant signal of high power (i.e. slow EEG waves) could "mask" other significant components (i.e. alpha rhythm). Technically speaking, this operation consists of multiplying any signal epoch by a given function that usually is equal to 0 at the extremes of the epoch.

6.2.1 EEG Parameters in the Frequency Domain

Once standard spectral analysis has been performed on an EEG signal, properly split into epochs and conditioned with the techniques described in the previous paragraph, the average spectrum of the analysed EEG signal is obtained. This spectrum is then split into parts that are normally used for the description of the EEG rhythm, which are delta, theta, alpha and beta, as shown in Fig. 6.5.

Splitting the spectrum this way allows the calculation of several other data that could summarize interesting charac-

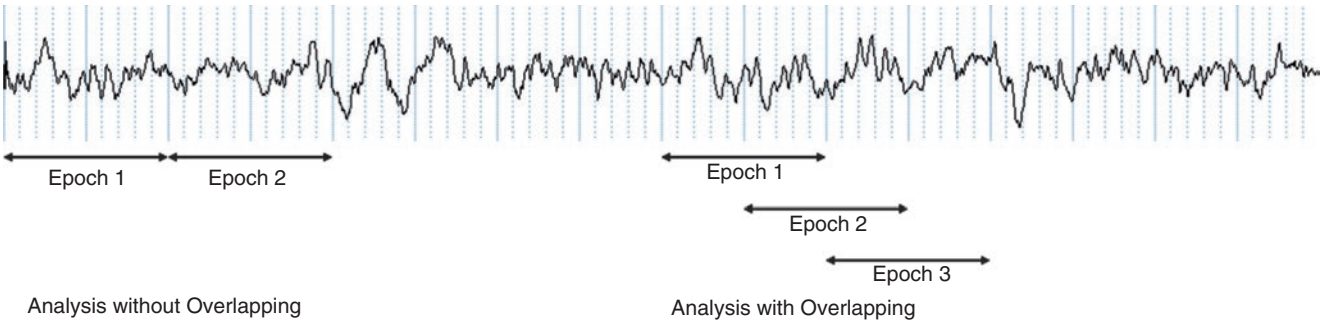

Fig. 6.3 Epoch selection with and without overlapping

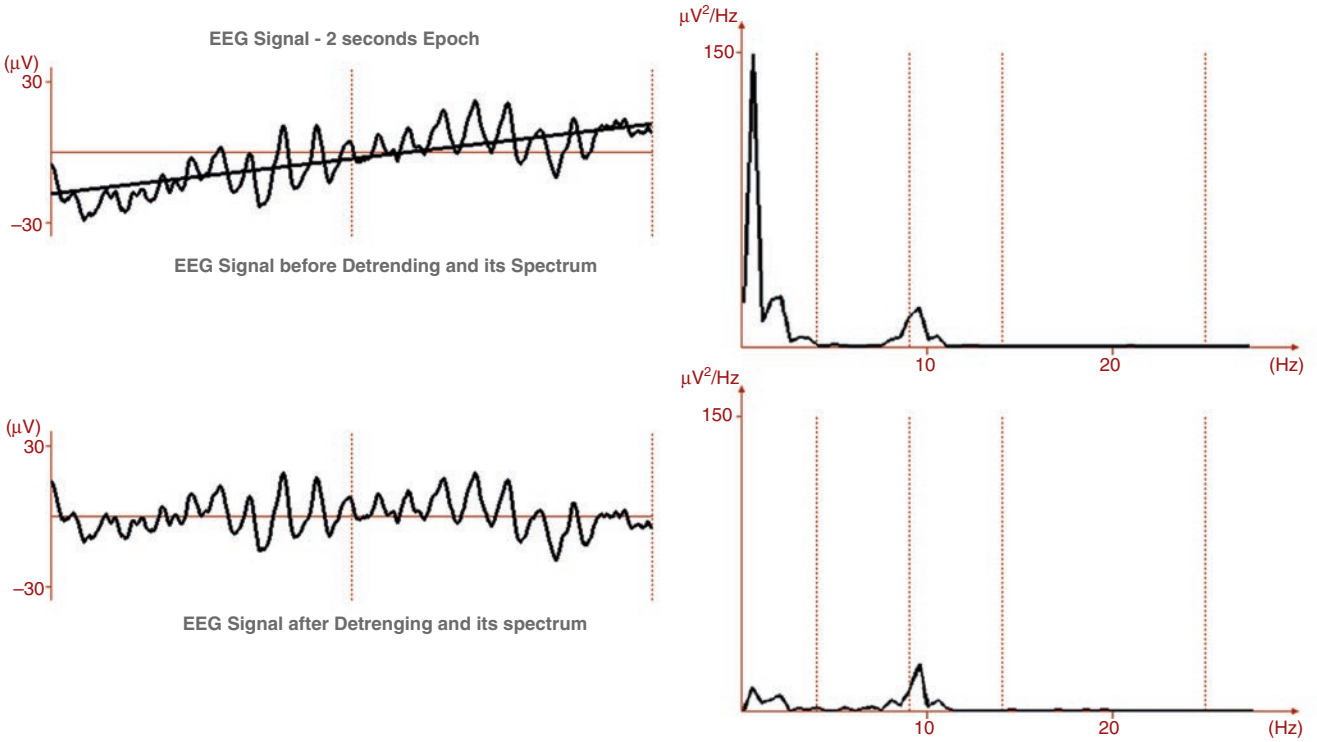

Fig. 6.4 Example of detrending of an EEG signal epoch

teristics of the EEG signal that quantify something that is normally determined with the visual inspection, like the following:

- *Absolute Power* in the different bands. These values are calculated as the area underlying the spectrum of the signal in the interval of frequency that defines each band,[1] as shown in (Fig. 6.6). Their measurement unit is μV^2.
- *Relative Power* in the different bands. These values are calculated as the ratio between absolute power in a band and the total power (i.e. the sum of the power in all the bands). Under the assumption to use the four standard bands, one could obtain:

$$P_{\mathrm{REL}}(\mathrm{alfa}) = \frac{P_{\mathrm{ABS}}(\mathrm{alfa})}{P_{\mathrm{ABS}}(\mathrm{delta}) + P_{\mathrm{ABS}}(\mathrm{theta}) + P_{\mathrm{ABS}}(\mathrm{alfa}) + P_{\mathrm{ABS}}(\mathrm{beta}) +}$$

- As a ratio between two homologous values, the result is a-dimensional and is normally expressed as a percentage.
- *PPF—Peak Power Frequency*. This refers to the frequency where the spectrum has its peak, as shown in Fig. 6.7. This calculation could be restricted to the frequency interval defined by each band. The measurement unit is that of frequency, that is, Hz or cycle/s.

[1] Mathematically it is the integral, in the frequency domain, of the PSD.

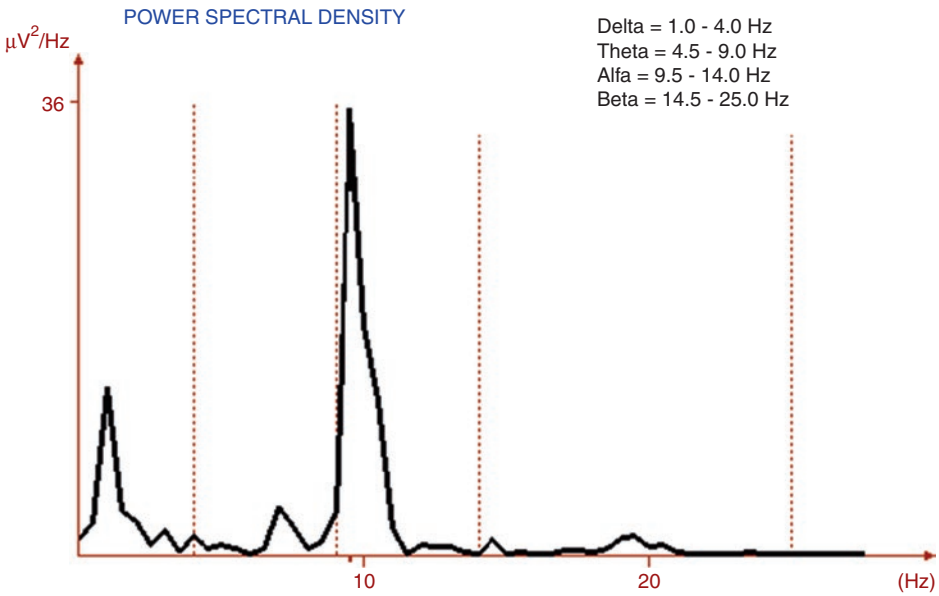

Fig. 6.5 PSD of an EEG signal split into standard bands

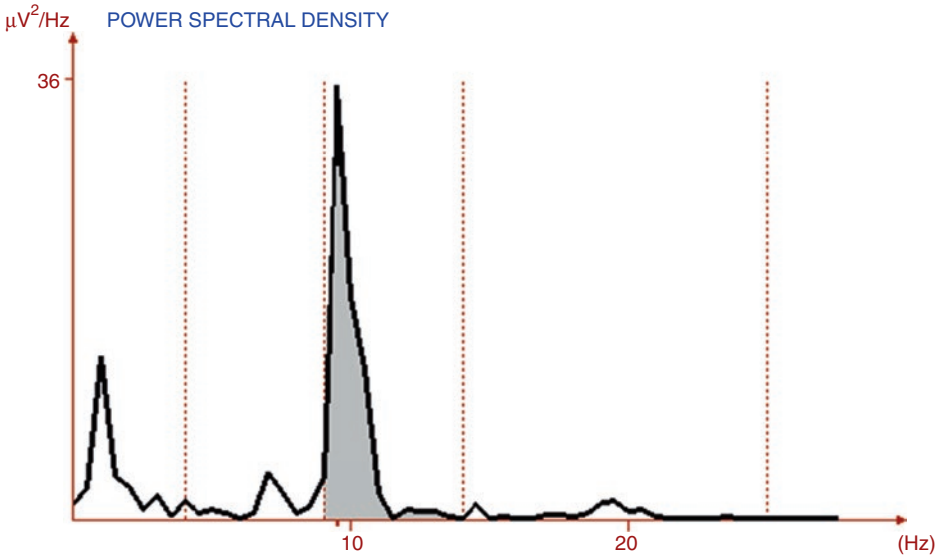

Fig. 6.6 Absolute power of the alpha band shown as area underlying the spectrum

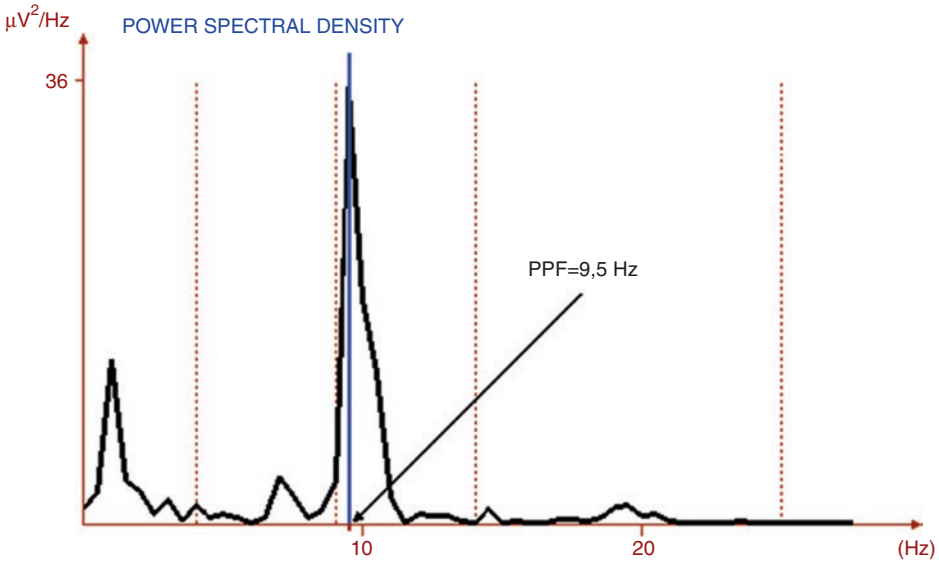

Fig. 6.7 Example of calculation of PPF on the spectrum of an EEG signal

- *MF—Median Frequency*. This is the frequency that splits the spectrum into two regions, each underlying 50% of the total power, as shown in Fig. 6.8. The measurement unit is that of frequency, that is Hz or cycle/s.
- *SEF—Spectral Edge Frequency*. This is defined as "size" of the spectrum. It can be obtained with different techniques, and quite often, it is defined as the interval of the spectrum that underlines 95% of the total power, as shown in Fig. 6.9. The measurement unit is that of frequency, that is, Hz or cycle/s.
- *MDF—Main Dominant Frequency*. This is the dominant frequency of the spectrum, defined as an average of the frequencies weighted by the power at each frequency. The calculation formula is:

$$\mathrm{MDF} = \frac{\sum_{f=0}^{f_{\mathrm{MAX}}} f \cdot \mathrm{PSD}[f]}{\sum_{f=0}^{f_{\mathrm{MAX}}} \mathrm{PSD}[f]}$$

- The measurement unit is that of frequency, that is, Hz or cycle/s.

All of these parameters can be used by themselves or in combination with each other to define new variables, often called *indexes*. A common example in the literature is the theta/alpha quotient that is calculated as the ratio between the absolute power in the theta band and the absolute power in the alpha band of the same signal. It is easy to understand that several other indexes could be defined as a function of

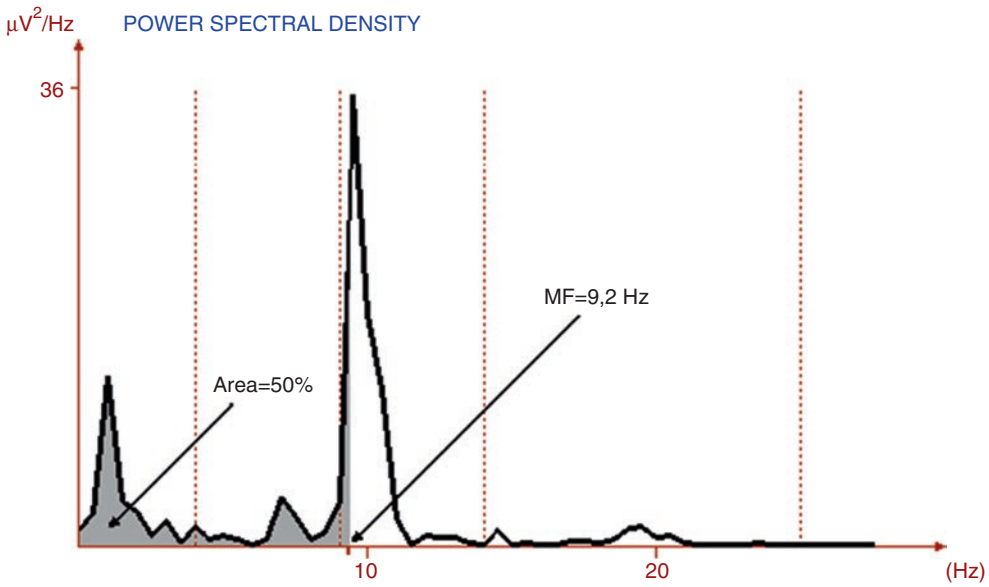

Fig. 6.8 Example of calculation of MF on the spectrum of an EEG signal

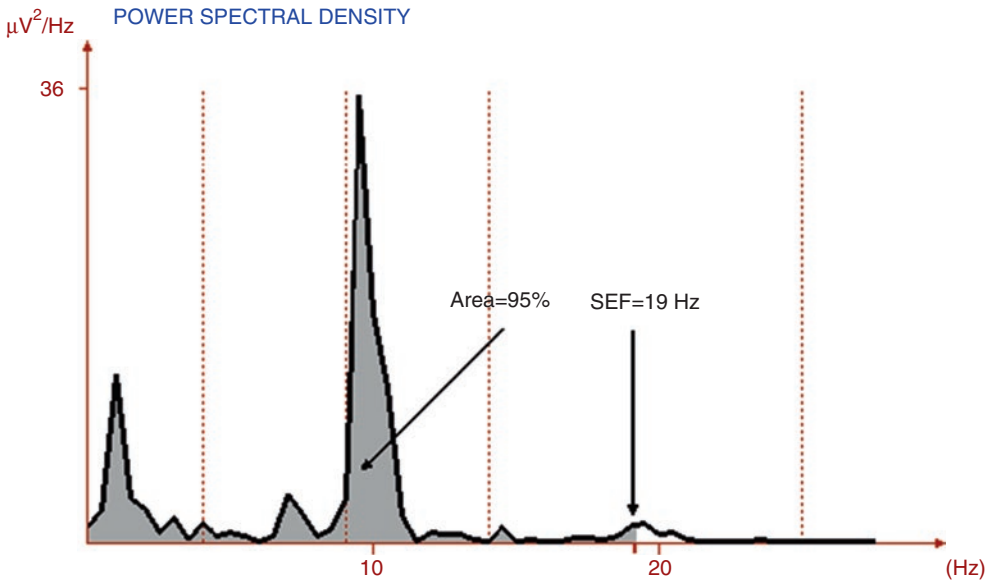

Fig. 6.9 Example of calculation of SEF on the spectrum of an EEG signal

parameters of the same signal, as well as function of parameters of different signals. An example of the latter could be the ratio between the same parameter of two electrodes on different sides of the brain, defining then a sort of asymmetry index.

Those indexes, being often the ratio between homologous entities, have some advantages:

- They can represent very complex characteristics of the signal in a very concise way.
- They are in general less sensitive to artefact, at least to those contaminating the electrodes in a similar way.
- They are generally less sensitive to big differences in the absolute power of the signal of different subjects, characteristics that they share with the relative power.

6.2.2 Data Calculation

A "historic" problem of the spectral analysis is the complexity of the calculation—the enormous amount of effort necessary to obtain and display data. For example, the fast Fourier transform (FFT) of a single epoch of one EEG channel sampled at 256 Hz requires 2048 multiplications plus the operations necessary to acquire data, its memorization and its display. This means that 1 min of 20 channels of EEG data requires over two million multiplications. This is to understand that, before the recent evolution of digital technology, such a calculation was very difficult thus limiting the diffusion of the technique. Today, the modern computer can easily perform such calculations, allowing for the deployment of the technique more widely.

6.3 EEG Signal Analysis in the Time Domain

EEG parameters calculated in the time domain are all measurements and/or calculations performed directly on the original signal, without any transformation as in the case of the spectral analysis.

6.3.1 EEG Parameters in the Time Domain

There exist several EEG parameters in the time domain, and, given the scope of this book, we will consider only those parameters that are often used and cited in the literature:

- *Zero Crossing*: defined as the number of times the EEG signal crosses the baseline, as shown in Fig. 6.10. Unfortunately, this parameter does not always represent what is referred to in EEG as the rhythm of the signal. Quite often the rhythm of interest is embedded into slow waves that make the calculation false. An example of this is in Fig. 6.10.
- Note that in the mentioned example, there are 32 crossings in 2 s, that is, 16 per second, which should lead to a rhythm of the signal of 8 Hz, but, in reality, it is about 10 Hz. The problem is in the crossings lost due to the drift the signal has in a certain interval that avoid it crossing the baseline.
- *Burst Suppression Ratio*: this is a parameter that quantifies the degree of suppression of an EEG signal [3]. It is calculated, on an epoch of fixed duration, as the ratio between the time the signal remains stable below a given threshold, i.e. ±5 μV, and the duration of the epoch itself as shown in Fig. 6.11. In order to consider an EEG signal suppressed, the signal doesn't have to exceed the threshold for at least 400–500 ms. If within an epoch there are multiple intervals of suppression, they should be added. This parameter sets, practically speaking, which percentage of the epoch is occupied by a suppressed signal.
- In this example there is a suppression interval of 0.810 s on an epoch of 2 s, giving then a BSR of 0.810/2.000 = 0.405, that is, 40.5%.

6.4 Data Display Technique

Data display is fundamental in any kind of analysis. This is why some paragraphs are dedicated to this point, dealing with the most commonly used display techniques.

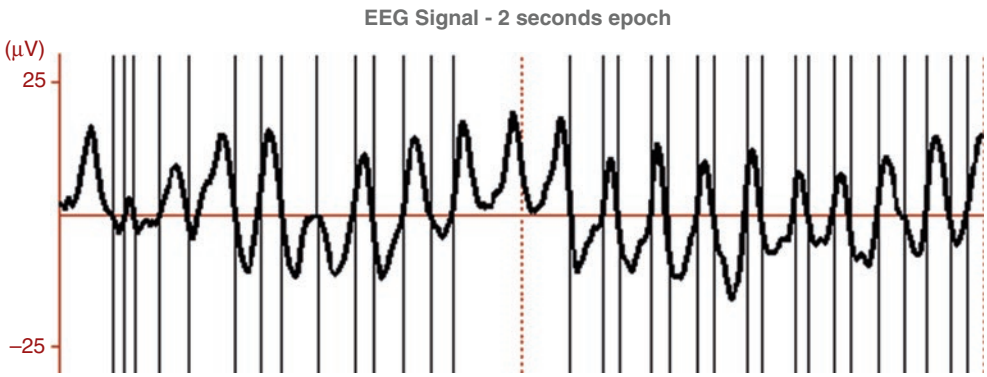

Fig. 6.10 Example of calculation of "Zero Crossing" of an EEG signal

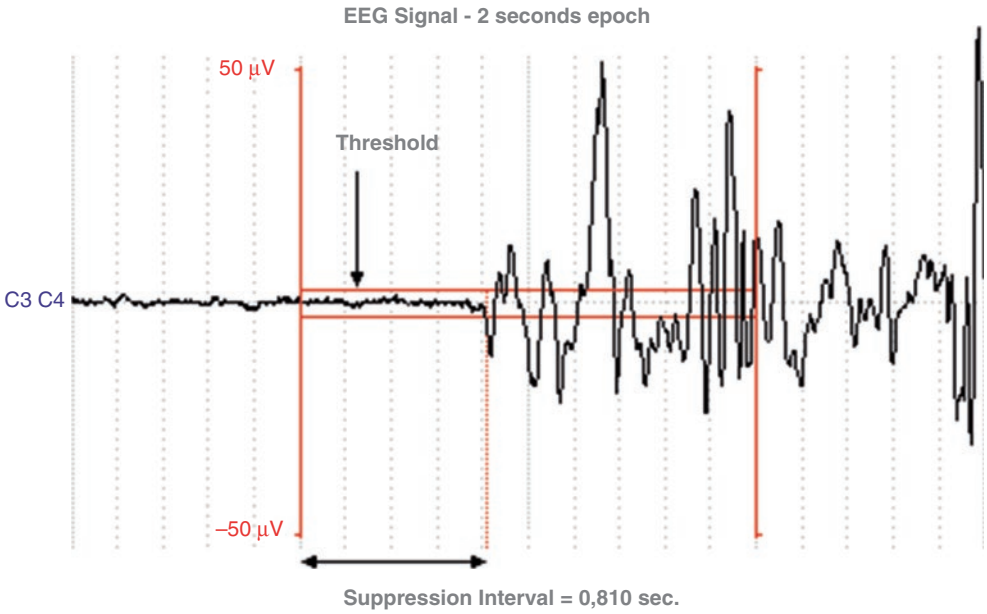

Fig. 6.11 Calculation of "Burst Suppression Ratio (BSR)" on an EEG signal

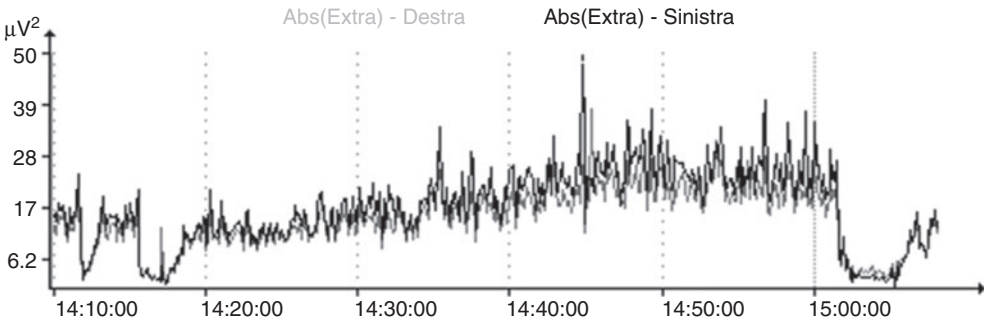

Fig. 6.12 Trend of absolute power on the right and left hemisphere

When choosing the display technique, one should focus on which characteristics should be highlighted:

- Evolution of the data over time
- Spatial distribution of the data

We will now analyse the most diffused display technique according to these two choices.

6.4.1 Display of Data Evolution over Time

All display techniques of data evolution over time share the same characteristic: a time axis along which all information are drawn. In order of complexity, some of the possible techniques are:

- *Histograms and Trends*. These are the simpler techniques, often the most efficient, to display time evolution of a parameter, with the down side of not allowing the display of a lot of variables on the same graphic in order to avoid compromised legibility. The display consists in a Cartesian graphic with the time in an axis (often the horizontal one), more or less compressed, on the other axis the parameter to display. This graphic can display any kind of parameter, calculated both in time and frequency domains. The example in Fig. 6.12 shows a trend with two absolute power calculated on all derivation of the right (light grey) and left (dark grey) hemisphere of an EEG recorded during carotid endarterectomy.
- *Compressed Spectral Array (CSA)*. This is a type of display often used in the past to display the spectral analysis. It was used for the first time in 1971 for the advantages it offers for the display of power spectrum over time. It consists in a vertical successive display of power spectrum obtained over time as shown in Fig. 6.13, obtaining then a graphic with a prospect effect.
- The *X*-axis shows frequency, the *Y*-axis shows the power and the step between each spectrum is the time between each interval so that *Z*-axis shows time. This kind of display is helpful and can easily show the variation over time of background rhythm. It still needs to be interpreted by an expert and is problematic in that big artefacts can easily hide all the graphic behind the last drawn spectrum. This is the reason this technique has been supplanted by the DSA.

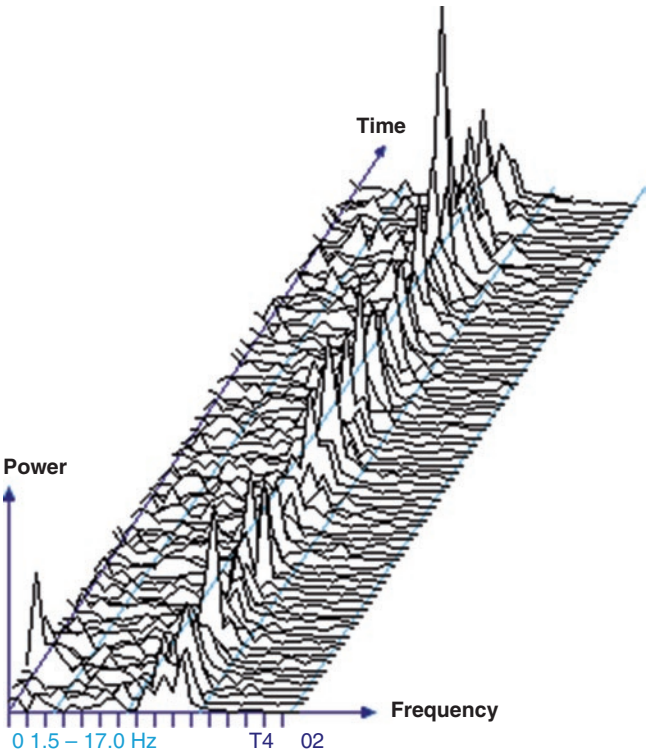

Fig. 6.13 CSA of an EEG characterized by an alpha rhythm

- *Density Spectral Array (DSA)*. This is another technique to display time evolution of the spectral analysis that uses a chromatic scale to display the power of each frequency quantum of the spectrum. This means that every power spectrum is represented by a coloured stripe (or greyscale stripe) where the *Y*-axis represents the frequency of the point; the colour of the point represents the power of the frequency spectrum at that frequency. The succession of such stripes represents the time evolution of the spectrums, that is, the DSA, as shown in Fig. 6.14.
- This type of display does not mask the previous components, as is the case with CSA, and can easily display very long sequences; however, the presence of very weak modification of power is not always as easy to localize as it was with the CSA.
- *Wavelet*. This is a technique very similar to DSA, which is a time-frequency graphic that uses a chromatic scale to display the power of each frequency component at a given time. The difference with the DSA stands in the spectral analysis technique used, not a simple Fourier transform but a more complex wavelet transform, which allows a better indication of the power of the frequency components for even the shortest intervals, in the order of milliseconds. This allows a more detailed data analysis, unfortunately losing the global overview characteristics, which is one of the bigger advantages of DSA. Wavelet transform is therefore used to analyse short time interval like evoked potentials or particular EEG pattern (i.e. spike) as shown in Fig. 6.15 but can in principle be used for longer EEG interval.
- *aEEG — Amplitude Integrated EEG*. This is a technique to display EEG in time domain that performs special data processing that can be summarized as follows:
  - Selective band-pass filter between 2 and 15 Hz
  - Transformation of the signal in semilogarithmic scale[2]
  - Rectification of the signal[3]
  - Smoothing to identify only maximum and minimum peaks of the resulting signal
  - Graphic of the result
- The graphic obtained with this technique shows condensed information about the amplitude of the signal, mainly showing the amplitude of the biggest peaks and that of the smallest peaks, as shown in Fig. 6.16.

  This technique, introduced decades ago [4] but still often used especially in neonatal intensive care units, is normally identified as CFM (cerebral function monitor), which is the name of the first device that used this technique.

6.4.2 Display of Spatial Distribution of Data

Brain Mapping is a technique that aims to display the spatial distribution on the scalp of an activity that is measured only on a few points of the scalp itself. Once such a distribution is calculated from the values at these points, it can be displayed obtaining the so-called maps.

The calculation performed to obtain such a mapping is an interpolation of the activity that is effectively measured on the scalp, and, depending on the kind of activity, the following results can be obtained:

- *Amplitude Maps*: this is a display of the distribution on the scalp of the amplitude of the EEG signal measured at a given time, that is, for a digital signal, at a given sample.
- *Frequency Maps*: this is a display of the distribution on the scalp of the average power in a given frequency band

[2]Semilogarithmic scale means that all values up to 10 μV remains linear and all values above 10 μV are transformed in a logarithmic scale.

[3]Rectification means turning to positive all negative signals. Mathematically this is the module of the value.

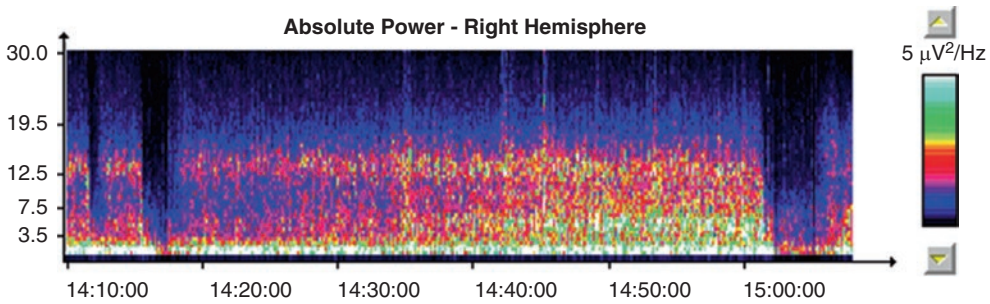

Fig. 6.14 DSA of an EEG trace

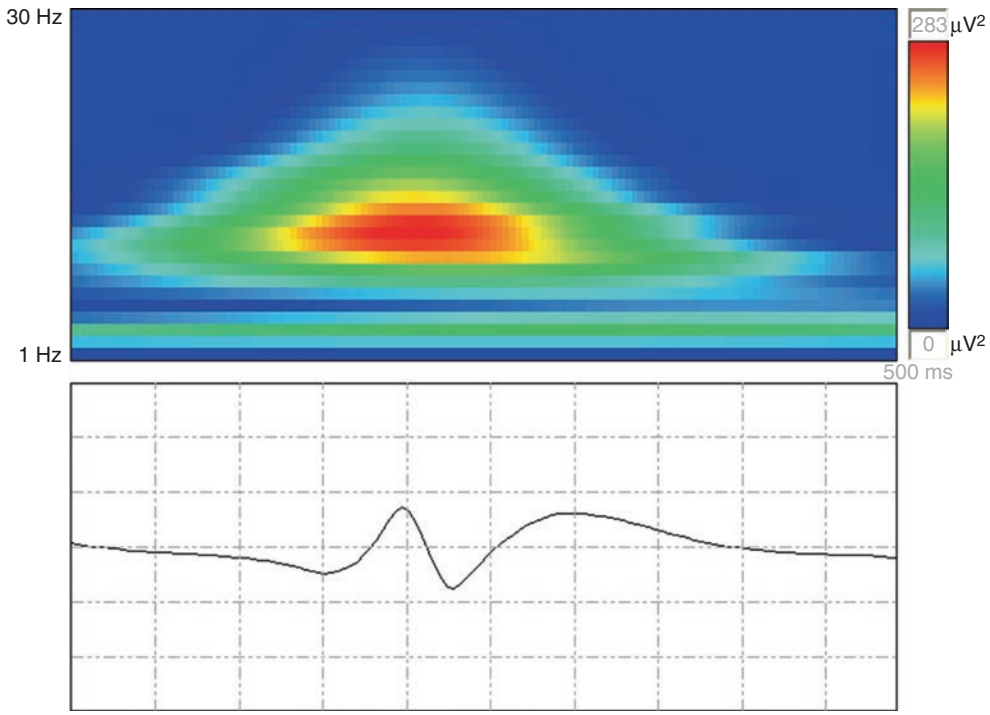

Fig. 6.15 Wavelet transform of a spike and wave signal

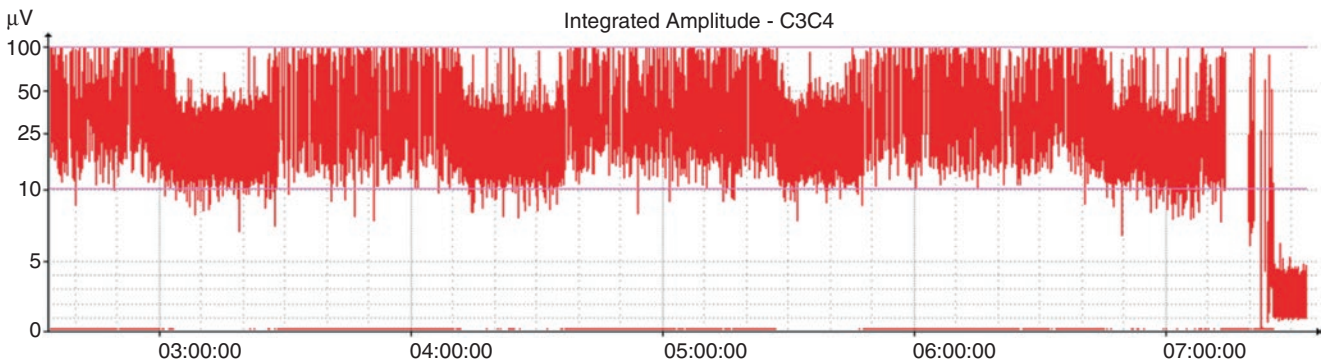

Fig. 6.16 EEG trace displayed as aEEG

of the EEG signal calculated in one or more selected time interval on which spectral analysis is performed.
- *Coherence Maps*: this is a display of the distribution on the scalp of the average coherence in a given frequency band of the EEG signal calculated in one or more selected time interval on which spectral analysis is performed.

This technique has evolved in recent time thanks to the integration of functional data (EEG, EP) with the structural data supplied by the MRI. In fact, if we were to display the activity all over the scalp, we have a few choices to create a model of the scalp, like using a simple mathematical model of the scalp, which is normally a circle (planar) or a sphere, or generating a realistic model of the scalp from the MRI.

In the following paragraphs, we will provide an overview of the basic elements of a correct brain mapping, always referring to a general entity to be mapped (amplitude, power or others).

6.4.2.1 Spatial Sampling

Brain mapping is based on the principle of spatial sampling. The theoretical fundamentals of this are the equivalent of the sampling theorem of EEG signals analysed on Chap. 5 but extended to two dimensions. A deep analysis of the spatial sampling is probably too complex in this context; it is only important to point out the principle that, in the different spatial directions, the signal should not have a too high modification compared to the number of measures (point of measure being the electrodes). If, as in the example in Fig. 6.17, in a space of 10 cm we apply 10 electrodes, getting then 10 measures (F_{SAMP} = 100 sample/m), the signal cannot exceed 50 "waves" per metre (50 = Max spatial frequency, that is, $F_{SAMP}/2$), which means a maximum of 5 "waves" in 10 cm under test. This, assuming a uniform spatial sampling, should be verified in all possible directions of the space.

Given that it is not possible to restrict the signal from having a certain spatial modification, one can simply adapt the number of point of measurement on the scalp in a way to properly cover all possible spatial modification of the signal to be examined.

Several experiments have been performed in order to properly identify the amount of spatial variation of the EEG signals, which is how the activity is different from one point to another, and the results led to the following:

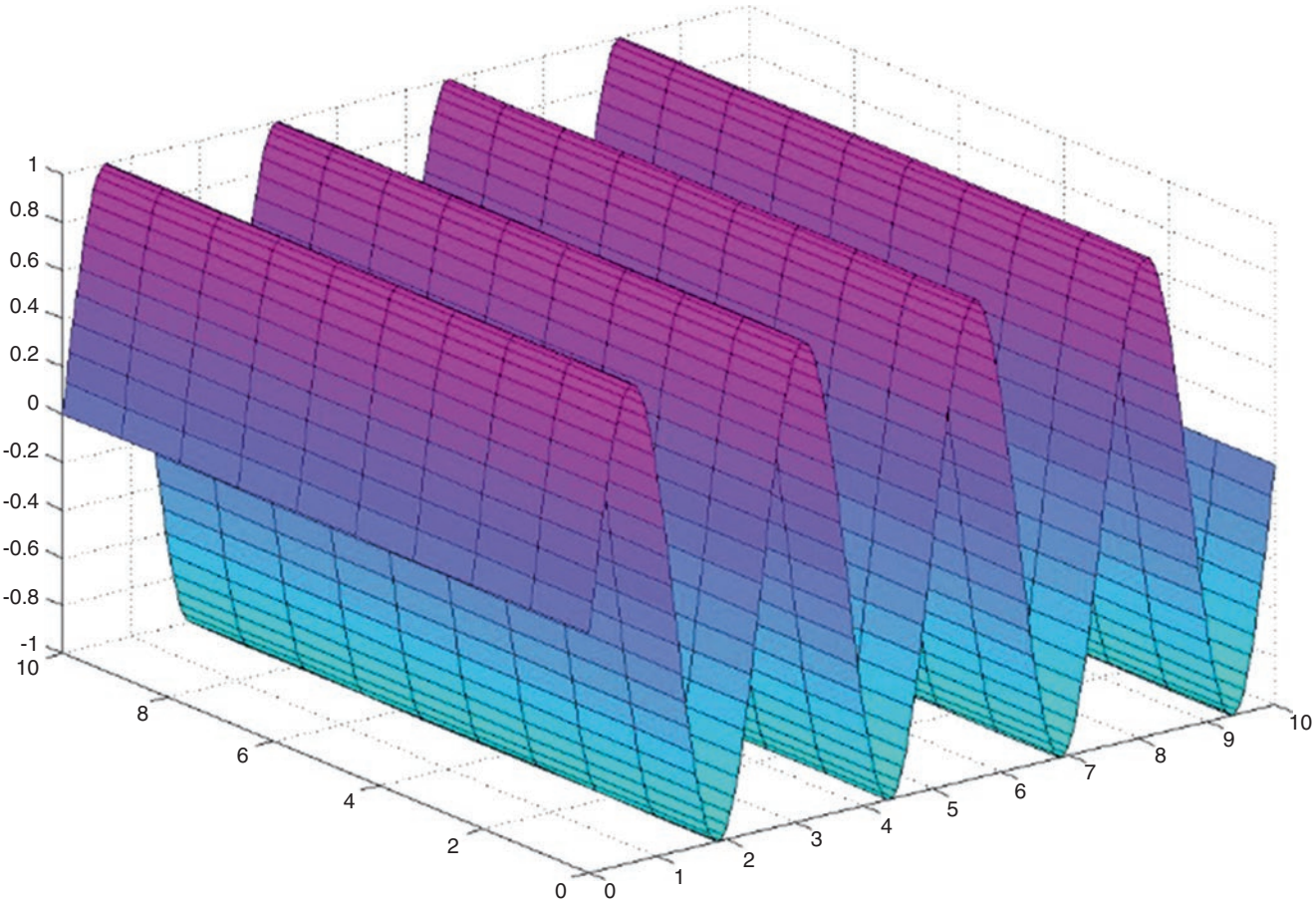

Fig. 6.17 Signal with four "waves" along the *X*-axis

- For a correct mapping of the cerebral EEG activity in *standard clinical application*, the minimum number of electrodes to be used is *25*, with positions based on the 20% and 10% of standardized measurements from anatomical landmarks on the skull [5]. These 25 electrodes, which used to be 19 [6], are Fp1, Fp2, F9, F7, F3, Fz, F4, F8, F10, T9, T7 (ex T3), C3, Cz, C4, T8 (ex T4), T10, P9, P7 (ex T5), P3, Pz, P4, P8 (ex T6), P10, O1 and O2, positioned according to the scheme in Fig. 6.18.
- For a correct mapping of the cerebral EEG activity requiring a *precise spatial localization* like source localization, a minimum number of *64* electrodes is required, positioned according to the scheme in Fig. 6.18. This kind of recording, using 64 up to 256 electrodes, is often referred as high-density EEG (HD-EEG) [5] and is nowadays widely used in clinical practice.

6.4.2.2 Scalp Models

As seen in the previous paragraphs, in order to achieve proper brain mapping, a correct scalp model needs to be defined. Once the scalp model is defined, the electrode positions need to be measured (or defined) using the same coordinate system of the model. Scalp models can be basically divided into three categories:

- *Planar Models*: these are models defined on a planar surface, where contours can be a circumference or a contour similar to that of a head or a brain (in this last case quite often, the brain circumvolution is drawn on the plane as well). These models, given their simplicity, have been and still are widely used. The coordinate system is Cartesian, which means that the position of each electrode is specified by a pair of numbers (x, y). The value of such coordinates is obtained as projection on the axial plane of the measured (or supposed) electrode positions.
- *Three-Dimensional Spherical Models*: these are more refined models as they approximate the scalp with a hemisphere on which electrodes are placed. These models have often been used in research, and their efficacy has proven to be better than the planar models. The coordinate system, in this case, could be specified by three coordinates (x, y, z), but very often, for the sake of simplicity, one assumes the sphere with unitary radium so that for each electrode one specifies just two coordinates, called

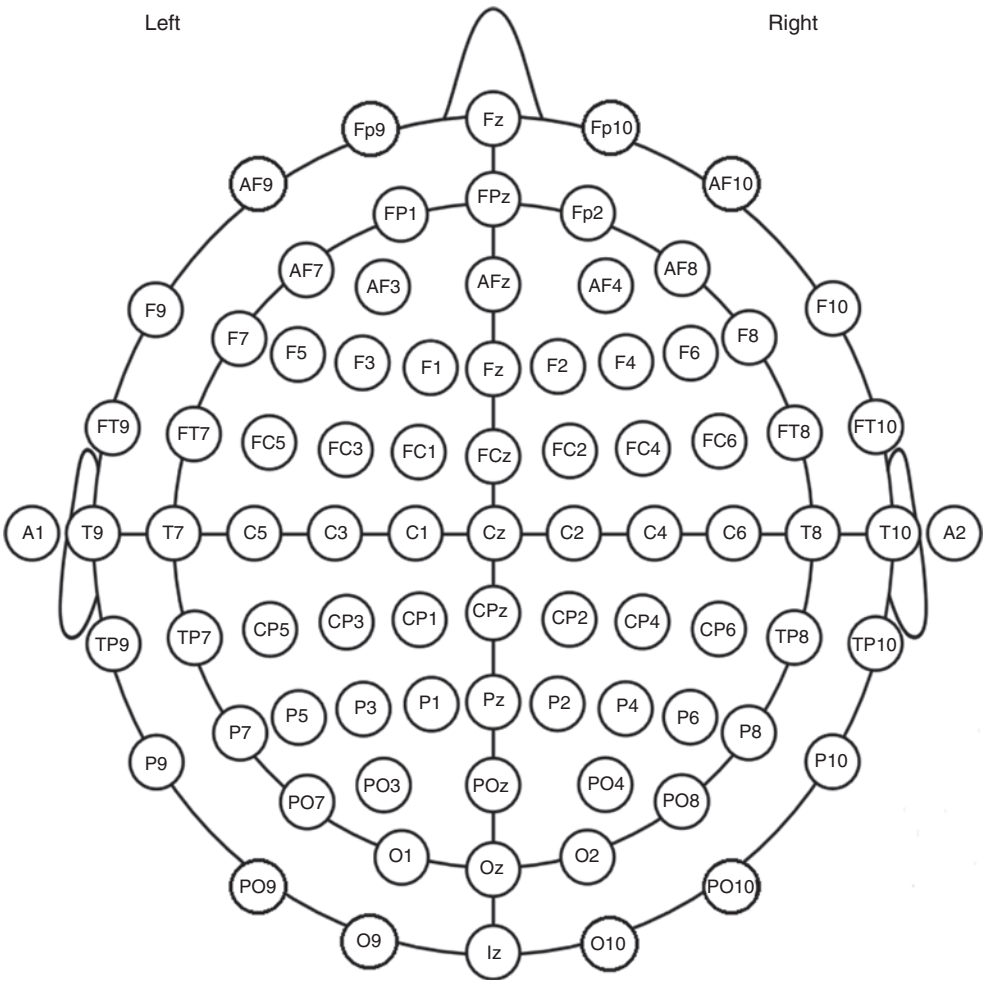

Fig. 6.18 Name and standard position of the IFCN standard 10/10 electrode system

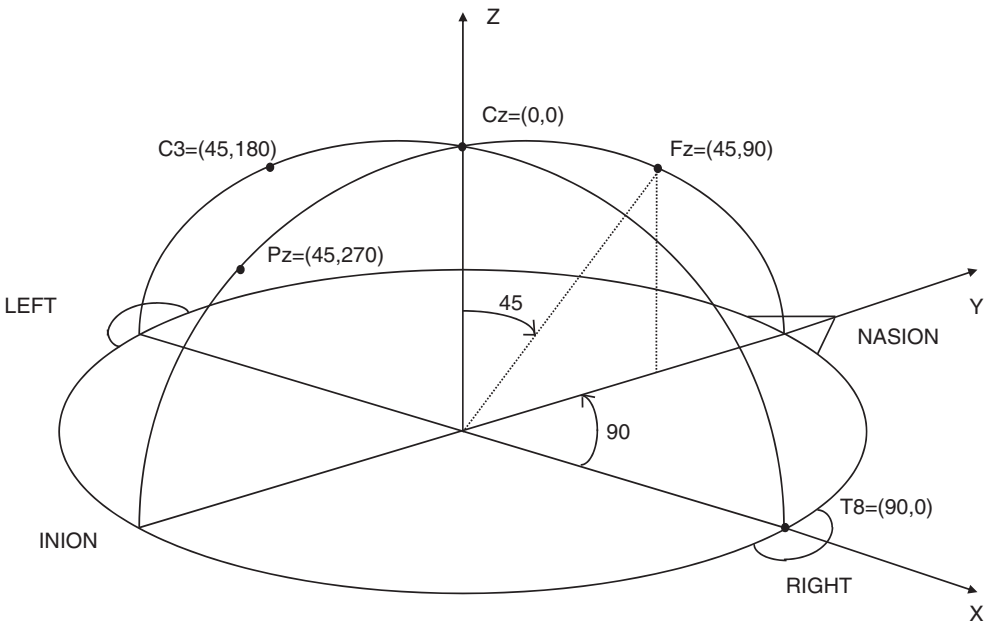

Fig. 6.19 Coordinate system for three-dimensional spherical models

latitude and longitude. Normally latitude is calculated with 0 in Cz, longitude with 0 in T8 (ex T4) as shown in the following picture (Fig. 6.19).

- An example of coordinates for the 10/10 system electrodes in Fig. 6.18 (excluding the lower ones), as latitude and longitude, could be those in Table 6.1.
- *Realistic Three-Dimensional Models*: these are models that try to minimize approximation by processing the MRI of the patient to obtain a model of the scalp surface. In order to do this, one needs dedicated software that reads MRI data, which is then processed to get a three-dimensional model of the head made of voxels and then create the model by, for example, drawing triangles that perfectly match the scalp surface. An example of such three-dimensional model and the related approximation of the scalp is shown in Fig. 6.20.

  The coordinate system, in case of realistic models, has to be Cartesian, defined by three coordinates (x, y, z). Such coordinates have to be precisely measured with dedicated tools that measure the exact position of a point in space, in all three dimensions, and use easy markers as a reference for the axis (i.e. nasion, inion, earlobes — easily identified in the MRI).[4]

6.4.2.3 Interpolation Techniques

As already discussed, brain mapping is the display of values of a certain signal on the scalp when the signal has been measured only on certain points. The fundamental operation is then the interpolation of the missing data, which can be obtained by means of several different algorithms; three of those algorithms, often used in practice, are analysed below:

1. *K-NN interpolation*: the K-NN method, which stands for K-Nearest Neighbours, is used to interpolate the value of the signal in a given point, by means of the values measured on the K nearest electrodes to the point itself. In general the value of the point can be calculated as a weighted average of the values of the K nearest electrodes, where the weight is proportional to the distance of the point from the electrodes. This is a very simple and fast technique that involves the placement of electrodes on the scalp and was the most used technique for brain mapping in the past, before technology provided automated calculation. It is a so-called "local" method, meaning that for the estimation of the value of the signal at a point, one uses a limited number of known measures, within the proximity of the point. This method shows another evident problem: the maximum and minimum values of the signal will always be located in one of the electrode positions, and this, clearly, is not likely to be accurate. This interpolation technique can be used with any of the scalp models discussed in the previous paragraphs.
2. *Interpolation based on planar SPLine*: this technique, which is applied in several other scientific domains [7], is a "global" technique versus "local", as all values of the measured electrodes are used to calculate the interpolated signal in a given point of the scalp model. Mathematically it is a very complex process, where the result is obtained by minimizing the curves of a plane that is forced to pass by all known points that can be placed at any position on the scalp. The continuous surface that is obtained is regular, and its maximum and minimum are not necessarily

[4]The devices that perform such measures are often called "3D tracker" and allow to measure with very good precision the position of the electrodes on the scalp.

Table 6.1 Coordinates of the standard electrodes as latitude and longitude

Electrode	Latitude	Longitude
Fp1	90	108
Fp2	90	72
F7	90	144
F3	61.8	130.7
Fz	45	90
F4	61.8	49.3
F8	90	36
T7 (ex T3)	90	180
C3	45	180
Cz	0	0
C4	45	0
T8 (ex T4)	90	0
P7 (ex T5)	90	216
P3	61.8	229.3
Pz	45	270
P4	61.8	310.7
P8 (ex T6)	90	324
O1	90	252
O2	90	288
Oz	90	270
Fpz	90	90
FC2	30	45
FC1	30	135
CP1	30	225
CP2	30	315
AF4	72.5	68
AF3	72.5	112
PO3	72.5	248
PO4	72.5	292
FC6	69.5	20
FC5	69.5	160
CP5	69.5	200
CP6	69.5	340
FT8	90	18
AF8	90	54
FPz	90	90
AF7	90	126
FT7	90	162
TP7	90	198
PO7	90	234
Oz	90	270
PO8	90	306
TP8	90	342
AFz	67.5	90
F5	75.5	139
F1	50	113
F2	50	67
F6	75.5	41
FC3	48	152.5
FCz	21	90
FC4	48	27.5
C5	67.5	180
C1	22.5	180
C2	22.5	0
C6	67.5	0
CP3	48	207.5
CPz	21	270
CP4	48	332.5
P5	75.5	221
P1	50	247
P2	50	293
P6	75.5	319
POz	67.5	270

located at the position of the electrodes. This interpolation technique can be applied to all scalp models discussed in previous paragraphs with minor adaptation.

3. *Interpolation based on spherical SPLine*: this technique is fairly similar to the previous one in terms of characteristics and properties and obtains the value of the interpolated signal by minimizing the curves of a sphere that is forced to pass by all known points. This is again a "global" interpolation technique that results in a continuous and regular surface that allows placing the electrodes at any position on the scalp but can be used only in conjunction with a three-dimensional model.

6.4.2.4 Choice of the Reference in Cerebral Mapping

As brain mapping aims to display the values of a signal in all points of the scalp, this signal should be measured in an absolute sense. In our case, such a signal is an electric potential that, as seen in the previous chapter, instruments measure only as difference of potential between two points. The measured values are then all referred to a "common electrode" that could have two fundamental characteristics:

- *Common electrode located in a neutral point:* in such hypothesis (which can be approximated by connecting both earlobes to the recording system common reference), the potentials could be used as they are recorded, without prior processing, as they should already identify an absolute value for each electrode.
- *Common electrode located in an active point:* in such hypothesis (which is usually the case as the common reference of the amplifier is connected to an electrode located in an active point of the scalp), the potentials need to be processed in order to subtract from them the activity of the common electrode. *Average Reference* and *Source Reference* are often used in this case, and they are described in the previous chapter.

6.5 Examples

This paragraph aims simply to show examples of application of the analysis and display techniques seen in this chapter. The first example is a spectral analysis with "frequency mapping". Figure 6.21 shows the 20-s segment of a 19-channel EEG (old standard 10/20) to be analysed. The data is displayed with average reference, expressly selected for mapping. Spectral analysis is performed with overlapping, detrending and tapering.

Figure 6.22 shows the results of the spectral analysis of each of the 19 channels that is the PSD. Figure 6.23 shows, instead, the frequency maps in the four main EEG bands (delta, theta, alpha, beta) for the very same EEG segment. The scalp model is three-dimensional and spherical with electrode coordinates expressed as latitude to longitude; the interpolation used is SPLine spherical. Please note that the chromatic scale has very different boundaries for the four different maps. One can notice the distribution of the alpha rhythm in the occipital region (but asymmetric as clearly evident in the EEG) with a power that is much higher than the other bands (see the boundary of the chromatic scale to better understand the real value).

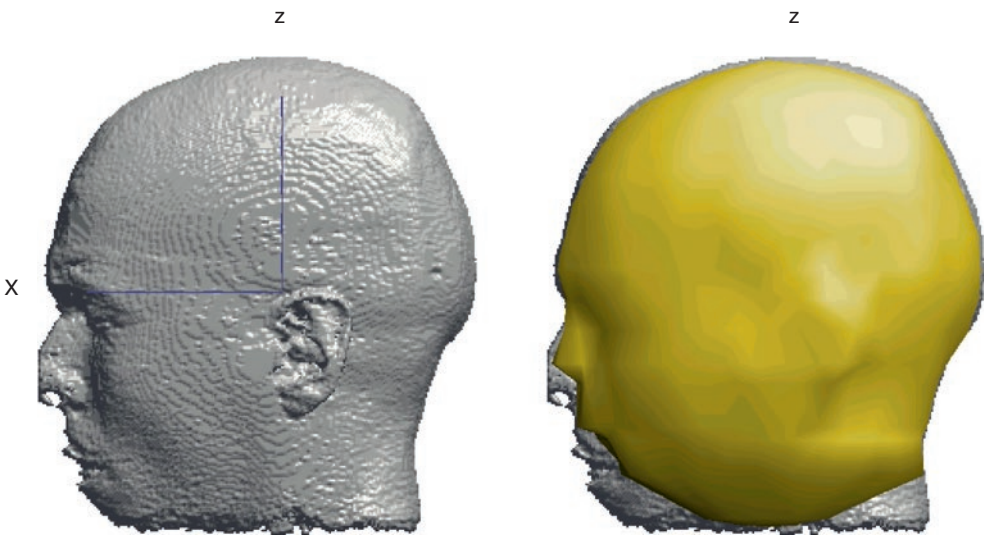

Fig. 6.20 3D head model obtained by MRI (left) and scalp model (right in yellow)

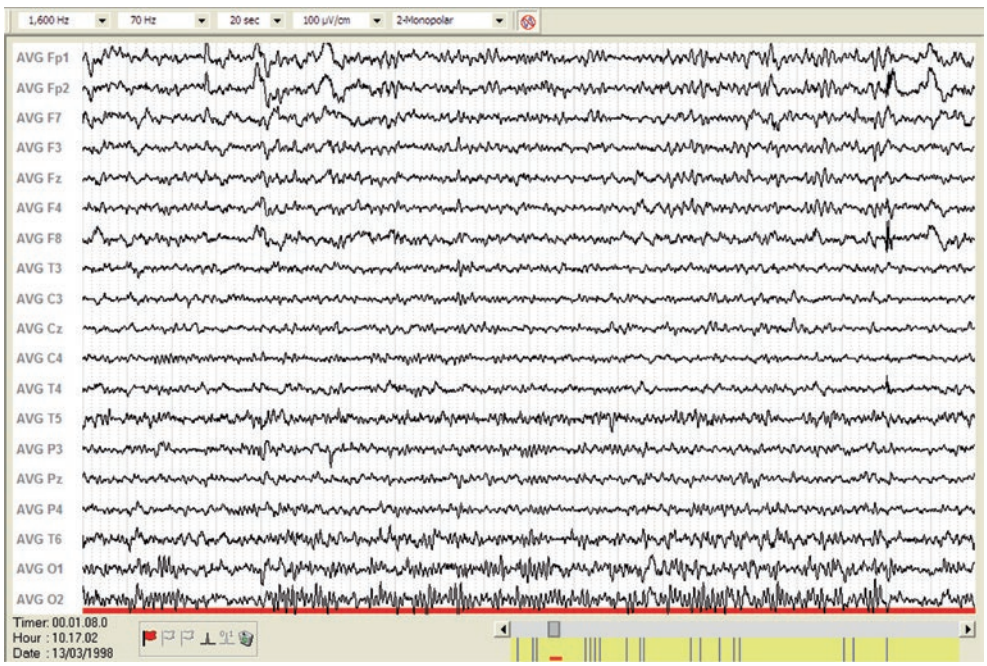

Fig. 6.21 EEG segment selected for spectral analysis

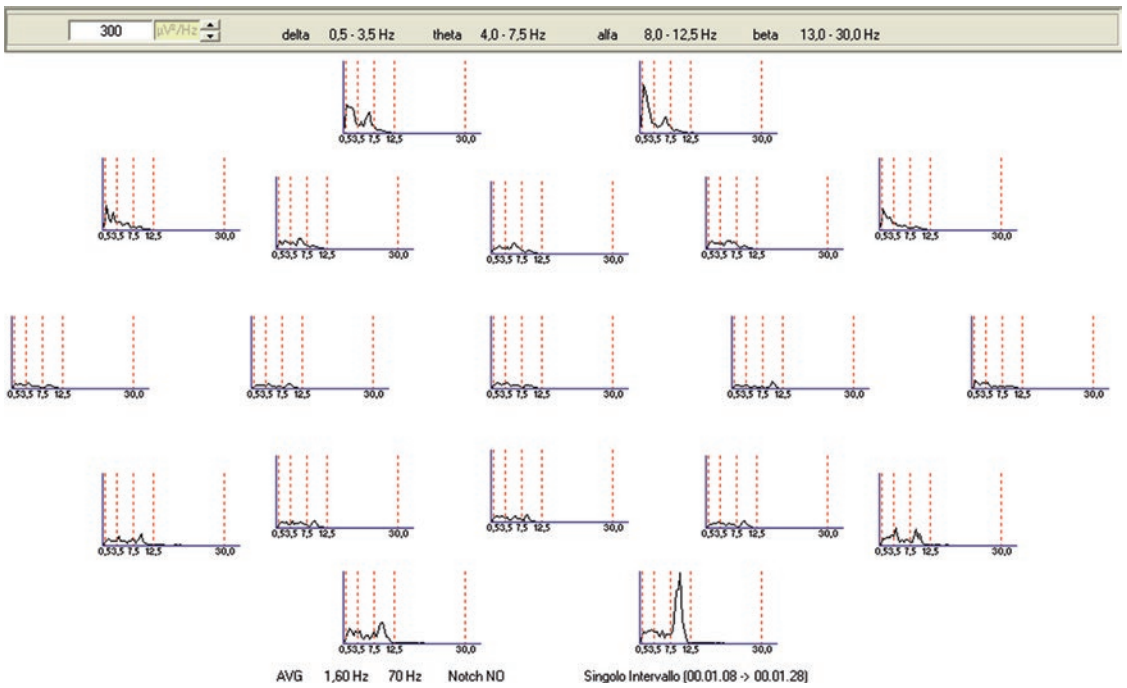

Fig. 6.22 PSD of the EEG segment in Fig. 6.21

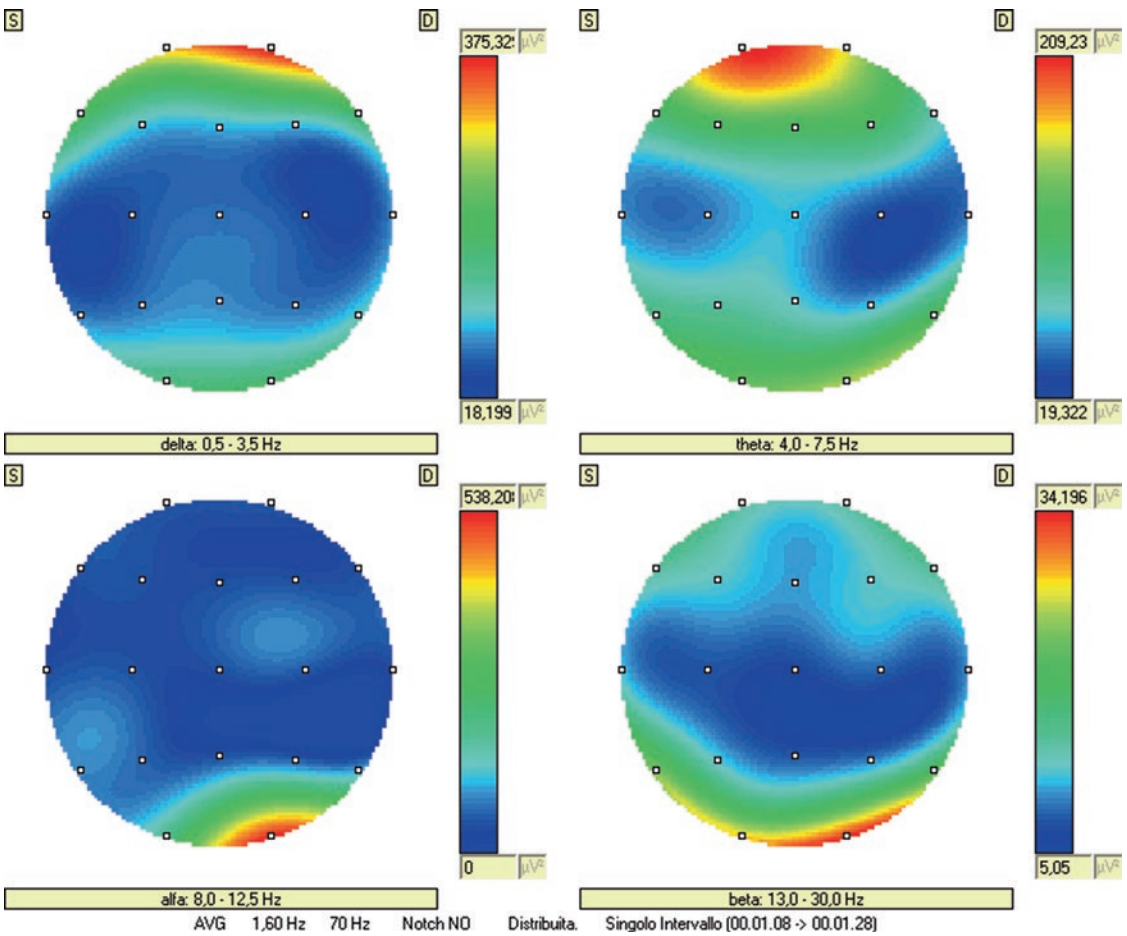

Fig. 6.23 Frequency maps of the EEG segment in Fig. 6.21

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Questionario di autovalutazione

1. **L'EEG di superficie è:**
   a. la risultante dei potentiali di campo, prodotti dalle fluttuazioni dell'attività elettrica di ampie popolazioni neuronali
   b. la rappresentazione dei potenziali postsinaptici eccitatori
   c. il prodotto dell'interazione tra i neuroni dei vari strati corticali
   d. l'effetto della sommazione dei potenziali d'azione dei neuroni

2. **I ritmi EEG originano dall'interazione tra talamo e corteccia cerebrale. Quale struttura riveste un ruolo cruciale in questo meccanismo di regolazione?**
   a. nucleo dorsale talamico
   b. tronco rostrale
   c. nucleo reticolare talamico
   d. nuclei del rafe

3. **Quale pattern EEG meglio evidenzia la connessione talamo-corticale?**
   a. ritmo alfa
   b. reazione d'arresto
   c. ipersincronia lenta
   d. fusi del sonno o spindles

4. **Gli elettrodi ad ago intradermico:**
   a. attenuano le frequenze EEG <1 Hz
   b. incrementano le frequenze rapide
   c. non determinano alcuna modificazione delle frequenze EEG
   d. creano distorsione del segnale registrato

5. **Per Sistema Internazionale 10-20 si intende:**
   a. un sistema internazionale per denominare gli elettrodi
   b. un sistema per posizionare gli elettrodi nei bambini e negli adulti
   c. un sistema internazionale che indica la posizione precisa degli elettrodi sullo scalpo partendo da precisi punti di repere anatomici, secondo distanze precise lungo linee ideali longitudinali e trasversali
   d. la determinazione numerica degli elettrodi da posizionare sullo scalpo

6. **Per registrazione in Referenza Comune si intende:**
   a. ogni elettrodo sullo scalpo riferito a un elettrodo in comune posto in un punto x
   b. ogni elettrodo riferito a Fz
   c. ogni elettrodo riferito a una referenza extracerebrale
   d. ogni elettrodo riferito alla media di tutti gli elettrodi applicati

7. **Per registrazione in Referenza Media (AVG) si intende:**
   a. ogni elettrodo riferito a un elettrodo posto al vertice
   b. il potenziale di ogni elettrodo rapportato alla media degli elettrodi adiacenti
   c. un sistema con un elettrodo di riferimento inerte
   d. ogni elettrodo riferito al potenziale medio, calcolato sommando il potenziale di tutti gli elettrodi applicati

8. **Per "source derivation" si intende:**
   a. ogni elettrodo riferito a una referenza costituita dalla media ponderata dei potenziali degli elettrodi a esso adiacenti
   b. una derivazione che permette di riconoscere la sede di origine di un potenziale specifico
   c. una particolare derivazione di tipo referenziale
   d. un metodo di registrazione in derivazione bipolare

9. **Per filtro *notch* nel nostro Paese si intende:**
   a. un filtro specifico per eliminare la frequenza di rete a 50 Hz
   b. un filtro specifico per eliminare la frequenza di rete a 60 Hz
   c. un filtro che elimina tutte le correnti "parassite"
   d. un filtro per eliminare il rumore interno dell'amplificatore

10. **Secondo il teorema del campionamento la misurazione del segnale è attendibile se il campionamento avviene a:**
   a. Frequenza uguale a quella del segnale EEG osservabile in analogico
   b. frequenza almeno doppia della massima frequenza che compone il segnale EEG
   c. frequenza tripla rispetto alla massima frequenza registrabile
   d. frequenza quadrupla rispetto alla massima frequenza registrabile

11. **La quantizzazione del segnale EEG rappresenta:**
   a. il calcolo della potenza assoluta delle varie bande
   b. il calcolo della potenza relativa delle varie bande
   c. il processo che riduce a un numero finito i valori dei campioni misurati in modo da memorizzarli in digitale
   d. il primo procedimento per la conversione analogico/digitale

Clicca qui per consultare le risposte ⟶

ITALEPT Levetiracetam

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

ITALEPT 500 mg compresse rivestite con film.
ITALEPT 1000 mg compresse rivestite con film.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Ogni compressa rivestita con film contiene 500 mg di levetiracetam. Ogni compressa rivestita con film contiene 1000 mg di levetiracetam.
Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

Compressa rivestita con film.
Compressa gialla, di forma oblunga, con linea di incisione, di circa 18 mm di lunghezza, con la scritta "500" impressa su un lato e una linea di incisione centrale. La compressa può essere divisa in due metà uguali.
Compressa bianca, di forma oblunga, con linea di incisione, di circa 22 mm di lunghezza, con la scritta "1000" impressa su un lato e linea di incisione centrale. La compressa può essere divisa in due metà uguali.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

ITALEPT è indicato come monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in adulti ed adolescenti a partire dai 16 anni di età con epilessia di nuova diagnosi. ITALEPT è indicato quale terapia aggiuntiva:

- nel trattamento delle crisi convulsive ad esordio parziale con o senza secondaria generalizzazione in adulti, adolescenti, bambini e infanti a partire da 1 mese di età con epilessia;
- nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile;
- nel trattamento delle crisi convulsive tonico-cloniche generalizzate primarie in adulti ed adolescenti a partire da 12 anni di età con epilessia idiopatica generalizzata.

4.2 Posologia e modo di somministrazione

Posologia

Monoterapia per adulti e adolescenti a partire da 16 anni di età La dose iniziale raccomandata è 250 mg due volte al giorno, da aumentare fino a una dose terapeutica iniziale di 500 mg due volte al giorno dopo due settimane. La dose può essere ulteriormente aumentata di 250 mg due volte al giorno ogni due settimane sulla base della risposta clinica. La dose massima è di 1500 mg due volte al giorno.

Terapia aggiuntiva per adulti (≥ 18 anni) ed adolescenti (da 12 a 17 anni) del peso di 50 kg o superiore

La dose terapeutica iniziale è 500 mg due volte al giorno. Questa dose può essere iniziata dal primo giorno di trattamento. Sulla base della risposta clinica e della tollerabilità, la dose giornaliera può essere aumentata fino ad un massimo di 1500 mg due volte al giorno. Gli aggiustamenti posologici possono essere fatti con aumenti o diminuzioni di 500 mg due volte al giorno ogni 2-4 settimane.

Interruzione del trattamento

In accordo con la pratica clinica corrente, se si deve interrompere il trattamento con ITALEPT si raccomanda una sospensione graduale (ad es. negli adulti e negli adolescenti di peso superiore a 50 kg: diminuzione di 500 mg due volte al giorno ad intervalli di tempo compresi tra due e quattro settimane; negli infanti di età superiore ai 6 mesi, nei bambini e negli adolescenti di peso inferiore a 50 kg: la diminuzione della dose non deve superare i 10 mg/kg due volte al giorno ogni due settimane; negli infanti (di età inferiore a 6 mesi): la diminuzione della dose non deve superare i 7 mg/kg due volte al giorno ogni due settimane).

Popolazioni speciali

Anziani (da 65 anni in poi) Si raccomanda un aggiustamento della posologia nei pazienti anziani con funzionalità renale compromessa (vedere più avanti "*Compromissione renale*).

Compromissione renale La dose giornaliera deve essere personalizzata in base alla funzionalità renale.
Per i pazienti adulti, fare riferimento alla tabella seguente e modificare la dose come indicato. Per utilizzare questa tabella posologica è necessario valutare la clearance della creatinina del paziente (CLcr) in ml/min. La CLcr in ml/min può essere calcolata dalla determinazione della creatinina sierica (mg/dl) utilizzando, per adulti e adolescenti di peso superiore o uguale a 50 kg, la seguente formula:

$$\text{CLcr (ml/min)} = \frac{[140 - \text{età (anni)}] \times \text{peso (kg)}}{72 \times \text{creatinina sierica (mg/dl)}} \quad (\times 0{,}85 \text{ nelle donne})$$

Inoltre, la CLcr viene aggiustata secondo l'area della superficie corporea (BSA) come segue:

$$\text{CLcr (ml/min/1,73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA del soggetto (m}^2\text{)}} \times 1{,}73$$

Aggiustamento posologico per pazienti adulti ed adolescenti di peso superiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/ 1,73 m²)	Dose e numero di somministrazioni
Normale	>80	500-1500 mg due volte al giorno
Lieve	50-79	500-1000 mg due volte al giorno
Moderata	30-49	250-750 mg due volte al giorno
Severa	<30	250-500 mg due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi[1]	-	500-1000 mg una volta al giorno[2]

[1] Una dose di carico pari a 750 mg è raccomandata nel primo giorno di trattamento con levetiracetam.
[2] Dopo la dialisi si raccomanda una dose supplementare compresa tra 250 e 500 mg.

Per bambini con ridotta funzionalità renale, la dose di levetiracetam deve essere adattata sulla base della funzionalità renale, perché la clearance del levetiracetam è correlata alla funzionalità renale. Questa raccomandazione si basa su uno studio condotto su pazienti adulti con ridotta funzionalità renale. Nei giovani adolescenti, nei bambini e negli infanti, la CLcr, in ml/min/1,73 m², può essere stimata dalla determinazione della creatinina sierica (in mg/dl) utilizzando la seguente formula (formula di Schwartz):

$$\text{CLcr (ml/min/1,73 m}^2\text{)} = \frac{\text{Altezza (cm)} \times \text{ks}}{\text{Creatinina sierica (mg/dl)}}$$

ks= 0,45 negli infanti nati a termine, di età fino a 1 anno; ks= 0,55 nei bambini di età inferiore a 13 anni e nelle femmine adolescenti; ks= 0,7 nei maschi adolescenti.

Aggiustamento posologico per infanti, bambini e adolescenti di peso inferiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/ 1,73 m²)	Dose e frequenza[1]	
		Infanti da 1 mese a meno di 6 mesi	Infanti da 6 a 23 mesi, bambini e adolescenti di peso inferiore ai 50 kg
Normale	>80	7-21 mg/ kg (0,07-0,21 ml/kg) due volte al giorno	10-30 mg/ kg (0,10-0,30 ml/kg) due volte al giorno
Lieve	50-79	7-14 mg/ kg (0,07-0,14 ml/kg) due volte al giorno	10-20 mg/ kg (0,10-0,20 ml/kg) due volte al giorno
Moderata	30-49	3,5-10,5 mg/ kg (0,035-0,105 ml/ kg) due volte al giorno	5-15 mg/ kg (0,05-0,15 ml/kg) due volte al giorno
Severa	<30	3,5-7 mg/ kg (0,035-0,07 ml/kg) due volte al giorno	5-10 mg/ kg (0,05-0,10 ml/kg) due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi	--	7-14 mg/ kg (0,07-0,14 ml/kg) una volta al giorno[2] [4]	10-20 mg/ kg (0,10-0,20 ml/kg) una volta al giorno[3] [5]

[1] Utilizzare ITALEPT soluzione orale per dosi inferiori a 250 mg, per dosi non multiple di 250 mg quando non è possibile ottenere la dose raccomandata assumendo un numero multiplo di compresse, e per i pazienti incapaci di deglutire le compresse.
[2] Si raccomanda una dose di carico di 10,5 mg/kg il primo giorno di trattamento con levetiracetam.
[3] Si raccomanda una dose di carico di 15 mg/kg il primo giorno di trattamento con levetiracetam.
[4] Dopo la dialisi, si raccomanda una dose supplementare di 3,5-7 mg/kg.
[5] Dopo la dialisi, si raccomanda una dose supplementare di 5-10 mg/kg.

Compromissione epatica
Non è necessario alcun adeguamento posologico nei pazienti con compromissione epatica di grado da lieve a moderato. In pazienti con compromissione epatica severa, la clearance della creatinina può far sottostimare il grado di insufficienza renale. Pertanto, quando la clearance della creatinina è <60 ml/min/1,73 m², si raccomanda una riduzione del 50% della dose di mantenimento giornaliera.
Popolazione pediatrica
Il medico deve prescrivere la forma farmaceutica, la presentazione e il dosaggio più appropriati in base all'età, al peso e alla dose. La formulazione in compresse non è adatta all'uso nella prima infanzia e nei bambini di età inferiore a 6 anni.
ITALEPT soluzione orale è la formulazione più indicata per questa popolazione di pazienti. Inoltre, i dosaggi disponibili per le compresse non sono indicati per il trattamento iniziale dei bambini di peso inferiore a 25 kg, dei pazienti incapaci di deglutire le compresse o per la somministrazione di dosi inferiori a 250 mg. In tutti questi casi deve essere utilizzato ITALEPT soluzione orale.
Monoterapia Non sono state ancora stabilite la sicurezza e l'efficacia di ITALEPT somministrato in monoterapia nei bambini e negli adolescenti di età inferiore a 16 anni. Non vi sono dati disponibili.
Terapia aggiuntiva per bambini piccoli da 6 a 23 mesi di età, bambini (da 2 a 11 anni) e adolescenti (da 12 a 17 anni) di peso inferiore a 50 kg ITALEPT soluzione orale è la formulazione più indicata nella prima infanzia e nei bambini di età inferiore a 6 anni. Per i bambini dai 6 anni in su, ITALEPT soluzione orale deve essere utilizzato per dosi inferiori ai 250 mg, per dosi non multiple di 250 mg quando la dose raccomandata non è raggiungibile con più compresse, e per i pazienti incapaci di deglutire le compresse. Deve essere utilizzata la più bassa dose efficace. La dose iniziale per un bambino o un adolescente di 25 kg deve essere 250 mg due volte al giorno, con una dose massima di 750 mg due volte al giorno. La dose in bambini di 50 kg o più è uguale a quella degli adulti.
Terapia aggiuntiva per lattanti da 1 mese a meno di 6 mesi di età La soluzione orale è la formulazione da utilizzare negli infanti.
Modo di somministrazione
Le compresse rivestite con film devono essere somministrate per via orale, deglutite con una sufficiente quantità di liquido e possono essere assunte con o senza cibo. La dose giornaliera va ripartita in due somministrazioni uguali.

4.3 Controindicazioni
Ipersensibilità al principio attivo o ad altri derivati pirrolidonici o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.

4.4 Avvertenze speciali e precauzioni di impiego
Compromissione renale
La somministrazione di ITALEPT in pazienti con compromissione renale può richiedere un aggiustamento posologico. In pazienti con funzionalità epatica gravemente compromessa si raccomanda di valutare la funzionalità renale prima di stabilire la posologia (vedere paragrafo 4.2).
Suicidio
Casi di suicidio, tentato suicidio, idea e comportamento suicida sono stati riportati in pazienti trattati con antiepilettici (incluso levetiracetam). Una meta-analisi di studi randomizzati e controllati con placebo, condotti con medicinali antiepilettici, ha mostrato un lieve incremento del rischio di idea e comportamento suicida. Il meccanismo di tale rischio non è noto.
Di conseguenza, i pazienti devono essere monitorati per quanto riguarda la comparsa di segni di depressione e/o idea e comportamento suicida, e deve essere preso in considerazione un trattamento appropriato. I pazienti (e coloro che se ne prendono cura) devono essere avvisati che, nel caso in cui compaiano segni di depressione e/o idea o comportamento suicida, è necessario consultare un medico.
Popolazione pediatrica
La formulazione in compresse non è adatta all'uso nella prima infanzia e nei bambini di età inferiore a 6 anni. Dai dati disponibili nei bambini non si evince un'influenza sulla crescita e sulla pubertà. Tuttavia, non sono noti gli effetti a lungo termine sull'apprendimento, l'intelligenza, la crescita, la funzione endocrina, la pubertà e sul potenziale riproduttivo nei bambini.

4.5 Interazioni con altri medicinali ed altre forme di interazione
Medicinali antiepilettici
I dati provenienti da studi clinici pre-marketing, condotti negli adulti, indicano che levetiracetam non influenza le concentrazioni sieriche degli antiepilettici esistenti (fenitoina, carbamazepina, acido valproico, fenobarbital, lamotrigina, gabapentin e primidone) e che questi antiepilettici non influenzano la farmacocinetica di levetiracetam.
Come negli adulti, nei pazienti pediatrici cui sono state somministrate dosi fino a 60 mg/kg/die di levetiracetam, non c'è evidenza di interazioni clinicamente significative con altri medicinali. Una valutazione retrospettiva di interazioni farmacocinetiche, in bambini e adolescenti affetti da epilessia (da 4 a 17 anni) ha confermato che la terapia aggiuntiva con levetiracetam somministrato per via orale non influenzava le concentrazioni sieriche allo stato stazionario di carbamazepina e valproato somministrati contemporaneamente. Tuttavia, i dati hanno suggerito una clearance del levetiracetam del 20% più elevata nei bambini che assumono medicinali antiepilettici con un effetto di induzione enzimatica. Non è richiesto un aggiustamento della dose.
Probenecid
Il probenecid (500 mg quattro volte al giorno), un agente bloccante della secrezione tubulare renale, ha mostrato di inibire la clearance renale del metabolita primario, ma non di levetiracetam. Tuttavia, la concentrazione di questo metabolita rimane bassa.

Metotrexato
È stato riportato che la somministrazione concomitante di levetiracetam e metotrexato diminuisce la clearance del metotressato, con conseguente concentrazione ematica di metotrexato aumentata/prolungata fino a livelli potenzialmente tossici. I livelli ematici di metotrexato e levetiracetam devono essere attentamente monitorati nei pazienti trattati in concomitanza con i due farmaci.
Contraccettivi orali e altre interazioni farmacocinetiche
Levetiracetam 1000 mg al giorno non ha influenzato la farmacocinetica dei contraccettivi orali (etinilestradiolo e levonorgestrel); i parametri endocrini (ormone luteinizzante e progesterone) non sono stati modificati. Levetiracetam 2000 mg al giorno non ha influenzato la farmacocinetica di digossina e warfarin; i tempi di protrombina non sono stati modificati. La somministrazione concomitante di digossina, contraccettivi orali e warfarin non ha influenzato la farmacocinetica di levetiracetam.
Lassativi
Sono stati riportati casi isolati di diminuita efficacia di levetiracetam quando il lassativo osmotico macrogol è stato somministrato in concomitanza con levetiracetam per via orale. Pertanto, macrogol non deve essere assunto per via orale da un'ora prima ad un'ora dopo l'assunzione di levetiracetam.
Cibo e alcool
L'entità dell'assorbimento di levetiracetam non è stata modificata dal cibo, ma la velocità di assorbimento era lievemente ridotta. Non sono disponibili dati sulle interazioni di levetiracetam con l'alcool.

4.6 Fertilità, gravidanza e allattamento

Gravidanza
Dati post-marketing di diversi registri prospettici di gravidanza hanno documentato i risultati della esposizione a levetiracetam in monoterapia in più di 1000 donne durante il primo trimestre di gravidanza. Nel complesso, questi dati non suggeriscono un sostanziale aumento del rischio di malformazioni congenite maggiori, sebbene un rischio teratogeno non possa essere completamente escluso. La terapia con più farmaci antiepilettici è associata ad un più alto rischio di malformazioni congenite rispetto alla monoterapia e, pertanto, la monoterapia deve essere presa in considerazione. Gli studi sugli animali hanno mostrato una tossicità riproduttiva (vedere paragrafo 5.3). ITALEPT non è raccomandato durante la gravidanza e nelle donne in età fertile che non utilizzano metodi contraccettivi, a meno che non sia clinicamente necessario. Le alterazioni fisiologiche durante la gravidanza possono influenzare le concentrazioni di levetiracetam. Durante la gravidanza, è stata osservata una riduzione delle concentrazioni plasmatiche di levetiracetam. Questa riduzione è più pronunciata durante il terzo trimestre (fino al 60% della concentrazione basale prima della gravidanza). Le donne in gravidanza trattate con levetiracetam devono essere accuratamente seguite dal punto di vista clinico. L'interruzione dei trattamenti antiepilettici può comportare una esacerbazione della malattia che può essere nociva per la madre e per il feto.
Allattamento
Levetiracetam è escreto nel latte materno. Pertanto, l'allattamento con latte materno non è raccomandato. Tuttavia, se il trattamento con levetiracetam è necessario durante l'allattamento, deve essere valutato il rapporto rischio/beneficio del trattamento, tenendo in considerazione l'importanza dell'allattamento con latte materno.
Fertilità
Non è stato rilevato alcun impatto sulla fertilità negli studi sugli animali (vedere paragrafo 5.3). Non sono disponibili dati clinici; il rischio potenziale nell'uomo è sconosciuto.

4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Levetiracetam ha una bassa o moderata influenza sulla capacità di guidare veicoli e sull'uso di macchinari. Data la possibile differente sensibilità individuale, alcuni pazienti possono manifestare sonnolenza o altri sintomi legati all'azione sul sistema nervoso centrale, specialmente all'inizio del trattamento o in seguito ad un incremento della dose. Si raccomanda pertanto cautela nei pazienti che sono impegnati in attività che richiedono elevata concentrazione, quali guidare autoveicoli o azionare macchinari. I pazienti devono essere avvertiti di non guidare o utilizzare macchinari finché non sia stato accertato che la loro abilità ad eseguire queste attività non sia compromessa.

4.8 Effetti indesiderati

Riassunto del profilo di sicurezza
Il profilo delle reazioni avverse di seguito presentato si basa sull'analisi degli studi clinici controllati verso placebo aggregati, relativi a tutte le indicazioni studiate, per un totale di 3.416 pazienti trattati con levetiracetam. Questi dati sono integrati con l'uso di levetiracetam in corrispondenti studi di estensione in aperto, così come dall'esperienza post-marketing.
Le reazioni avverse più frequentemente riportate sono state rinofaringite, sonnolenza, cefalea, affaticamento e capogiro. Il profilo di sicurezza del levetiracetam è generalmente simile nell'ambito dei diversi gruppi di età (pazienti adulti e pediatrici) e delle indicazioni approvate nel trattamento dell'epilessia.
Tabella delle reazioni avverse
Le reazioni avverse segnalate nel corso di studi clinici (adulti, adolescenti, bambini ed infanti di età superiore ad 1 mese) e nell'esperienza post-marketing sono elencate nella tabella seguente secondo la classificazione per sistemi e organi e per frequenza. Le reazioni avverse sono presentate in ordine decrescente di gravità e la loro frequenza è definita come segue: molto comune (≥1/10), comune (≥1/100, <1/10), non comune (≥1/1000, <1/100), raro (≥1/10.000, <1/1000) e molto raro (<1/10.000).

Classificazione per sistemi e organi (MedDRA)	Categoria di frequenza			
	Molto comune	Comune	Non comune	Raro
Infezioni ed infestazioni	Rinofaringite			Infezione
Patologie del sistema emolinfopoietico			Trombocitopenia, leucopenia	Pancitopenia, neutropenia, agranulocitosi
Disturbi del sistema immunitario				Reazione a farmaco con eosinofilia e sintomi sistemici (DRESS), ipersensibilità (incluso angioedema e anafilassi)
Disturbi del metabolismo e della nutrizione		Anoressia	Perdita di peso, aumento di peso	Iponatriemia
Disturbi psichiatrici		Depressione, ostilità/aggressività, ansia, insonnia, nervosismo/irritabilità	Tentato suicidio, idea suicida, disturbo psicotico, comportamento anormale, allucinazioni, collera, stato confusionale, attacco di panico, labilità affettiva/sbalzi d'umore, agitazione	Suicidio riuscito, disturbo della personalità, pensiero anormale

Classificazione per sistemi e organi (MedDRA)	Categoria di frequenza			
	Molto comune	Comune	Non comune	Raro
Patologie del sistema nervoso	Sonnolenza, cefalea	Convulsione, disturbo dell'equilibrio, capogiro, letargia, tremore	Amnesia, compromissione della memoria, coordinazione anormale/atassia, parestesia, alterazione dell'attenzione	Coreoatetosi, discinesia, ipercinesia
Patologie dell'occhio			Diplopia, visione offuscata	
Patologie dell'orecchio e del labirinto		Vertigine		
Patologie respiratorie, toraciche e mediastiniche		Tosse		
Patologie gastrointestinali		Dolore addominale, diarrea, dispepsia, vomito, nausea		Pancreatite
Patologie epatobiliari			Test della funzionalità epatica anormali	Insufficienza epatica, epatite
Patologie della cute e del tessuto sottocutaneo		Rash	Alopecia, eczema, prurito	Necrolisi epidermica tossica, sindrome di Stevens-Johnson, eritema multiforme
Patologie del sistema muscolo-scheletrico e del tessuto connettivo			Debolezza muscolare, mialgia	
Patologie sistemiche e condizioni relative alla sede di somministrazione		Astenia/ affaticamento		
Traumatismo, avvelenamento e complicazioni da procedura			Traumatismo	

Descrizione di determinate reazioni avverse

Il rischio di anoressia è più elevato quando assieme al levetiracetam viene somministrato il topiramato. In numerosi casi di alopecia, è stata osservata guarigione dopo la sospensione del trattamento con levetiracetam.

In alcuni dei casi di pancitopenia è stata identificata soppressione del midollo osseo.

Popolazione pediatrica

In pazienti di età compresa tra 1 mese e meno di 4 anni, un totale di 190 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. Sessanta (60) di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In pazienti di età compresa tra 4 e 16 anni, un totale di 645 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. 233 di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In entrambi questi intervalli di età pediatrica, questi dati sono integrati con l'esperienza post-marketing relativa all'uso di levetiracetam.

Inoltre, 101 bambini di età inferiore a 12 mesi sono stati esposti in uno studio di sicurezza post-autorizzazione. Non sono stati identificati nuovi problemi di sicurezza per levetiracetam in infanti di età inferiore a 12 mesi con epilessia.

Il profilo delle reazioni avverse del levetiracetam è generalmente simile nell'ambito dei diversi gruppi di età e delle indicazioni approvate nel trattamento dell'epilessia. Negli studi clinici controllati con placebo, i risultati sulla sicurezza nei pazienti pediatrici sono stati coerenti con il profilo di sicurezza di levetiracetam negli adulti, ad eccezione delle reazioni avverse comportamentali e psichiatriche che sono state più comuni nei bambini rispetto che negli adulti. Nei bambini e negli adolescenti di età compresa tra 4 e 16 anni, sono stati riportati più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo vomito (molto comune, 11,2%), agitazione (comune, 3,4%), sbalzi d'umore (comune, 2,1%), labilità affettiva (comune, 1,7%), aggressività (comune, 8,2%), comportamento anormale (comune, 5,6%) e letargia (comune, 3,9%). In infanti e bambini di età compresa tra 1 mese e meno di 4 anni, sono state riportate più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo irritabilità (molto comune, 11,7%) e coordinazione anormale (comune, 3,3%). Uno studio di sicurezza sui pazienti pediatrici, condotto secondo un disegno di non inferiorità, in doppio cieco e controllato con placebo, ha valutato gli effetti cognitivi e neuro-psicologici di levetiracetam in bambini da 4 a 16 anni di età con crisi convulsive a esordio parziale. Il levetiracetam si è dimostrato non differente (non inferiore) rispetto al placebo per quanto riguarda la modifica rispetto al basale nel punteggio ottenuto ai test "Attenzione e Memoria" della scala di Leiter-R (*Memory Screen Composite score*) nella popolazione per protocol. I risultati correlati alle funzioni comportamentali ed emozionali hanno indicato un peggioramento, nei pazienti trattati con levetiracetam, del comportamento aggressivo misurato in maniera standardizzata e sistematica, con l'utilizzo di uno strumento validato (*CBCL-Achenbach Child Behavior Checklist*).

Tuttavia, i soggetti che hanno assunto levetiracetam nello studio in aperto di follow-up a lungo termine non hanno manifestato, in media, un peggioramento delle loro funzioni comportamentali ed emozionali; in particolare, le valutazioni dell'aggressività nei comportamenti non sono peggiorate rispetto al basale.

Segnalazione delle reazioni avverse sospette

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione dell'Agenzia Italiana del Farmaco, Sito web: http://www.agenziafarmaco.gov.it/it/responsabili.

4.9 Sovradosaggio

Sintomi

Sonnolenza, agitazione, aggressività, ridotto livello di coscienza,

depressione respiratoria e coma sono stati osservati con sovradosaggi di levetiracetam.

Trattamento del sovradosaggio

Dopo un sovradosaggio acuto, lo stomaco può essere svuotato mediante lavanda gastrica o induzione del vomito. Non esiste un antidoto specifico per levetiracetam. Il trattamento del sovradosaggio dovrà essere sintomatico e può includere l'emodialisi. L'efficienza di estrazione mediante dialisi è del 60% per levetiracetam e del 74% per il metabolita primario.

5. PROPRIETÀ FARMACOLOGICHE

5.1 Proprietà farmacodinamiche

Categoria farmacoterapeutica: antiepilettici, altri antiepilettici. Codice ATC: N03AX14.

Il principio attivo, levetiracetam, è un derivato pirrolidonico (S-enantiomero dell'α-etil- 2-oxo-1-pirrolidin acetamide), non correlato chimicamente con sostanze ad attività antiepilettica esistenti.

Meccanismo d'azione

Il meccanismo d'azione di levetiracetam non è stato ancora del tutto spiegato. Esperimenti *in vitro* ed *in vivo* suggeriscono che levetiracetam non altera le caratteristiche cellulari di base e la normale neurotrasmissione.

Studi *in vitro* dimostrano che levetiracetam agisce sui livelli intraneuronali di Ca^{2+} attraverso la parziale inibizione delle correnti di Ca^{2+} di tipo N e riducendo il rilascio di Ca^{2+} dai depositi intraneuronali. Inoltre, il farmaco inverte parzialmente la riduzione, indotta da zinco e β-carboline, delle correnti indotte da GABA e glicina. Studi *in vitro* hanno inoltre evidenziato che levetiracetam si lega ad uno specifico sito nel tessuto cerebrale dei roditori. Questo sito di legame è la proteina 2A della vescicola sinaptica, che si ritiene sia coinvolta nella fusione della vescicola e nell'esocitosi del neurotrasmettitore. Levetiracetam e i relativi analoghi mostrano un grado di affinità per il legame alla proteina 2A della vescicola sinaptica che è correlato con la potenza della loro protezione antiepilettica nel modello audiogenico di epilessia nel topo. Questa scoperta suggerisce che l'interazione tra levetiracetam e la proteina 2A della vescicola sinaptica sembra aver parte nel meccanismo d'azione antiepilettica del medicinale.

Effetti farmacodinamici

Il levetiracetam induce un'azione di protezione nei confronti delle crisi epilettiche in un ampio spettro di modelli animali di epilessia parziale e generalizzata primaria, senza avere un effetto pro-convulsivante. Il metabolita primario è inattivo. Nell'uomo, un'attività in condizioni di epilessia sia parziale che generalizzata (scarica epilettiforme/risposta fotoparossistica) ha confermato l'ampio spettro del profilo farmacologico del levetiracetam.

Efficacia e sicurezza clinica

Terapia aggiuntiva nel trattamento delle crisi parziali con o senza generalizzazione secondaria in adulti, adolescenti, bambini ed infanti a partire da 1 mese di età con epilessia Negli adulti, l'efficacia di levetiracetam è stata dimostrata in 3 studi in doppio cieco, controllati con placebo, con dosi di 1000 mg, 2000 mg o 3000 mg/die, suddivise in 2 somministrazioni, per una durata di trattamento fino a 18 settimane. In una analisi globale, la percentuale di pazienti che ha ottenuto una riduzione della frequenza delle crisi parziali per settimana, nel periodo di trattamento a dose stabile (12/14 settimane), uguale o superiore al 50% rispetto al basale, è stata del 27,7%, 31,6% e 41,3% dei pazienti trattati rispettivamente con 1000, 2000 o 3000 mg di levetiracetam e del 12,6% per i pazienti trattati con placebo.

Popolazione pediatrica L'efficacia di levetiracetam nei pazienti pediatrici (dai 4 ai 16 anni di età) è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 198 pazienti ed ha avuto una durata di trattamento di 14 settimane. In questo studio, i pazienti hanno assunto levetiracetam alla dose fissa di 60 mg/kg/die (con due somministrazioni giornaliere).

Il 44,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo ha avuto, rispetto al basale, una riduzione della frequenza delle crisi convulsive a esordio parziale per settimana uguale o superiore al 50%.

Con il trattamento continuato a lungo termine, l'11,4% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,2% è rimasto libero da crisi per almeno 1 anno.

Nei pazienti pediatrici (da 1 mese a meno di 4 anni di età), l'efficacia di levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 116 pazienti e ha avuto una durata di trattamento di 5 giorni. In questo studio è stata prescritta ai pazienti una dose giornaliera di 20 mg/kg, 25 mg/kg, 40 mg/kg o 50 mg/kg di soluzione orale, basandosi sullo schema di titolazione della dose riferito alla loro età. Nello studio sono state utilizzate le seguenti dosi: 20 mg/kg/die, titolata a 40 mg/kg/die, per infanti da un mese a meno di sei mesi di età; 25 mg/kg/die, titolata a 50 mg/kg/die, per infanti e bambini da 6 mesi a meno di 4 anni di età. La dose totale giornaliera è stata suddivisa in due somministrazioni al giorno. Il principale parametro dell'efficacia del trattamento è stato il tasso di pazienti responsivi (percentuale di pazienti con una riduzione della frequenza media giornaliera delle crisi convulsive a esordio parziale ≥50% rispetto ai valori basali), valutato da un esaminatore unico in cieco utilizzando un video EEG per un periodo di 48 ore. L'analisi dell'efficacia è stata effettuata su 109 pazienti che erano stati sottoposti a video EEG per almeno 24 ore, sia durante il periodo basale che durante il periodo di valutazione. Il 43,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo sono stati considerati responsivi. I risultati sono coerenti nei diversi gruppi di età. Nel trattamento continuato a lungo termine, l'8,6% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,8% è stato libero da crisi per almeno 1 anno. 35 infanti di età inferiore ad 1 anno, dei quali solo 13 di età inferiore ai 6 mesi, con crisi ad esordio parziale sono stati esposti in studi clinici controllati con placebo.

Monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in pazienti a partire da 16 anni di età con epilessia di nuova diagnosi L'efficacia del levetiracetam in monoterapia è stata dimostrata in uno studio comparativo di non inferiorità in doppio cieco, a gruppi paralleli, verso carbamazepina a rilascio controllato (CR), in 576 pazienti di 16 anni di età o più, con epilessia di nuova o recente diagnosi. I pazienti dovevano presentare solo crisi parziali non provocate oppure crisi tonico-cloniche generalizzate. I pazienti sono stati randomizzati a carbamazepina CR 400-1200 mg/die o levetiracetam 1000-3000 mg/die e il trattamento ha avuto una durata fino a 121 settimane in base alla risposta.

La libertà dalle crisi per un periodo di 6 mesi è stata ottenuta nel 73,0% dei pazienti trattati con levetiracetam e nel 72,8% dei pazienti trattati con carbamazepina CR; la differenza assoluta corretta tra i trattamenti è stata dello 0,2% (IC 95%:-7,8 8,2). Più della metà dei soggetti è rimasta libera da crisi per 12 mesi (56,6% e 58,5% dei soggetti trattati rispettivamente con levetiracetam e carbamazepina CR).

In uno studio che rifletteva la pratica clinica, il trattamento antiepilettico concomitante ha potuto essere sospeso in un numero limitato di pazienti che avevano risposto alla terapia aggiuntiva con levetiracetam (36 pazienti adulti su 69).

Terapia aggiuntiva nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile L'efficacia del levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, della durata di 16 settimane, in pazienti a partire dai 12 anni di età e oltre, affetti da epilessia generalizzata idiopatica con crisi miocloniche in differenti sindromi. La maggioranza dei pazienti presentava epilessia mioclonica giovanile.

In questo studio, la dose di levetiracetam è stata di 3000 mg/die, somministrata in due dosi separate.

Il 58,3% dei pazienti trattati con levetiracetam e il 23,3% dei pazienti trattati con placebo ha avuto almeno una riduzione del 50% dei giorni con crisi miocloniche per settimana. A seguito del trattamento continuato a lungo termine, il 28,6% dei pazienti è rimasto libero da crisi miocloniche per almeno 6 mesi ed il 21,0% dei pazienti è rimasto libero da crisi miocloniche per almeno 1 anno.

Terapia aggiuntiva nel trattamento delle crisi tonico-cloniche generalizzate primarie in adulti e adolescenti a partire da 12 anni di età con epilessia generalizzata idiopatica L'efficacia del levetiracetam è stata dimostrata in uno studio di 24 settimane in doppio cieco, controllato con placebo, che ha incluso adulti, adolescenti e un numero limitato di bambini affetti da epilessia generalizzata idiopatica con crisi tonico-cloniche generalizzate primarie (PGTC) in differenti sindromi (epilessia mioclonica giovanile, epilessia giovanile da assenza, epilessia infantile da assenza oppure epilessia con crisi da grande male al risveglio). In questo studio, la dose di levetiracetam è stata di 3000 mg/die per adulti e adolescenti oppure di 60 mg/kg/die per i bambini, somministrata in due dosi separate.

Il 72,2% dei pazienti trattati con levetiracetam e il 45,2% dei pazienti trattati con placebo ha avuto una riduzione della frequenza delle crisi PGTC per settimana uguale o superiore al 50%. A

seguito del trattamento continuato a lungo termine, il 47,4% dei pazienti è rimasto libero da crisi tonico-cloniche per almeno 6 mesi e il 31,5% è stato libero da crisi tonico-cloniche per almeno 1 anno.

5.2 Proprietà farmacocinetiche

Levetiracetam è un composto estremamente solubile e permeabile. Il profilo farmacocinetico è lineare, con una scarsa variabilità intra- ed inter-individuale. Non c'è modificazione della clearance dopo somministrazioni ripetute. Non c'è evidenza di alcuna rilevante variabilità circadiana e per sesso e razza. Il profilo farmacocinetico è comparabile nei volontari sani e nei pazienti con epilessia. Dato il suo completo e lineare assorbimento, i livelli plasmatici di levetiracetam possono essere predetti dalla dose orale espressa come mg/kg di peso corporeo. Perciò non c'è bisogno di monitorare i livelli plasmatici di levetiracetam. È stata evidenziata negli adulti e nei bambini una significativa correlazione tra le concentrazioni nella saliva e nel plasma (il rapporto delle concentrazioni saliva/plasma variava in un intervallo da 1 a 1,7 per la formulazione orale in compresse e, dopo 4 ore dall'assunzione, per la formulazione orale in soluzione).

Adulti e adolescenti

Assorbimento

Levetiracetam è assorbito rapidamente dopo somministrazione orale. La biodisponibilità orale assoluta è prossima al 100%. Le concentrazioni al picco plasmatico (C_{max}) sono raggiunte 1,3 ore dopo l'assunzione. Lo stato stazionario è raggiunto dopo due giorni di somministrazione di due dosi quotidiane. Le concentrazioni al picco plasmatico (C_{max}) sono tipicamente di 31 e 43 µg/ml in seguito, rispettivamente, ad una singola dose di 1000 mg e a una dose di 1000 mg ripetuta due volte al giorno. L'entità di assorbimento non è dose dipendente e non è influenzata dal cibo.

Distribuzione

Non sono disponibili dati sulla distribuzione tissutale nell'uomo. Né levetiracetam né il suo metabolita primario si legano significativamente alle proteine plasmatiche (<10%). Il volume di distribuzione di levetiracetam va approssimativamente da 0,5 a 0,7 l/kg, ed è un valore prossimo al volume totale corporeo di acqua.

Biotrasformazione

Levetiracetam non è ampiamente metabolizzato nell'uomo. La principale via metabolica (24% della dose) è l'idrolisi enzimatica del gruppo acetamide. La produzione del metabolita primario, ucb L057, non è supportata dalle isoforme del citocromo P450 epatico. L'idrolisi del gruppo acetamide è stata misurabile in numerosi tessuti, comprese le cellule ematiche. Il metabolita ucb L057 è farmacologicamente inattivo.

Sono stati inoltre identificati due metaboliti minori. Uno è stato ottenuto dall'idrossilazione dell'anello pirrolidonico (1,6% della dose) e l'altro dall'apertura dell'anello pirrolidonico (0,9% della dose). Altri componenti non noti erano responsabili soltanto dello 0,6% della dose. *In vivo* non sono state evidenziate interconversioni enantiomeriche né per levetiracetam né per il suo metabolita primario. *In vitro*, levetiracetam ed il suo metabolita primario hanno mostrato di non inibire le attività delle principali isoforme del citocromo P450 epatico umano (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 e 1A2), della glucuronil transferasi (UGT1A1 e UGT1A6) e dell'epossido idrossilasi. Inoltre, levetiracetam non influenza la glucuronazione *in vitro* dell'acido valproico. In colture di epatociti umani, levetiracetam ha avuto un effetto minimo o nullo su CYP1A2, SULT1E1 o UGT1A1. Levetiracetam ha causato una moderata induzione del CYP2B6 e del CYP3A4 I dati *in vitro* ed i dati *in vivo* relativi alla interazione con contraccettivi orali, digossina e warfarin indicano che non è attesa alcuna significativa induzione enzimatica *in vivo*. Quindi, l'interazione di ITALEPT con altre sostanze, o viceversa, è improbabile.

Eliminazione

L'emivita plasmatica negli adulti è di 7±1 ore e non si modifica in relazione alla dose, alla via di somministrazione o alla somministrazione ripetuta. La clearance totale corporea media è di 0,96 ml/min/kg. La principale via di escrezione è la via urinaria, responsabile in media dell'eliminazione del 95% della dose somministrata (approssimativamente il 93% della dose è stato escreto entro 48 ore). L'eliminazione fecale rappresenta solo lo 0,3% della dose. L'escrezione cumulativa urinaria di levetiracetam e del suo metabolita primario è responsabile rispettivamente dell'eliminazione del 66% e del 24% della dose, nell'arco delle prime 48 ore. La clearance renale di levetiracetam e di ucb L057 è rispettivamente di 0,6 e 4,2 ml/min/kg, indicando che il levetiracetam è escreto mediante filtrazione glomerulare con successivo riassorbimento tubulare e che il metabolita primario è escreto anche mediante secrezione tubulare attiva oltre che con filtrazione glomerulare. L'eliminazione di levetiracetam è correlata alla clearance della creatinina.

Anziani

Nell'anziano, l'emivita è aumentata di circa il 40% (da 10 a 11 ore). Ciò è dovuto alla riduzione della funzionalità renale in questa popolazione (vedere paragrafo 4.2).

Compromissione renale

La clearance corporea apparente sia di levetiracetam sia del suo metabolita primario è correlata alla clearance della creatinina. Nei pazienti con insufficienza renale di grado moderato e grave si raccomanda pertanto di aggiustare la dose giornaliera di mantenimento di ITALEPT, basandosi sulla clearance della creatinina (vedere paragrafo 4.2).

Nei soggetti adulti affetti da anuria con malattia renale allo stadio terminale, l'emivita è risultata approssimativamente pari a 25 e 3,1 ore, rispettivamente nei periodi tra le dialisi e durante la dialisi.

La frazione del levetiracetam rimossa era del 51% nel corso di una tipica seduta di dialisi di 4 ore.

Compromissione epatica

In soggetti con insufficienza epatica lieve e moderata non è stata rilevata alcuna modificazione significativa della clearance del levetiracetam. Nella maggioranza dei soggetti con compromissione epatica grave, la clearance del levetiracetam è stata ridotta di oltre il 50% a causa della compromissione renale concomitante (vedere paragrafo 4.2).

Popolazione pediatrica

Bambini (dai 4 ai 12 anni)

In seguito ad una singola somministrazione orale (20 mg/kg) in bambini (da 6 a 12 anni) con epilessia, l'emivita di levetiracetam è risultata di 6,0 ore. La clearance apparente corretta in funzione del peso corporeo è risultata approssimativamente più alta del 30% rispetto agli adulti con epilessia.

In seguito a somministrazione orale per dosi ripetute (da 20 a 60 mg/kg/die) in bambini epilettici (da 4 a 12 anni), il levetiracetam è stato rapidamente assorbito. Il picco di concentrazione plasmatica è stato osservato a 0,5 - 1,0 ora dalla somministrazione. Sono stati osservati aumenti lineari e proporzionali alla dose per il picco delle concentrazioni plasmatiche e per l'area sotto la curva. L'emivita di eliminazione è risultata pari a circa 5 ore. La clearance corporea apparente è stata di 1,1 ml/min/kg.

Infanti e bambini (da 1 mese a 4 anni)

A seguito di somministrazione di una dose singola (20 mg/kg) di soluzione orale 100 mg/ml in bambini epilettici (da 1 mese a 4 anni), il levetiracetam è stato rapidamente assorbito e le concentrazioni plasmatiche di picco sono state osservate circa 1 ora dopo la somministrazione. I risultati farmacocinetici hanno indicato che l'emivita è più breve (5,3 ore) che negli adulti (7,2 ore) e la clearance apparente è risultata più veloce (1,5 ml/min/kg) rispetto agli adulti (0,96 ml/min/kg). Nelle analisi farmacocinetiche di popolazione condotte in pazienti da 1 mese a 16 anni di età, il peso corporeo era significativamente correlato alla clearance apparente (la clearance aumentava all'aumentare del peso corporeo) ed al volume di distribuzione apparente. Anche l'età ha influenzato entrambi i parametri. Questo effetto è risultato marcato per i bambini più piccoli e attenuato con l'aumentare dell'età, per poi diventare trascurabile intorno ai 4 anni di età. In entrambe le analisi farmacocinetiche di popolazione, vi è stato un aumento del 20% circa della clearance apparente del levetiracetam quando somministrato assieme a un farmaco antiepilettico induttore enzimatico.

5.3 Dati preclinici di sicurezza

I dati non-clinici non rivelano rischi particolari per l'uomo sulla base di studi convenzionali di sicurezza farmacologica, genotossicità e potenziale cancerogeno.

Gli effetti indesiderati non osservati negli studi clinici, ma visti nel ratto e in minore entità nel topo, a livelli di esposizione simili ai livelli di esposizione nell'uomo e con possibile rilevanza per l'uso clinico, sono state variazioni epatiche come indice di una risposta adattativa, quali aumento ponderale ed ipertrofia centro lobulare, infiltrazione adiposa ed innalzamento degli enzimi epatici nel plasma.

Nel ratto non si sono osservate reazioni avverse sulla fertilità maschile e femminile o sulla capacità riproduttiva a dosi fino a 1800 mg/kg/die (6 volte la dose massima giornaliera raccomandata nell'uomo -MRHD, *Maximum Recommended Human Daily*

Dose- in base ai mg/m^2 o in base all'esposizione), sia nella generazione parentale che nella generazione F1.
Due studi sullo sviluppo embriofetale (EFD: *Embryo-Fetal Development*) sono stati condotti nel ratto a 400, 1200 e 3600 mg/kg/die. A 3600 mg/kg/die, in uno solo dei 2 studi EFD si è registrato un lieve calo di peso fetale associato ad un aumento marginale delle alterazioni scheletriche/anomalie minori. Non si è verificato alcun effetto sulla mortalità embrionale, né vi è stato un aumento dell'incidenza di malformazioni. Il NOAEL (*No Observed Adverse Effect Level*) è stato di 3600 mg/kg/die per le femmine di ratto gravide (12 volte la MRHD in base ai mg/m^2) e 1200 mg/kg/die per i feti.
Quattro studi sullo sviluppo embrio-fetale sono stati condotti sul coniglio utilizzando dosi di 200, 600, 800, 1200 e 1800 mg/kg/die. La dose di 1800 mg/kg/die ha indotto una marcata tossicità materna e una diminuzione del peso fetale, in associazione con una maggiore incidenza di feti con anomalie cardiovascolari/scheletriche. Il NOAEL è stato <200 mg/kg/die per le madri e di 200 mg/kg/die per i feti (equivalente alla MRHD in base ai mg/m^2). Uno studio sullo sviluppo peri- e post-natale è stato condotto sul ratto con dosi di levetiracetam di 70, 350 e 1800 mg/kg/die. Il NOAEL è stato ≥1800 mg/kg/die per le femmine F0 e per la generazione F1 per quanto riguarda la sopravvivenza, l'accrescimento e lo sviluppo fino allo svezzamento (6 volte la MRHD in base ai mg/m^2). Studi nel ratto e nel cane, nell'animale neonato e giovane, hanno dimostrato che non si manifestano effetti indesiderati in alcuno degli endpoint standard di sviluppo o di maturazione a dosi fino a 1800 mg/kg/die (6-17 volte la MRHD in base ai mg/m^2).

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

Nucleo della compressa:
amido di mais
povidone K 30
talco
diossido di silicio colloidale
magnesio stearato (E572).
Compresse rivestite con film da 500 mg
Film di rivestimento:
polivinil alcol, parz. idrolizzato
titanio diossido (E171)
macrogol 3350
talco
ferro ossido giallo (E172)
Compresse rivestite con film da 1000 mg
Film di rivestimento:
polivinil alcol, parz. idrolizzato
titanio diossido (E171)
macrogol 3350
talco.

6.2 Incompatibilità

Non pertinente.

6.3 Periodo di validità

3 anni.

6.4 Precauzioni particolari per la conservazione

Compresse rivestite con film da 500 mg
Questo medicinale non richiede alcuna condizione particolare di conservazione.
Compresse rivestite con film da 1000 mg
Non conservare a temperatura superiore a 30°C.

6.5 Natura e contenuto del contenitore

Blister in alluminio/PVC con:
Compresse rivestite con film da 500 mg 60 compresse rivestite con film.
Compresse rivestite con film da 1000 mg 30 compresse rivestite con film.
È possibile che non tutte le confezioni siano commercializzate.

6.6 Precauzioni particolari per lo smaltimento e la manipolazione

Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità
alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

So.Se.PHARM S.r.l. - Via dei Castelli Romani, 22- 00071 Pomezia (Roma) Italia. Concessionario per la vendita: Istituto Luso Farmaco D'Italia SpA – Milanofiori - Strada 6 - Edificio L - Rozzano (MI).

8. NUMERO(I) DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

AIC 040273017 - "500 mg compresse rivestite con film" 60 compresse in blister PVC/Al.
AIC 040273029 - "1000 mg compresse rivestite con film" 30 compresse in blister PVC/Al.

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Prima Autorizzazione: 19 Luglio 2012.
Rinnovo: 19 luglio 2016.

10. DATA DI REVISIONE DEL TESTO

14 Settembre 2016.

ITALEPT 500 mg 60 compresse rivestite con film
Prezzo SSN € 37,67* Classe A - Ricetta ripetibile.
ITALEPT 1000 mg 30 compresse rivestite con film
Prezzo SSN € 36,16* Classe A - Ricetta ripetibile.

**Prezzo comprensivo delle riduzioni temporanee di cui alle determinazioni AIFA, 3 luglio 2006 e 27 settembre 2006.*

ITALEPT Levetiracetam

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

ITALEPT 100 mg/ml soluzione orale.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Ogni ml contiene 100 mg di levetiracetam.
Eccipienti con effetti noti:
Ogni ml contiene 2,7 mg di metile paraidrossibenzoato (E218), 0,3 mg di propile paraidrossibenzoato (E216) e 300 mg di maltitolo liquido.
Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

Soluzione orale. Liquido limpido.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

ITALEPT è indicato come monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in adulti ed adolescenti a partire dai 16 anni di età con epilessia di nuova diagnosi. ITALEPT è indicato quale terapia aggiuntiva:

- nel trattamento delle crisi convulsive ad esordio parziale con o senza secondaria generalizzazione in adulti, adolescenti, bambini e infanti a partire da 1 mese di età con epilessia;
- nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile;
- nel trattamento delle crisi convulsive tonico-cloniche generalizzate primarie in adulti ed adolescenti a partire da 12 anni di età con epilessia idiopatica generalizzata.

4.2 Posologia e modo di somministrazione

Posologia

Monoterapia per adulti e adolescenti a partire da 16 anni di età La dose iniziale raccomandata è 250 mg due volte al giorno, da aumentare fino a una dose terapeutica iniziale di 500 mg due volte al giorno dopo due settimane. La dose può essere ulteriormente aumentata di 250 mg due volte al giorno ogni due settimane sulla base della risposta clinica. La dose massima è di 1500 mg due volte al giorno.

Terapia aggiuntiva per adulti (≥18 anni) ed adolescenti (da 12 a 17 anni) del peso di 50 kg o superiore La dose terapeutica iniziale è 500 mg due volte al giorno. Questa dose può essere iniziata dal primo giorno di trattamento. Sulla base della risposta clinica e della tollerabilità, la dose giornaliera può essere aumentata fino ad un massimo di 1500 mg due volte al giorno. Gli aggiustamenti posologici possono essere fatti con aumenti o diminuzioni di 500 mg due volte al giorno ogni 2 - 4 settimane.

Interruzione del trattamento

In accordo con la pratica clinica corrente, se si deve interrompere il trattamento con ITALEPT si raccomanda una sospensione graduale (ad es. negli adulti e negli adolescenti di peso superiore a 50 kg: diminuzione di 500 mg due volte al giorno ad intervalli di tempo compresi tra due e quattro settimane; negli infanti di età superiore ai 6 mesi, nei bambini e negli adolescenti di peso inferiore a 50 kg: la diminuzione della dose non deve superare i 10 mg/kg due volte al giorno ogni due settimane; negli infanti (di età inferiore a 6 mesi): la diminuzione della dose non deve superare i 7 mg/kg due volte al giorno ogni due settimane).

Popolazioni speciali

Anziani (da 65 anni in poi) Si raccomanda un aggiustamento della posologia nei pazienti anziani con funzionalità renale compromessa (vedere più avanti "*Compromissione renale*).

Compromissione renale La dose giornaliera deve essere personalizzata in base alla funzionalità renale.
Per i pazienti adulti, fare riferimento alla tabella seguente e modificare la dose come indicato. Per utilizzare questa tabella posologica è necessario valutare la clearance della creatinina del paziente (CLcr) in ml/min. La CLcr in ml/min può essere calcolata dalla determinazione della creatinina sierica (mg/dl) utilizzando, per adulti e adolescenti di peso superiore o uguale a 50 kg, la seguente formula:

$$\text{CLcr (ml/min)} = \frac{[140\text{-età (anni)}] \times \text{peso (kg)}}{72 \times \text{creatinina sierica (mg/dl)}} \quad (\times 0{,}85 \text{ nelle donne})$$

Inoltre, la CLcr viene aggiustata secondo l'area della superficie corporea (BSA) come segue:

$$\text{CLcr (ml/min/1,73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA del soggetto (m}^2\text{)}} \times 1{,}73$$

Aggiustamento posologico per pazienti adulti ed adolescenti di peso superiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/1,73 m²)	Dose e numero di somministrazioni
Normale	>80	500-1500 mg due volte al giorno
Lieve	50-79	500-1000 mg due volte al giorno
Moderata	30-49	250-750 mg due volte al giorno
Severa	<30	250-500 mg due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi[1]	-	500-1000 mg una volta al giorno[2]

[1] Una dose di carico pari a 750 mg è raccomandata nel primo giorno di trattamento con levetiracetam.
[2] Dopo la dialisi si raccomanda una dose supplementare compresa tra 250 e 500 mg.

Per bambini con ridotta funzionalità renale, la dose di levetiracetam deve essere adattata sulla base della funzionalità renale, perché la clearance del levetiracetam è correlata alla funzionalità renale. Questa raccomandazione si basa su uno studio condotto su pazienti adulti con ridotta funzionalità renale.
Nei giovani adolescenti, nei bambini e negli infanti, la CLcr, in ml/min/1,73 m², può essere stimata dalla determinazione della creatinina sierica (in mg/dl) utilizzando la seguente formula (formula di Schwartz):

$$\text{CLcr (ml/min/1,73 m}^2\text{)} = \frac{\text{Altezza (cm)} \times \text{ks}}{\text{Creatinina sierica (mg/dl)}}$$

ks= 0,45 negli infanti nati a termine, di età fino a 1 anno; ks= 0,55 nei bambini di età inferiore a 13 anni e nelle femmine adolescenti; ks= 0,7 nei maschi adolescenti.

Aggiustamento posologico per infanti, bambini e adolescenti di peso inferiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/1,73 m²)	Dose e frequenza[1]	
		Infanti da 1 mese a meno di 6 mesi	Infanti da 6 a 23 mesi, bambini e adolescenti di peso inferiore ai 50 kg
Normale	>80	7-21 mg/kg (0,07-0,21 ml/kg) due volte al giorno	10-30 mg/kg (0,10-0,30 ml/kg) due volte al giorno
Lieve	50-79	7-14 mg/kg (0,07-0,14 ml/kg) due volte al giorno	10-20 mg/kg (0,10-0,20 ml/kg) due volte al giorno
Moderata	30-49	3,5-10,5 mg/kg (0,035-0,105 ml/kg) due volte al giorno	5-15 mg/kg (0,05-0,15 ml/kg) due volte al giorno
Severa	<30	3,5-7 mg/kg (0,035-0,07 ml/kg) due volte al giorno	5-10 mg/kg (0,05-0,10 ml/kg) due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi	--	7-14 mg/kg (0,07-0,14 ml/kg) una volta al giorno[2] [4]	10-20 mg/kg (0,10-0,20 ml/kg) una volta al giorno[3] [5]

[1] Utilizzare ITALEPT soluzione orale per dosi inferiori a 250 mg, per dosi non multiple di 250 mg quando non è possibile ottenere la dose raccomandata assumendo un numero multiplo di compresse, e per i pazienti incapaci di deglutire le compresse.
[2] Si raccomanda una dose di carico di 10,5 mg/kg il primo giorno di trattamento con levetiracetam.
[3] Si raccomanda una dose di carico di 15 mg/kg (0,15 ml/kg) il primo giorno di trattamento con levetiracetam.
[4] Dopo la dialisi, si raccomanda una dose supplementare di 3,5-7 mg/kg (0,035-0,07 ml/kg).
[5] Dopo la dialisi, si raccomanda una dose supplementare di 5-10 mg/kg (0,05-0,10 ml/kg).

Compromissione epatica
Non è necessario alcun adeguamento posologico nei pazienti con compromissione epatica di grado da lieve a moderato. In pazienti con compromissione epatica severa, la clearance della creatinina può far sottostimare il grado di insufficienza renale. Pertanto, quando la clearance della creatinina è <60 ml/min/1,73 m², si raccomanda una riduzione del 50% della dose di mantenimento giornaliera.
Popolazione pediatrica
Il medico deve prescrivere la forma farmaceutica, la presentazione e il dosaggio più appropriati in base all'età, al peso e alla dose.
ITALEPT soluzione orale è la formulazione più indicata nella prima infanzia e nei bambini di età inferiore ai 6 anni. Inoltre, i dosaggi disponibili per le compresse non sono indicati per il trattamento iniziale dei bambini di peso inferiore a 25 kg, dei pazienti incapaci di deglutire le compresse o per la somministrazione di dosi inferiori a 250 mg. In tutti questi casi deve essere utilizzato ITALEPT soluzione orale.
Monoterapia Non sono state ancora stabilite la sicurezza e l'efficacia di ITALEPT somministrato in monoterapia nei bambini e negli adolescenti di età inferiore a 16 anni.
Non vi sono dati disponibili.
Terapia aggiuntiva per bambini piccoli da 6 a 23 mesi di età, bambini (da 2 a 11 anni) e adolescenti (da 12 a 17 anni) di peso inferiore a 50 kg La dose terapeutica iniziale è di 10 mg/kg due volte al giorno.
Sulla base della risposta clinica e della tollerabilità, la dose può essere aumentata fino a 30 mg/kg due volte al giorno.
Gli aggiustamenti posologici non devono superare aumenti o diminuzioni di 10 mg/kg due volte al giorno ogni due settimane. Deve essere usata la dose efficace più bassa. La dose in bambini di 50 kg o più è uguale a quella degli adulti.

Dose raccomandata nella prima infanzia a partire da 6 mesi di età, nei bambini e negli adolescenti:

Peso	Dose iniziale: 10 mg/kg due volte al giorno	Dose massima: 30 mg/kg due volte al giorno
6 kg[1]	60 mg (0,6 ml) due volte al giorno	180 mg (1,8 ml) due volte al giorno
10 kg[1]	100 mg (1 ml) due volte al giorno	300 mg (3 ml) due volte al giorno
15 kg[1]	150 mg (1,5 ml) due volte al giorno	450 mg (4,5 ml) due volte al giorno
20 kg[1]	200 mg (2 ml) due volte al giorno	600 mg (6 ml) due volte al giorno
25 kg	250 mg due volte al giorno	750 mg due volte al giorno
Da 50 kg[2]	500 mg due volte al giorno	1500 mg due volte al giorno

[1] I bambini dal peso di 25 kg o inferiore devono preferibilmente iniziare il trattamento con ITALEPT 100 mg/ml soluzione orale.
[2] La dose in bambini e adolescenti dal peso di 50 kg o superiore è uguale a quella degli adulti.

Terapia aggiuntiva per infanti da 1 mese a meno di 6 mesi di età La dose terapeutica iniziale è di 7 mg/kg due volte al giorno. Sulla base della risposta clinica e della tollerabilità, la dose può essere aumentata fino a 21 mg/kg due volte al giorno. Gli aggiustamenti posologici non devono superare aumenti o diminuzioni di 7 mg/kg due volte al giorno ogni due settimane. Deve essere usata la dose efficace più bassa. Gli infanti devono iniziare il trattamento con ITALEPT 100 mg/ml soluzione orale.

Dose raccomandata per infanti di età compresa tra 1 mese e meno di 6 mesi:

Peso	Dose iniziale: 7 mg/kg due volte al giorno	Dose massima: 21 mg/kg due volte al giorno
4 kg	28 mg (0,3 ml) due volte al giorno	84 mg (0,85 ml) due volte al giorno
5 kg	35 mg (0,35 ml) due volte al giorno	105 mg (1,05 ml) due volte al giorno
7 kg	49 mg (0,5 ml) due volte al giorno	147 mg (1,5 ml) due volte al giorno

È disponibile una presentazione:
- Un flacone da 300 ml con siringa graduata da 10 ml per uso orale (contenente fino a 1000 mg di levetiracetam), con una tacca graduata ogni 0,25 ml (corrispondente a 25 mg).

Questa presentazione deve essere prescritta ai bambini di età pari o superiore ai 4 anni, agli adolescenti e agli adulti.
Modo di somministrazione
La soluzione orale può essere diluita in un bicchiere d'acqua o nel biberon e può essere assunta con o senza cibo. Con ITALEPT vengono forniti una siringa graduata per somministrazione orale, un adattatore per la siringa e le istruzioni per l'uso nel foglio illustrativo.
La dose giornaliera va ripartita in due somministrazioni uguali.

4.3 Controindicazioni
Ipersensibilità al principio attivo o ad altri derivati pirrolidonici o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.

4.4 Avvertenze speciali e precauzioni di impiego
Compromissione renale
La somministrazione di ITALEPT in pazienti con compromissione renale può richiedere un aggiustamento posologico. In pazienti con funzionalità epatica gravemente compromessa si racco-

manda di valutare la funzionalità renale prima di stabilire la posologia (vedere paragrafo 4.2).

Suicidio

Casi di suicidio, tentato suicidio, idea e comportamento suicida sono stati riportati in pazienti trattati con antiepilettici (incluso levetiracetam). Una meta-analisi di studi randomizzati e controllati con placebo, condotti con medicinali antiepilettici, ha mostrato un lieve incremento del rischio di idea e comportamento suicida. Il meccanismo di tale rischio non è noto.

Di conseguenza, i pazienti devono essere monitorati per quanto riguarda la comparsa di segni di depressione e/o idea e comportamento suicida, e deve essere preso in considerazione un trattamento appropriato. I pazienti (e coloro che se ne prendono cura) devono essere avvisati che, nel caso in cui compaiano segni di depressione e/o idea o comportamento suicida, è necessario consultare un medico.

Popolazione pediatrica

Dai dati disponibili nei bambini non si evince un'influenza sulla crescita e sulla pubertà. Tuttavia, non sono noti gli effetti a lungo termine sull'apprendimento, l'intelligenza, la crescita, la funzione endocrina, la pubertà e sul potenziale riproduttivo nei bambini.

Eccipienti

ITALEPT 100 mg/ml soluzione orale contiene metil paraidrossibenzoato (E218) e propil paraidrossibenzoato (E216), che possono causare reazioni allergiche (anche ritardate). Il prodotto contiene inoltre maltitolo liquido; i pazienti affetti da rari problemi ereditari di intolleranza al fruttosio non devono assumere questo medicinale.

4.5 Interazioni con altri medicinali ed altre forme di interazione

Medicinali antiepilettici

I dati provenienti da studi clinici pre-marketing, condotti negli adulti, indicano che levetiracetam non influenza le concentrazioni sieriche degli antiepilettici esistenti (fenitoina, carbamazepina, acido valproico, fenobarbital, lamotrigina, gabapentin e primidone) e che questi antiepilettici non influenzano la farmacocinetica di levetiracetam.

Come negli adulti, nei pazienti pediatrici cui sono state somministrate dosi fino a 60 mg/kg/die di levetiracetam, non c'è evidenza di interazioni clinicamente significative con altri medicinali.

Una valutazione retrospettiva di interazioni farmacocinetiche, in bambini e adolescenti affetti da epilessia (da 4 a 17 anni) ha confermato che la terapia aggiuntiva con levetiracetam somministrato per via orale non influenzava le concentrazioni sieriche allo stato stazionario di carbamazepina e valproato somministrati contemporaneamente.

Tuttavia, i dati hanno suggerito una clearance del levetiracetam del 20% più elevata nei bambini che assumono medicinali antiepilettici con un effetto di induzione enzimatica. Non è richiesto un aggiustamento della dose.

Probenecid

Il probenecid (500 mg quattro volte al giorno), un agente bloccante della secrezione tubulare renale, ha mostrato di inibire la clearance renale del metabolita primario, ma non di levetiracetam. Tuttavia, la concentrazione di questo metabolita rimane bassa.

Metotrexato

È stato riportato che la somministrazione concomitante di levetiracetam e metotrexato diminuisce la clearance del metotrexato, con conseguente concentrazione ematica di metotrexato aumentata/prolungata fino a livelli potenzialmente tossici. I livelli ematici di metotrexato e levetiracetam devono essere attentamente monitorati nei pazienti trattati in concomitanza con i due farmaci.

Contraccettivi orali e altre interazioni farmacocinetiche

Levetiracetam 1000 mg al giorno non ha influenzato la farmacocinetica dei contraccettivi orali (etinilestradiolo e levonorgestrel); i parametri endocrini (ormone luteinizzante e progesterone) non sono stati modificati. Levetiracetam 2000 mg al giorno non ha influenzato la farmacocinetica di digossina e warfarin; i tempi di protrombina non sono stati modificati.

La somministrazione concomitante di digossina, contraccettivi orali e warfarin non ha influenzato la farmacocinetica di levetiracetam.

Lassativi

Sono stati riportati casi isolati di diminuita efficacia di levetiracetam quando il lassativo osmotico macrogol è stato somministrato in concomitanza con levetiracetam per via orale. Pertanto, macrogol non deve essere assunto per via orale da un'ora prima ad un'ora dopo l'assunzione di levetiracetam.

Cibo e alcool

L'entità dell'assorbimento di levetiracetam non è stata modificata dal cibo, ma la velocità di assorbimento era lievemente ridotta. Non sono disponibili dati sulle interazioni di levetiracetam con l'alcool.

4.6 Fertilità, gravidanza e allattamento

Gravidanza

Dati post-marketing di diversi registri prospettici di gravidanza hanno documentato i risultati della esposizione a levetiracetam in monoterapia in più di 1.000 donne durante il primo trimestre di gravidanza. Nel complesso, questi dati non suggeriscono un sostanziale aumento del rischio di malformazioni congenite maggiori, sebbene un rischio teratogeno non possa essere completamente escluso. La terapia con più farmaci antiepilettici è associata ad un più alto rischio di malformazioni congenite rispetto alla monoterapia e pertanto la monoterapia deve essere presa in considerazione.

Gli studi sugli animali hanno mostrato una tossicità riproduttiva (vedere paragrafo 5.3). ITALEPT non è raccomandato durante la gravidanza e nelle donne in età fertile che non utilizzano metodi contraccettivi, a meno che non sia strettamente necessario.

Le alterazioni fisiologiche durante la gravidanza possono influenzare le concentrazioni di levetiracetam. Durante la gravidanza, è stata osservata una riduzione delle concentrazioni plasmatiche di levetiracetam. Questa riduzione è più pronunciata durante il terzo trimestre (fino al 60% della concentrazione basale prima della gravidanza).

Le donne in gravidanza trattate con levetiracetam devono essere accuratamente seguite dal punto di vista clinico.

L'interruzione dei trattamenti antiepilettici può comportare una esacerbazione della malattia che può essere nociva per la madre e per il feto.

Allattamento

Levetiracetam è escreto nel latte materno. Pertanto, l'allattamento con latte materno non è raccomandato. Tuttavia, se il trattamento con levetiracetam è necessario durante l'allattamento, deve essere valutato il rapporto rischio/beneficio del trattamento, tenendo in considerazione l'importanza dell'allattamento con latte materno.

Fertilità

Non è stato rilevato alcun impatto sulla fertilità negli studi sugli animali (vedere paragrafo 5.3). Non sono disponibili dati clinici; il rischio potenziale nell'uomo è sconosciuto.

4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Levetiracetam ha una bassa o moderata influenza sulla capacità di guidare veicoli e sull'uso di macchinari. Data la possibile differente sensibilità individuale, alcuni pazienti possono manifestare sonnolenza o altri sintomi legati all'azione sul sistema nervoso centrale, specialmente all'inizio del trattamento o in seguito ad un incremento della dose.

Si raccomanda pertanto cautela nei pazienti che sono impegnati in attività che richiedono elevata concentrazione, quali guidare autoveicoli o azionare macchinari.

I pazienti devono essere avvertiti di non guidare o utilizzare macchinari finché non sia stato accertato che la loro abilità ad eseguire queste attività non sia compromessa.

4.8 Effetti indesiderati

Riassunto del profilo di sicurezza

Le reazioni avverse più frequentemente riportate sono state rinofaringite, sonnolenza, cefalea, affaticamento e capogiro. Il profilo delle reazioni avverse di seguito presentato si basa sull'analisi degli studi clinici controllati verso placebo aggregati, relativi a tutte le indicazioni studiate, per un totale di 3.416 pazienti trattati con levetiracetam.

Questi dati sono integrati con l'uso di levetiracetam in corrispondenti studi di estensione in aperto, così come dall'esperienza post-marketing. Il profilo di sicurezza del levetiracetam è ge-

neralmente simile nell'ambito dei diversi gruppi di età (pazienti adulti e pediatrici) e delle indicazioni approvate nel trattamento dell'epilessia.

Tabella delle reazioni avverse

Le reazioni avverse segnalate nel corso di studi clinici (adulti, adolescenti, bambini ed infanti di età superiore ad 1 mese) e nell'esperienza post-marketing sono elencate nella tabella seguente secondo la classificazione per sistemi e organi e per frequenza.

Le reazioni avverse sono presentate in ordine decrescente di gravità e la loro frequenza è definita come segue: molto comune (≥1/10), comune (≥1/100, <1/10), non comune (≥1/1000, <1/100), raro (≥1/10.000, <1/1000) e molto raro (<1/10.000).

Classificazione per sistemi e organi (MedDRA)	Categoria di frequenza			
	Molto comune	Comune	Non comune	Raro
Infezioni ed infestazioni	Rinofaringite			Infezione
Patologie del sistema emolinfopoietico			Trombocitopenia, leucopenia	Pancitopenia, neutropenia, agranulocitosi
Disturbi del sistema immunitario				Reazione a farmaco con eosinofilia e sintomi sistemici (DRESS), ipersensibilità (incluso angioedema e anafilassi)
Disturbi del metabolismo e della nutrizione		Anoressia	Perdita di peso, aumento di peso	Iponatriemia
Disturbi psichiatrici		Depressione, ostilità/aggressività, ansia, insonnia, nervosismo/irritabilità	Tentato suicidio, idea suicida, disturbo psicotico, comportamento anormale, allucinazioni, collera, stato confusionale, attacco di panico, labilità affettiva/sbalzi d'umore, agitazione	Suicidio riuscito, disturbo della personalità, pensiero anormale
Patologie del sistema nervoso	Sonnolenza, cefalea	Convulsione, disturbo dell'equilibrio, capogiro, letargia, tremore	Amnesia, compromissione della memoria, coordinazione anormale/atassia, parestesia, alterazione dell'attenzione	Coreoatetosi, discinesia, ipercinesia
Patologie dell'occhio			Diplopia, visione offuscata	
Patologie dell'orecchio e del labirinto		Vertigine		
Patologie respiratorie, toraciche e mediastiniche		Tosse		
Patologie gastrointestinali		Dolore addominale, diarrea, dispepsia, vomito, nausea		Pancreatite
Patologie epatobiliari			Test della funzionalità epatica anormali	Insufficienza epatica, epatite
Patologie della cute e del tessuto sottocutaneo		Rash	Alopecia, eczema, prurito	Necrolisi epidermica tossica, sindrome di Stevens-Johnson, eritema multiforme
Patologie del sistema muscolo-scheletrico e del tessuto connettivo			Debolezza muscolare, mialgia	
Patologie sistemiche e condizioni relative alla sede di somministrazione		Astenia/ affaticamento		
Traumatismo, avvelenamento e complicazioni da procedura			Traumatismo	

Descrizione di determinate reazioni avverse
Il rischio di anoressia è più elevato quando assieme al levetiracetam viene somministrato il topiramato. In numerosi casi di alopecia, è stata osservata guarigione dopo la sospensione del trattamento con levetiracetam. In alcuni dei casi di pancitopenia è stata identificata soppressione del midollo osseo.
Popolazione pediatrica
In pazienti di età compresa tra 1 mese e meno di 4 anni, un totale di 190 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. Sessanta (60) di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In pazienti di età compresa tra 4 e 16 anni, un totale di 645 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. 233 di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In entrambi questi intervalli di età pediatrica, questi dati sono integrati con l'esperienza post-marketing relativa all'uso di levetiracetam.
Inoltre, 101 bambini di età inferiore a 12 mesi sono stati esposti in uno studio di sicurezza post-autorizzazione. Non sono stati identificati nuovi problemi di sicurezza per levetiracetam in infanti di età inferiore a 12 mesi con epilessia. Il profilo delle reazioni avverse del levetiracetam è generalmente simile nell'ambito dei diversi gruppi di età e delle indicazioni approvate nel trattamento dell'epilessia. Negli studi clinici controllati con placebo, i risultati sulla sicurezza nei pazienti pediatrici sono stati coerenti con il profilo di sicurezza di levetiracetam negli adulti, ad eccezione delle reazioni avverse comportamentali e psichiatriche che sono state più comuni nei bambini rispetto che negli adulti. Nei bambini e negli adolescenti di età compresa tra 4 e 16 anni, sono stati riportati più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo vomito (molto comune, 11,2%), agitazione (comune, 3,4%), sbalzi d'umore (comune, 2,1%), labilità affettiva (comune, 1,7%), aggressività (comune, 8,2%), comportamento anormale (comune, 5,6%) e letargia (comune, 3,9%). In infanti e bambini di età compresa tra 1 mese e meno di 4 anni, sono state riportate più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo irritabilità (molto comune, 11,7%) e coordinazione anormale (comune, 3,3%).
Uno studio di sicurezza sui pazienti pediatrici, condotto secondo un disegno di non inferiorità, in doppio cieco e controllato con placebo, ha valutato gli effetti cognitivi e neuro-psicologici di levetiracetam in bambini da 4 a 16 anni di età con crisi convulsive a esordio parziale. Il levetiracetam si è dimostrato non differente (non inferiore) rispetto al placebo per quanto riguarda la modifica rispetto al basale nel punteggio ottenuto ai test "Attenzione e Memoria" della scala di Leiter-R (*Memory Screen Composite score*) nella popolazione per-protocol. I risultati correlati alle funzioni comportamentali ed emozionali hanno indicato un peggioramento, nei pazienti trattati con levetiracetam, del comportamento aggressivo misurato in maniera standardizzata e sistematica, con l'utilizzo di uno strumento validato (*CBCL – Achenbach Child Behavior Checklist*).
Tuttavia, i soggetti che hanno assunto levetiracetam nello studio in aperto di follow-up a lungo termine non hanno manifestato, in media, un peggioramento delle loro funzioni comportamentali ed emozionali; in particolare, le valutazioni dell'aggressività nei comportamenti non sono peggiorate rispetto al basale.
Segnalazione delle reazioni avverse sospette
La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione dell'Agenzia Italiana del Farmaco, Sito web: http://www.agenziafarmaco.gov.it/it/responsabili.

4.9 Sovradosaggio
Sintomi
Sonnolenza, agitazione, aggressività, ridotto livello di coscienza, depressione respiratoria e coma sono stati osservati con sovradosaggi di levetiracetam.
Trattamento del sovradosaggio
Dopo un sovradosaggio acuto, lo stomaco può essere svuotato mediante lavanda gastrica o induzione del vomito. Non esiste un antidoto specifico per levetiracetam. Il trattamento del sovradosaggio dovrà essere sintomatico e può includere l'emodialisi. L'efficienza di estrazione mediante dialisi è del 60% per levetiracetam e del 74% per il metabolita primario.

5. PROPRIETÀ FARMACOLOGICHE

5.1 Proprietà farmacodinamiche
Categoria farmacoterapeutica: antiepilettici, altri antiepilettici, codice ATC: N03AX14.
Il principio attivo, levetiracetam, è un derivato pirrolidonico (S-enantiomero dell'α-etil- 2-oxo-1-pirrolidin acetamide), non correlato chimicamente con sostanze ad attività antiepilettica esistenti.
Meccanismo d'azione
Il meccanismo d'azione di levetiracetam non è stato ancora del tutto spiegato. Esperimenti *in vitro* ed *in vivo* suggeriscono che levetiracetam non altera le caratteristiche cellulari di base e la normale neurotrasmissione.
Studi *in vitro* dimostrano che levetiracetam agisce sui livelli intraneuronali di Ca^{2+} attraverso la parziale inibizione delle correnti di Ca^{2+} di tipo N e riducendo il rilascio di Ca^{2+} dai depositi intraneuronali. Inoltre, il farmaco inverte parzialmente la riduzione, indotta da zinco e β-carboline, delle correnti indotte da GABA e glicina. Studi *in vitro* hanno inoltre evidenziato che levetiracetam si lega ad uno specifico sito nel tessuto cerebrale dei roditori.
Questo sito di legame è la proteina 2A della vescicola sinaptica, che si ritiene sia coinvolta nella fusione della vescicola e nell'esocitosi del neurotrasmettitore. Levetiracetam e i relativi analoghi mostrano un grado di affinità per il legame alla proteina 2A della vescicola sinaptica che è correlato con la potenza della loro protezione antiepilettica nel modello audiogenico di epilessia nel topo. Questa scoperta suggerisce che l'interazione tra levetiracetam e la proteina 2A della vescicola sinaptica sembra aver parte nel meccanismo d'azione antiepilettica del medicinale.
Effetti farmacodinamici
Il levetiracetam induce un'azione di protezione nei confronti delle crisi epilettiche in un ampio spettro di modelli animali di epilessia parziale e generalizzata primaria, senza avere un effetto pro-convulsivante. Il metabolita primario è inattivo. Nell'uomo, un'attività in condizioni di epilessia sia parziale che generalizzata (scarica epilettiforme/risposta fotoparossistica) ha confermato l'ampio spettro del profilo farmacologico del levetiracetam.
Efficacia e sicurezza clinica
Terapia aggiuntiva nel trattamento delle crisi parziali con o senza generalizzazione secondaria in adulti, adolescenti, bambini ed infanti a partire da 1 mese di età con epilessia
Negli adulti, l'efficacia di levetiracetam è stata dimostrata in 3 studi in doppio cieco, controllati con placebo, con dosi di 1000 mg, 2000 mg o 3000 mg/die, suddivise in 2 somministrazioni, per una durata di trattamento fino a 18 settimane. In una analisi globale, la percentuale di pazienti che ha ottenuto una riduzione della frequenza delle crisi parziali per settimana, nel periodo di trattamento a dose stabile (12/14 settimane), uguale o superiore al 50% rispetto al basale, è stata del 27,7%, 31,6% e 41,3% dei pazienti trattati rispettivamente con 1000, 2000 o 3000 mg di levetiracetam e del 12,6% per i pazienti trattati con placebo.
Popolazione pediatrica L'efficacia di levetiracetam nei pazienti pediatrici (dai 4 ai 16 anni di età) è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 198 pazienti ed ha avuto una durata di trattamento di 14 settimane. In questo studio, i pazienti hanno assunto levetiracetam alla dose fissa di 60 mg/kg/die (con due somministrazioni giornaliere).
Il 44,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo ha avuto, rispetto al basale, una riduzione della frequenza delle crisi convulsive a esordio parziale per settimana uguale o superiore al 50%. Con il trattamento continuato a lungo termine, l'11,4% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,2% è rimasto libero da crisi per almeno 1 anno.
Nei pazienti pediatrici (da 1 mese a meno di 4 anni di età), l'efficacia di levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 116 pazienti e ha avuto una durata di trattamento di 5 giorni. In questo studio è stata prescritta ai pazienti una dose giornaliera di 20 mg/kg,

25 mg/kg, 40 mg/kg o 50 mg/kg di soluzione orale, basandosi sullo schema di titolazione della dose riferito alla loro età. Nello studio sono state utilizzate le seguenti dosi: 20 mg/kg/die, titolata a 40 mg/kg/die, per infanti da un mese a meno di sei mesi di età; 25 mg/kg/die, titolata a 50 mg/kg/die, per infanti e bambini da 6 mesi a meno di 4 anni di età. La dose totale giornaliera è stata suddivisa in due somministrazioni al giorno.
Il principale parametro dell'efficacia del trattamento è stato il tasso di pazienti responsivi (percentuale di pazienti con una riduzione della frequenza media giornaliera delle crisi convulsive a esordio parziale ≥50% rispetto ai valori basali), valutato da un esaminatore unico in cieco utilizzando un video EEG per un periodo di 48 ore. L'analisi dell'efficacia è stata effettuata su 109 pazienti che erano stati sottoposti a video EEG per almeno 24 ore, sia durante il periodo basale che durante il periodo di valutazione. Il 43,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo sono stati considerati responsivi. I risultati sono coerenti nei diversi gruppi di età. Nel trattamento continuato a lungo termine, l'8,6% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,8% è stato libero da crisi per almeno 1 anno.
35 infanti di età inferiore ad 1 anno, dei quali solo 13 di età inferiore ai 6 mesi, con crisi ad esordio parziale sono stati esposti in studi clinici controllati con placebo.
Monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in pazienti a partire da 16 anni di età con epilessia di nuova diagnosi
L'efficacia del levetiracetam in monoterapia è stata dimostrata in uno studio comparativo di non inferiorità in doppio cieco, a gruppi paralleli, verso carbamazepina a rilascio controllato (CR), in 576 pazienti di 16 anni di età o più, con epilessia di nuova o recente diagnosi. I pazienti dovevano presentare solo crisi parziali non provocate oppure crisi tonico-cloniche generalizzate. I pazienti sono stati randomizzati a carbamazepina CR 400-1200 mg/die o levetiracetam 1000-3000 mg/die e il trattamento ha avuto una durata fino a 121 settimane in base alla risposta.
La libertà dalle crisi per un periodo di 6 mesi è stata ottenuta nel 73,0% dei pazienti trattati con levetiracetam e nel 72,8% dei pazienti trattati con carbamazepina CR; la differenza assoluta corretta tra i trattamenti è stata dello 0,2% (IC 95%:-7,8 8,2). Più della metà dei soggetti è rimasta libera da crisi per 12 mesi (56,6% e 58,5% dei soggetti trattati rispettivamente con levetiracetam e carbamazepina CR).
In uno studio che rifletteva la pratica clinica, il trattamento antiepilettico concomitante ha potuto essere sospeso in un numero limitato di pazienti che avevano risposto alla terapia aggiuntiva con levetiracetam (36 pazienti adulti su 69).
Terapia aggiuntiva nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile L'efficacia del levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, della durata di 16 settimane, in pazienti a partire dai 12 anni di età e oltre, affetti da epilessia generalizzata idiopatica con crisi miocloniche in differenti sindromi. La maggioranza dei pazienti presentava epilessia mioclonica giovanile.
In questo studio, la dose di levetiracetam è stata di 3000 mg/die, somministrata in due dosi separate.
Il 58,3% dei pazienti trattati con levetiracetam e il 23,3% dei pazienti trattati con placebo ha avuto almeno una riduzione del 50% dei giorni con crisi miocloniche per settimana.
A seguito del trattamento continuato a lungo termine, il 28,6% dei pazienti è rimasto libero da crisi miocloniche per almeno 6 mesi ed il 21,0% dei pazienti è rimasto libero da crisi miocloniche per almeno 1 anno.
Terapia aggiuntiva nel trattamento delle crisi tonico-cloniche generalizzate primarie in adulti e adolescenti a partire da 12 anni di età con epilessia generalizzata idiopatica L'efficacia del levetiracetam è stata dimostrata in uno studio di 24 settimane in doppio cieco, controllato con placebo, che ha incluso adulti, adolescenti e un numero limitato di bambini affetti da epilessia generalizzata idiopatica con crisi tonico-cloniche generalizzate primarie (PGTC) in differenti sindromi (epilessia mioclonica giovanile, epilessia giovanile da assenza, epilessia infantile da assenza oppure epilessia con crisi da grande male al risveglio). In questo studio, la dose di levetiracetam è stata di 3000 mg/die per adulti e adolescenti oppure di 60 mg/kg/die per i bambini, somministrata in due dosi separate.
Il 72,2% dei pazienti trattati con levetiracetam e il 45,2% dei pazienti trattati con placebo ha avuto una riduzione della frequenza delle crisi PGTC per settimana uguale o superiore al 50%. A seguito del trattamento continuato a lungo termine, il 47,4% dei pazienti è rimasto libero da crisi tonico-cloniche per almeno 6 mesi e il 31,5% è stato libero da crisi tonico-cloniche per almeno 1 anno.

5.2 Proprietà farmacocinetiche

Levetiracetam è un composto estremamente solubile e permeabile. Il profilo farmacocinetico è lineare, con una scarsa variabilità intra- ed inter-individuale. Non c'è modificazione della clearance dopo somministrazioni ripetute. Non c'è evidenza di alcuna rilevante variabilità circadiana e per sesso e razza. Il profilo farmacocinetico è comparabile nei volontari sani e nei pazienti con epilessia.
Dato il suo completo e lineare assorbimento, i livelli plasmatici di levetiracetam possono essere predetti dalla dose orale espressa come mg/kg di peso corporeo. Perciò non c'è bisogno di monitorare i livelli plasmatici di levetiracetam.
È stata evidenziata negli adulti e nei bambini una significativa correlazione tra le concentrazioni nella saliva e nel plasma (il rapporto delle concentrazioni saliva/plasma variava in un intervallo da 1 a 1,7 per la formulazione orale in compresse e, dopo 4 ore dall'assunzione, per la formulazione orale in soluzione).
Adulti e adolescenti
Assorbimento
Levetiracetam è assorbito rapidamente dopo somministrazione orale. La biodisponibilità orale assoluta è prossima al 100%.
Le concentrazioni al picco plasmatico (C_{max}) sono raggiunte 1,3 ore dopo l'assunzione. Lo stato stazionario è raggiunto dopo due giorni di somministrazione di due dosi quotidiane.
Le concentrazioni al picco plasmatico (C_{max}) sono tipicamente di 31 e 43 µg/ml in seguito, rispettivamente, ad una singola dose di 1000 mg e a una dose di 1000 mg ripetuta due volte al giorno.
L'entità di assorbimento non è dose dipendente e non è influenzata dal cibo.
Distribuzione
Non sono disponibili dati sulla distribuzione tissutale nell'uomo.
Né levetiracetam né il suo metabolita primario si legano significativamente alle proteine plasmatiche (<10%). Il volume di distribuzione di levetiracetam va approssimativamente da 0,5 a 0,7 l/kg, ed è un valore prossimo al volume totale corporeo di acqua.
Biotrasformazione
Levetiracetam non è ampiamente metabolizzato nell'uomo. La principale via metabolica (24% della dose) è l'idrolisi enzimatica del gruppo acetamide. La produzione del metabolita primario, ucb L057, non è supportata dalle isoforme del citocromo P450 epatico.
L'idrolisi del gruppo acetamide è stata misurabile in numerosi tessuti, comprese le cellule ematiche. Il metabolita ucb L057 è farmacologicamente inattivo.
Sono stati inoltre identificati due metaboliti minori. Uno è stato ottenuto dall'idrossilazione dell'anello pirrolidonico (1,6% della dose) e l'altro dall'apertura dell'anello pirrolidonico (0,9% della dose). Altri componenti non noti erano responsabili soltanto dello 0,6% della dose.
In vivo non sono state evidenziate interconversioni enantiomeriche né per levetiracetam né per il suo metabolita primario.
In vitro, levetiracetam ed il suo metabolita primario hanno mostrato di non inibire le attività delle principali isoforme del citocromo P450 epatico umano (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 e 1A2), della glucuronil transferasi (UGT1A1 e UGT1A6) e dell'epossido idrossilasi. Inoltre, levetiracetam non influenza la glucuronazione *in vitro* dell'acido valproico.
In colture di epatociti umani, levetiracetam ha avuto un effetto minimo o nullo su CYP1A2, SULT1E1 o UGT1A1. Levetiracetam ha causato una moderata induzione del CYP2B6 e del CYP3A4. I dati *in vitro* ed i dati *in vivo* relativi alla interazione con contraccettivi orali, digossina e warfarin indicano che non è attesa alcu-

na significativa induzione enzimatica *in vivo*. Quindi, l'interazione di ITALEPT con altre sostanze, o *viceversa*, è improbabile.

Eliminazione

L'emivita plasmatica negli adulti è di 7±1 ore e non si modifica in relazione alla dose, alla via di somministrazione o alla somministrazione ripetuta. La clearance totale corporea media è di 0,96 ml/min/kg.

La principale via di escrezione è la via urinaria, responsabile in media dell'eliminazione del 95% della dose somministrata (approssimativamente il 93% della dose è stato escreto entro 48 ore). L'eliminazione fecale rappresenta solo lo 0,3% della dose.

L'escrezione cumulativa urinaria di levetiracetam e del suo metabolita primario è responsabile rispettivamente dell'eliminazione del 66% e del 24% della dose, nell'arco delle prime 48 ore.

La clearance renale di levetiracetam e di ucb L057 è rispettivamente di 0,6 e 4,2 ml/min/kg, indicando che il levetiracetam è escreto mediante filtrazione glomerulare con successivo riassorbimento tubulare e che il metabolita primario è escreto anche mediante secrezione tubulare attiva oltre che con filtrazione glomerulare.

L'eliminazione di levetiracetam è correlata alla clearance della creatinina.

Anziani

Nell'anziano, l'emivita è aumentata di circa il 40% (da 10 a 11 ore). Ciò è dovuto alla riduzione della funzionalità renale in questa popolazione (vedere paragrafo 4.2).

Compromissione renale

La clearance corporea apparente sia di levetiracetam sia del suo metabolita primario è correlata alla clearance della creatinina. Nei pazienti con insufficienza renale di grado moderato e grave si raccomanda pertanto di aggiustare la dose giornaliera di mantenimento di ITALEPT, basandosi sulla clearance della creatinina (vedere paragrafo 4.2).

Nei soggetti adulti affetti da anuria con malattia renale allo stadio terminale, l'emivita è risultata approssimativamente pari a 25 e 3,1 ore, rispettivamente nei periodi tra le dialisi e durante la dialisi.

La frazione del levetiracetam rimossa era del 51% nel corso di una tipica seduta di dialisi di 4 ore.

Compromissione epatica

In soggetti con insufficienza epatica lieve e moderata non è stata rilevata alcuna modificazione significativa della clearance del levetiracetam. Nella maggioranza dei soggetti con compromissione epatica grave, la clearance del levetiracetam è stata ridotta di oltre il 50% a causa della compromissione renale concomitante (vedere paragrafo 4.2).

Popolazione pediatrica

Bambini (dai 4 ai 12 anni)

In seguito ad una singola somministrazione orale (20 mg/kg) in bambini (da 6 a 12 anni) con epilessia, l'emivita di levetiracetam è risultata di 6,0 ore.

La clearance apparente corretta in funzione del peso corporeo è risultata approssimativamente più alta del 30% rispetto agli adulti con epilessia.

In seguito a somministrazione orale per dosi ripetute (da 20 a 60 mg/kg/die) in bambini epilettici (da 4 a 12 anni), il levetiracetam è stato rapidamente assorbito. Il picco di concentrazione plasmatica è stato osservato a 0,5-1,0 ora dalla somministrazione. Sono stati osservati aumenti lineari e proporzionali alla dose per il picco delle concentrazioni plasmatiche e per l'area sotto la curva. L'emivita di eliminazione è risultata pari a circa 5 ore. La clearance corporea apparente è stata di 1,1 ml/min/kg.

Infanti e bambini (da 1 mese a 4 anni)

A seguito di somministrazione di una dose singola (20 mg/kg) di soluzione orale 100 mg/ml in bambini epilettici (da 1 mese a 4 anni), il levetiracetam è stato rapidamente assorbito e le concentrazioni plasmatiche di picco sono state osservate circa 1 ora dopo la somministrazione. I risultati farmacocinetici hanno indicato che l'emivita è più breve (5,3 ore) che negli adulti (7,2 ore) e la clearance apparente è risultata più veloce (1,5 ml/min/kg) rispetto agli adulti (0,96 ml/min/kg).

Nelle analisi farmacocinetiche di popolazione condotte in pazienti da 1 mese a 16 anni di età, il peso corporeo era significativamente correlato alla clearance apparente (la clearance aumentava all'aumentare del peso corporeo) ed al volume di distribuzione apparente. Anche l'età ha influenzato entrambi i parametri. Questo effetto è risultato marcato per i bambini più piccoli e attenuato con l'aumentare dell'età, per poi diventare trascurabile intorno ai 4 anni di età.

In entrambe le analisi farmacocinetiche di popolazione, vi è stato un aumento del 20% circa della clearance apparente del levetiracetam quando somministrato assieme a un farmaco antiepilettico induttore enzimatico.

5.3 Dati preclinici di sicurezza

I dati non-clinici non rivelano rischi particolari per l'uomo sulla base di studi convenzionali di sicurezza farmacologica, genotossicità e potenziale cancerogeno.

Gli effetti indesiderati non osservati negli studi clinici, ma visti nel ratto e in minore entità nel topo, a livelli di esposizione simili ai livelli di esposizione nell'uomo e con possibile rilevanza per l'uso clinico, sono state variazioni epatiche come indice di una risposta adattativa, quali aumento ponderale ed ipertrofia centrolobulare, infiltrazione adiposa ed innalzamento degli enzimi epatici nel plasma.

Nel ratto non si sono osservate reazioni avverse sulla fertilità maschile e femminile o sulla capacità riproduttiva a dosi fino a 1800 mg/kg/die (6 volte la dose massima giornaliera raccomandata nell'uomo -MRHD, *Maximum Recommended Human Daily Dose*- in base ai mg/m^2 o in base all'esposizione), sia nella generazione parentale che nella generazione F1.

Due studi sullo sviluppo embrio-fetale (EFD: *Embryo-Fetal Development*) sono stati condotti nel ratto a 400, 1200 e 3600 mg/kg/die. A 3600 mg/kg/die, in uno solo dei 2 studi EFD si è registrato un lieve calo di peso fetale associato ad un aumento marginale delle alterazioni scheletriche/anomalie minori. Non si è verificato alcun effetto sulla mortalità embrionale, né vi è stato un aumento dell'incidenza di malformazioni. Il NOAEL (*No Observed Adverse Effect Level*) è stato di 3600 mg/kg/die per le femmine di ratto gravide (12 volte la MRHD in base ai mg/m^2) e 1200 mg/kg/die per i feti.

Quattro studi sullo sviluppo embrio-fetale sono stati condotti sul coniglio utilizzando dosi di 200, 600, 800, 1200 e 1800 mg/kg/die. La dose di 1800 mg/kg/die ha indotto una marcata tossicità materna e una diminuzione del peso fetale, in associazione con una maggiore incidenza di feti con anomalie cardiovascolari/scheletriche. Il NOAEL è stato <200 mg/kg/die per le madri e di 200 mg/kg/die per i feti (equivalente alla MRHD in base ai mg/m^2).

Uno studio sullo sviluppo peri- e post-natale è stato condotto sul ratto con dosi di levetiracetam di 70, 350 e 1800 mg/kg/die. Il NOAEL è stato ≥1800 mg/kg/die per le femmine F0 e per la generazione F1 per quanto riguarda la sopravvivenza, l'accrescimento e lo sviluppo fino allo svezzamento (6 volte la MRHD in base ai mg/m^2).

Studi nel ratto e nel cane, nell'animale neonato e giovane, hanno dimostrato che non si manifestano effetti indesiderati in alcuno degli endpoint standard di sviluppo o di maturazione a dosi fino a 1800 mg/kg/die (6-17 volte la MRHD in base ai mg/m^2).

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

Sodio citrato diidrato
Acido citrico monoidrato
Metil paraidrossibenzoato (E218)
Propil paraidrossibenzoato (E216)
Ammonio glicirrizinato
Glicerolo (E422)
Maltitolo liquido (E965)
Acesulfame potassio (E950)
Aroma di pompelmo
Acqua purificata

6.2 Incompatibilità

Non pertinente.

6.3 Periodo di validità

3 anni.

Dopo la prima apertura: 7 mesi.

6.4 Precauzioni particolari per la conservazione

Conservare nella confezione originale per proteggere il medicinale dalla luce.
Conservare il flacone in posizione verticale.

6.5 Natura e contenuto del contenitore

300 ml di soluzione in un flacone di vetro ambrato (tipo III) con chiusura a prova di bambino (polipropilene), in una scatola di cartone contenente anche una siringa da 10 ml per uso orale, con tacca graduata ogni 0,25 ml (polipropilene, polietilene), e un adattatore per la siringa (polietilene).

6.6 Precauzioni particolari per lo smaltimento e la manipolazione

Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità
alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

So.Se.PHARM S.r.l. - Via dei Castelli Romani, 22-00071 Pomezia (Roma) Italia. Concessionario per la vendita: Istituto Luso Farmaco D'Italia SpA – Milanofiori - Strada 6 - Edificio L - Rozzano (MI).

8. NUMERO(I) DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

AIC 040273031 - "100 mg/ml soluzione orale" 1 flacone da 300 ml + 1 siringa orale da 10 ml.

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Prima Autorizzazione: 19 Luglio 2012.
Rinnovo: 19 Luglio 2016.

10 DATA DI REVISIONE DEL TESTO

14 Settembre 2016.

ITALEPT 100 mg/ml soluzione orale
Prezzo SSN € 37,97* Classe A - Ricetta ripetibile.

**Prezzo comprensivo delle riduzioni temporanee di cui alle determinazioni AIFA, 3 luglio 2006 e 27 settembre 2006.*

Depositato in AIFA in data 02/11/2020 - Cod. ITAL 20-08