POLITECNICO DI TORINO

MASTER THESIS IN BIOMEDICAL ENGINEERING

BIOMEDICAL INSTRUMENTATION

The Readiness Potential: a systematic review about the influencing factors and the development of an algorithm for automatic features extraction

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Abstract

The goals that this thesis work wants to achieve are twofold. One objective is to provide a schematic review about the Readiness Potential, the components it is made of (early BP, late BP and LRP) and the factors modulating its waveform. The other one is to write a program that performs onsets and amplitudes measurements using methods found in literature and to compare these results to evaluate the robustness of the different algorithms. These include peak and mean amplitude measurements using different parameters, as well as many onsets measurements, divided in criterion-based, baseline-based and regression-based methods.

To understand the robustness of these techniques we divided our dataset in three categories: high-quality, medium-quality and low-quality data. For high-quality data, as expected, no problem arises and the measurements are correctly performed, while for lower quality data many measurements are impossible or produce implausible results.

As for amplitudes methods, the least reliable one is that based on the work from Wright et al. [66], while the other two produce reliable results in medium and high-quality conditions. As for onset measurements, the least reliable turned out to be the criterion-based method, while the most reliable are the regression-based methods.

The cleanliness of data on which the proposed algorithms are performed is crucial for the measurements quality. The most problematic issues are the biases and the superimposed brain activities that we are not interested in, especially during the baseline period.

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List of acronyms

- CNS: Central nervous system
- CT: computed tomography
- EEG: electroencephalography
- EMG: electromyography
- EOG: electrooculography
- ERP: event-related potential
- ICA: independent component analysis
- LRP: lateralized readiness potential
- MP: motor potential
- MRCP: motor-related cortical potential
- MRI: magnetic resonance imaging
- NS′: negative slope
- PET: positron emission tomography
- PMP: pre-motion positivity
- PSP: Post-synaptic potential
- r-LRP: response-locked lateralized readiness potential
- RP: readiness potential
- SCCN: Swartz Centre for Computational Neuroscience
- s-LRP: stimulus-locked lateralized readiness potential
- SNR: signal-to-noise ratio
- SR: segmented regression

Chapter 1

Introduction

1.1 The EEG

The electroencephalography (EEG) is a non-invasive technique to measure the electrical brain activity on the scalp surface using electrodes placed on the head. The first human EEG recording is from Hans Berger in 1924, and until today this technique has seen many different clinical applications like sleep, epilepsy and anesthesia monitoring or coma diagnosis.

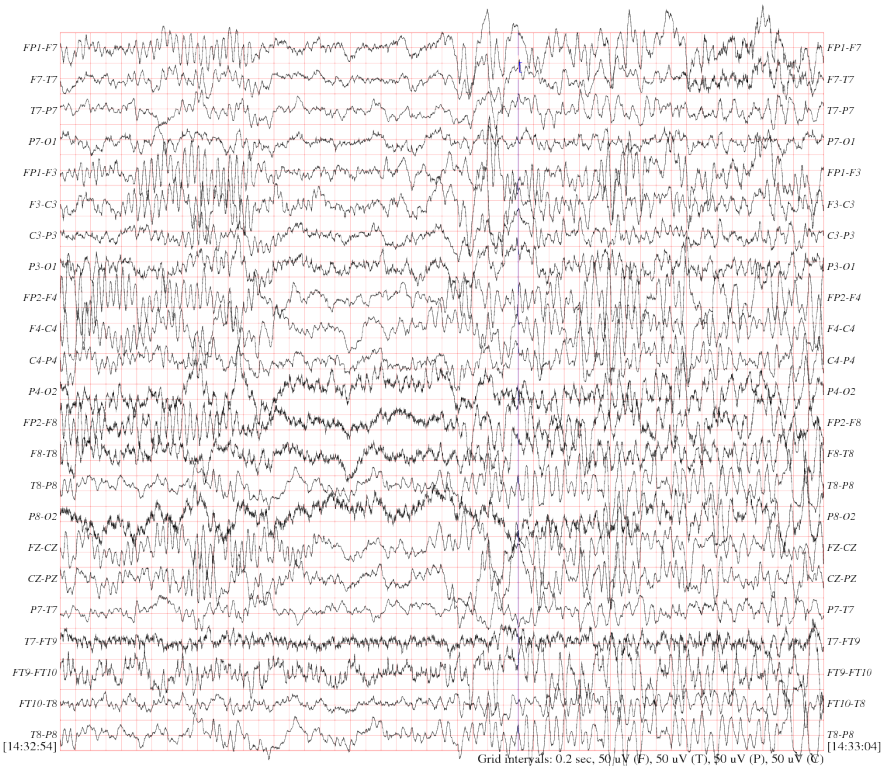


Figure 1.1: Typical EEG recording [49]

The advantages of EEG with respect to other brain-imaging techniques like computed tomography (CT), positron emission tomography (PET) or magnetic resonance imaging (MRI) are:

- Millisecond range temporal resolution
- Mobility of the EEG equipment
- Very low invasiveness
- Low hardware costs

Despite these interesting properties, the low spatial resolution of EEG makes other techniques more reliable in tasks like the detection of strokes, tumors and other focal brain disorders. In EEG the recorded activity is mostly the superficial cortex activity, and complex analysis is needed to investigate deeper parts of the brain, which exhibit a very low signal-to-noise ratio (SNR) because of the superposition of low-amplitude deep-area signals with high-amplitude surface signals.

The number of active employed electrodes is very variable and dependent on the study. Usually the electrodes are between 16 and 32, with higher numbers for specific localization tasks, located following the international 10-20 system (which will be covered later in the chapter) but for certain applications 5 or 6 electrodes are enough. Having a very high number of electrodes is not usually recommended because of the increased difficulty of ensuring high data quality [39]. Typical numbers for EEG recordings are:

- Signal amplitude under 100 μV
- Gain between 10^3 and 10^5
- Sampling frequency between 200 Hz and 1 kHz

1.2 The international 10-20 system

The international 10-20 system is the most common system to describe the location of each electrode through labels [29]. Each electrode has a name given by one or two letters to locate the brain area and a number to indicate the distance from the midline sagittal plane of the skull. The letters are:

- Pre-frontal (Fp)
- Frontal (F)
- Temporal (T)
- Parietal (P)
- Occipital (O)
- Central (C)

Even numbers (2,4,6,8) refer to the right side of the brain and odd numbers (1,3,5,7) refer to the left side. Electrodes in the midline are referred to with the letter "z" (Fpz, Fz, Tz, Pz, Oz, Cz).

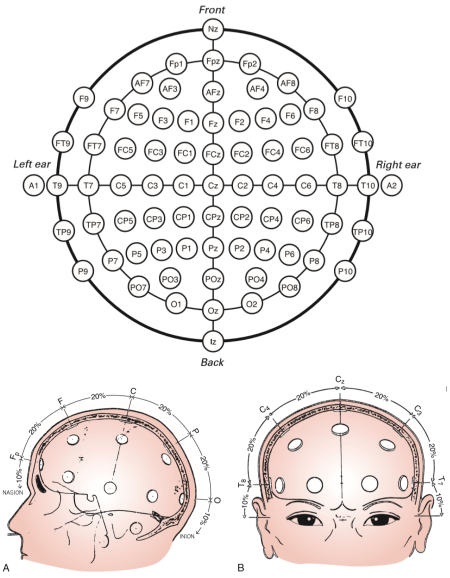


Figure 1.2: 10-20 system labels [39]

The name "10-20" of the system refers to the fact that the distances between electrodes are always 10% or 20% of the nasion-to-inion line or the ear-to-ear distance (called equator). During the cap montage it is important to check that the Cz electrode is exactly in the center: equally distant from nasion and inion on the midline.

Other systems can be preferred in non-standard situations, especially for very large electrode numbers [39].

1.3 EEG analysis

1.3.1 Frequency-domain analysis

The most common analysis applied to EEG data is frequency-domain analysis, also known as spectral analysis, using the Fourier transform. Using this technique, it is possible to obtain the frequency power distribution (spectrum) of a piece of signal. The EEG signal band extends from 1 to 50 Hz, and most of the information is under 30 Hz. In many tasks it is interesting to monitor the power distribution in the different frequency bands of the signal that are identified based on the different condition in which they are observed:

Activity	Frequency range	Description
γ (gamma)	>30 Hz	Typical of high alert state
β (beta)	13-30 Hz	Dominant rhythm for subjects in concentrated or anxious conditions
α (alpha)	8-13 Hz	Appears with eyes closed, it's the dominant rhythm for adults in a relaxed state
θ (theta)	4-8 Hz	Typical for sleep state in adults and in awake children up to 13 years
δ (delta)	<4 Hz	Highest in amplitude, occurs during deep sleep state and it's the dominant rhythm in infants up to one year

Table 1.1: EEG frequency bands [39]

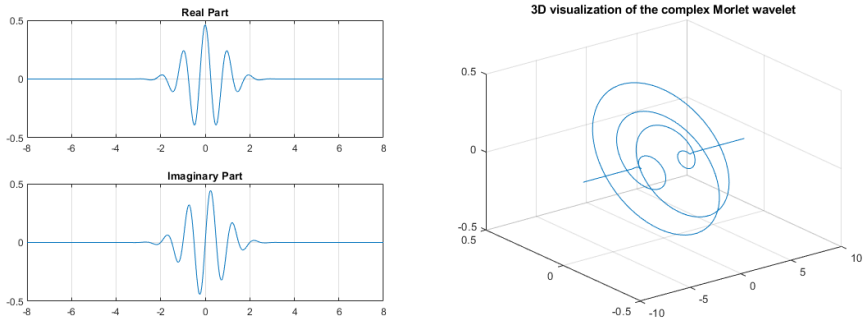
When analyzing the spectrum it is important to remember that power at a given frequency does not mean that the voltage on the brain surface was oscillating with that frequency [39] but that an oscillating waveform with that frequency and amplitude is needed to reconstruct the signal using sine waves. A common error is to interpret the mathematical equivalence between a signal and its Fourier transform with a physiological equivalence: while a "brain oscillation" at a certain frequency will always appear in the signal spectrum, a frequency in the spectrum does not always correspond to a physiological oscillation.

1.3.2 Time-frequency domain analysis

Another useful tool for EEG analysis is time-frequency analysis. This enables the study of how power is distributed in the different frequency bands in time and resolves the two problems of Fourier transform applied to EEG signal: the non-stationarity of the signal and the lack of temporal localization of the frequency information. Two frequently used techniques for time-frequency analysis are:

- Complex Morlet wavelet convolution
- Hilbert transform

Complex Morlet Wavelets are obtained by multiplying a complex sine wave to a gaussian curve. Wavelets are sine waves coupled with a certain window, usually gaussian, obtaining the Morlet wavelet, but a variety of wavelets are possible to use with different properties of frequency and temporal resolution of the obtained power and phase information.



(a) Real and imaginary part

(b) 3d representation

Figure 1.3: The complex Morlet wavelet

With the Hilbert transform we want to extract the analytic signal. With respect to convolution with the Morlet wavelet, the Hilbert transform allows more control over the filter. In fact, while the Morlet wavelet always follows the gaussian curve, in this case it is possible to use any curve. The steps for the implementation of the Hilbert transform are the following:

1. Compute the Fourier transform on the signal and save the coefficients multiplied with the complex operator
2. Rotate positive frequencies coefficients one-quarter cycle counterclockwise (done by simply multiplying the coefficients to $-i$) and negative frequencies coefficients one-quarter cycle clockwise (done by multiplying the coefficients to i). This will double the positive-frequency coefficients and nullify the negative-frequency coefficients
3. Take the inverse Fourier transform of the obtained coefficients, obtaining the analytic signal

The advantage of working with the analytic signal is that redundant information of negative-frequency component is canceled.

1.3.3 Time-domain analysis

The analysis of how the signal amplitude changes in time is called time-domain analysis. The main features of the time-domain are amplitude, polarity and latency. Further actors are the mean, the variance and other time-varying factors. This kind of analysis for EEG is impossible without the application of techniques like averaging or filtering, given the signal properties. Some of the main techniques used in this thesis are:

- **Epoching**: the division of the whole signal in specific segments of interest called epochs, that have equal duration and are usually time-locked to a specific event
- **Averaging**: the computation of the mean of the different epochs to enhance the SNR, increasing the amplitude of the time-locked component of the signal and reducing all the non-time-locked components.

1.3.4 Event-related potentials analysis

An event-related potential (ERP) is a scalp recorded neural signal generated in a specific neuroanatomical module when a specific computational operation is performed [39]. Another way to describe the concept of ERP component is: a source of controlled, observable variability [13], and the repeatability of the ERP component waveform is what makes the ERP analysis through averaging possible. In fact, while the ERP is time-locked to the event, the rest of the signal is not, and averaging the epochs increases the SNR, making possible to study the morphology of the obtained waveform. However, because of the averaging, the obtained waveform differs from the single-trial waveforms registered in every single epoch in that it exhibits of smaller amplitude and a more spread shape [39] and needs to be interpreted carefully.

Peaks are important to determine the latencies of the various components, but since the waveform is the result of many sources that superimpose on each other (the "superposition problem") a better estimate of a component amplitude is the mean amplitude, rather than the peak amplitude [39].

1.4 Objectives of the study

What this study wants to achieve is a systematic review about the factors influencing the Readiness Potential, an ERP component linked to voluntary movements known since 1964 [35], to better understand its role in voluntary and involuntary motor tasks. At the same time, the study wants to create an algorithm to automatically extract a number of features from the ERP waveform using methods found in literature, in order to determine a space of features where recordings with different experimental conditions can be distinguished.

Chapter 2

The central nervous system

2.1 What is it

The Central Nervous System (CNS) is composed by two main structures: the brain and the spinal cord. The whole system is contained in the dorsal body cavity, that can be divided in the cranial cavity, containing and protecting the brain, and the spinal canal, which does the same for the spinal cord.

The brain plays a central role in most functions, such as awareness, movements, perception, speech and memory. The spinal cord carries the messages of the brain to peripheral nerves, and while movements control is brain competence, some reflex movement is controlled directly by the spinal cord to allow faster response. In our study we will focus on the brain.

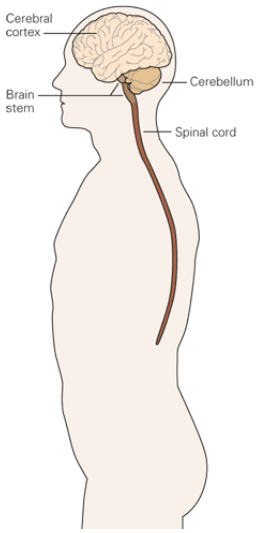


Figure 2.1: The central nervous system [30]

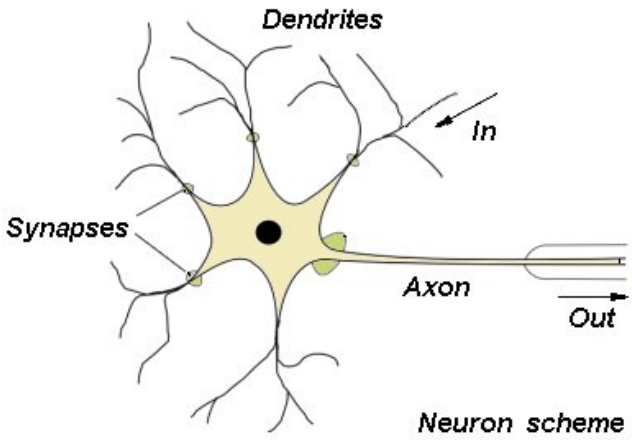


Figure 2.2: The scheme of neuron (cell) and its components (AGH University of Science and Technology webpage 2014)

2.2 Components

CNS is composed by neurons and glial cells. Neurons are the excitable part, able to communicate through electric and chemical signals with other cells. Neurons are cells specialized in processing and transmission of signals, with:

- *Body* (the soma) containing the nucleus; they can have very different dimensions, between 4 and 100 μm in diameter
- *Dendrites* forming the dendritic tree, extrusions of the cell and extend typically a few hundred micrometers from the soma
- An *axon*, a long channel starting from the soma that can reach lengths of thousand times the diameter of the body, and despite each neuron having only one axon, it can branch to reach multiple cells. Moreover, the part of the soma when the axon starts is the most excitable part, having the grater density of sodium channels. The terminal part of the axon contains synapses, structures necessary for chemical communication.

The estimated number of neurons in human brain is around 86 billion [24]. The other component of the CNS, the glial cells, includes different type of cells, like microglia, astrocytes, oligodendrocytes and ependymal cells. While the neurons function is to communicate, the glial cells have a support role. Their very name suggests this support function, deriving from the Greek $\gamma\lambda\iota\alpha$ and $\gamma\lambda o\iota\alpha$ ("glue"), since the first impression is that glial cells tie the whole system together. They protect and hold the neurons, they have an insulating function and supply the system with nutrients and oxygen. Glial cells are also important in supporting communication between neurons, speeding up the signal conduction in nerve fibers, and form the blood-brain barrier.

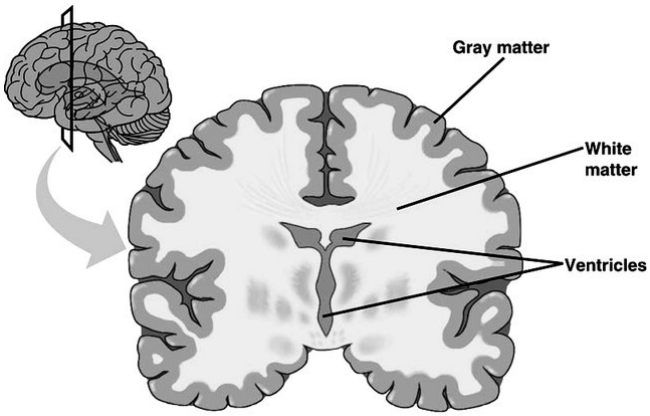


Figure 2.3: White and gray matter distribution inside the brain [10]

2.3 White matter and grey matter

Two different tissues are distinguished : white matter (about 60% of the total) and grey matter (the remaining 40%). The difference is in the content of myelinated axons: in grey matter they are relatively few respect to the cell bodies, while white matter contains a lot more myelinated axons. Since the lipids of myelin are of a white clear color, the difference is noticeable by just looking at the two different tissues: grey matter is darker and pinkish while white matter is clearer.

Grey matter is what the external layer of the brain (cerebral cortex) and of the cerebellum (cerebellar cortex) are made of, while the white matter forms the deeper parts of the brain. Aggregates of grey matter can be found inside white matter clusters. In the spinal cord the inverse happens: white matter is on the surface while grey matter forms the deeper structures.

2.4 The brain

The brain (or encephalon) consists of three parts: cerebrum, brainstem and cerebellum. The cerebrum is the largest part, and the center of the cerebral functions. This is divided in two hemispheres, linked by the callosal commissure, and we can identify for each hemisphere four main regions, called lobes, based on their overlying neurocranial bones:

- **Frontal lobe**:

  located near the front of the head, it is the last region of the brain to evolve. The main functions of the frontal lobe are speech and language production (Broca's area), memory formation, empathy, personality, attention, part of the motor skills (primary motor cortex) and objects comparison.

- **Occipital lobe**:

  located in the posterior part of the head, it is the center of visualization processing including motion perception.

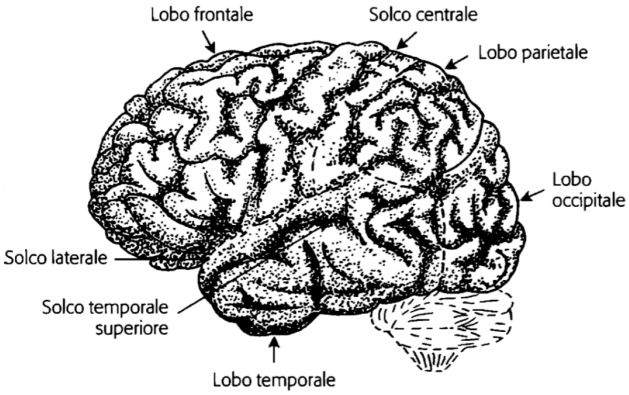


Figure 2.4: The brain [51]

- **Temporal lobe**:

  located in the "sides", the main functions of the temporal lobe are emotion association, long-term memory, visual memory and language comprehension (Wernicke's area).

- **Parietal lobe**:

  located above the temporal lobe and divided from parietal lobe by the central sulcus, its main functions are sensory elaboration (somatosensory cortex), spatial sense and manipulation of objects. Areas of the parietal lobe are involved in language processing.

2.5 Brainstem and cerebellum

Brainstem is the connection between the brain and the spinal cord. Its role is important for both motor and sensory system, since all the connections between the brain and the body pass through it. Brainstem is also vital for some fundamental functions as respiration, sleep-wake cycle, eating and the maintaining of consciousness.

Cerebellum is mostly important for motor control and coordination. It receives inputs from both the brain and the spinal cord, and uses them to coordinate the movements, maintain equilibrium and posture. Cerebellum is also involved in many motor learning processes.

2.6 Physiological bases of Electroencephalography

There are two ways in which neurons perturbate the electric and, consequently, magnetic field:

- Action potentials
- Post-synaptic potentials (PSP)

Action potentials occur when a depolarization happens on the membrane of an axon, and causes the depolarization of adjacent locations, spreading the impulse along the length of the axon. Action potentials are involved mostly in cell-to-cell communication. The resting-potential of neurons is about -70 mV, and the depolarization starts when the voltage near the voltage-gated ion channels in the cell membrane crosses a certain threshold, that is about -55 mV, opening the channel and allowing a flow of sodium ions which affects the electrical gradient in an explosive reaction.

When the polarity of the membrane reverses, the channels close and the ions are actively pumped outside, returning the gradient at the resting level. Axon hillocks, being particularly rich of ion channels, are very likely to start action potentials. The presence of myelin sheaths along the axon speeds up the depolarization transmission.

Post-synaptic potentials are generated in the postsynaptic terminal of a chemical synapse. The generation happens when the presynaptic cell releases the neurotransmitter in the synaptic cleft of the postsynaptic cell. The neurotransmitter causes the opening of ion channels and the consequent ion flow inside the membrane. Positive electric flow entering the cell causes depolarization when a certain threshold is crossed, with an excitatory effect that "fires" an electrical impulse. Negative electric flow, instead, causes hyperpolarization: the voltage inside the cell becomes more negative, with an inhibitory effect. A single cell can have many synaptic clefts, inhibitory or excitatory, with the property of summation both spatially (many synapses send signals at the same time) and temporally (the same synapse sends many signals in a short time).

What EEG records is mostly the PSPs of cortical neurons directed perpendicularly to the scalp, but a single neuron's electrical activity is too small to be detected. What we record, indeed, is the synchronous activity of thousands of neurons orientated in a similar way. Since pyramidal neurons of the cortex are particularly similar in orientation, near to the scalp and synchronous, they are thought to produce the majority of EEG signal.

Action potentials, in the vast majority of cases, are not detectable on the scalp surface. This is because of the physical arrangement of axons and the timing of the action potentials: if two action potentials are "fired" in opposite directions along two parallel axons the signals will cancel and if the action potentials are sent exactly in the same moment and in the same direction the signals will sum. Since neurons send their action potentials at slightly different times the recording of action potentials at the surface is usually impossible, although there are some exceptions like for the brainstem auditory evoked response, which reflects the simultaneous action potentials passing through the auditory nerve.

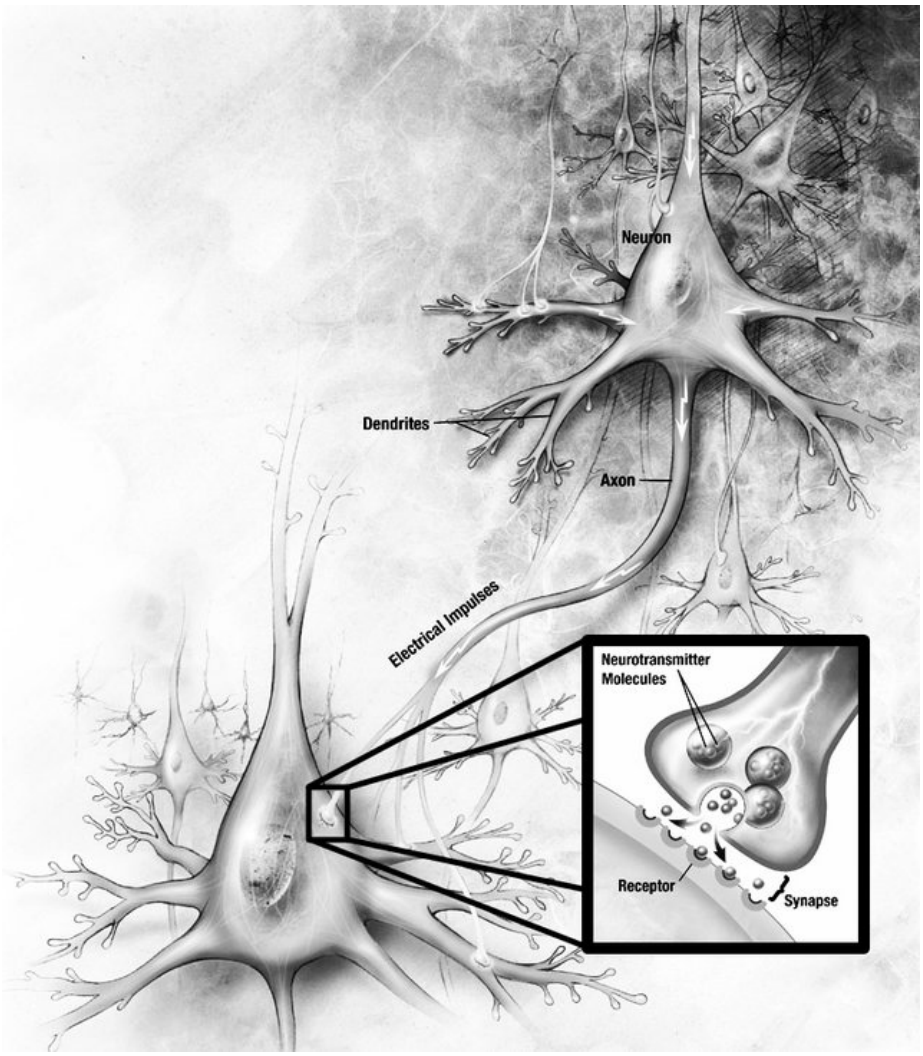


Figure 2.5: Schematic drawing of neurons and, in particular, of the neurotransmission mechanism [10]

2.7 Neurophysiological mechanisms of Event-related potentials

ERPs are small time-locked voltages that arise corresponding to sensory, cognitive, or motor events. It is not possible to observe an ERP waveform in single trials because of how small the potential is respect to all the remaining EEG, and it is necessary to increase the SNR through averaging.

While for EEG is not possible to study the signal morphology, what we are interested to in ERP studies is the waveform and its parameters, and the factors influencing the amplitudes and latencies.

The ERPs reflect the coordinate PSPs activity of many thousands of neurons in response to internal or external stimuli; they are directly related to neurotransmission and can be used as biomarkers because of their sensitivity for individual differences [42].

Chapter 3

The Readiness Potential

3.1 What is the Readiness Potential

The Readiness Potential (RP or, as the discoverers first called it, the Bereitshaftspotential) is a slow negative cortical potential known since 1964, discovered by Hans Helmut Kornhuber and Lüder Deecke [35]. This potential is elicited by an actual, intended or imagined movement, and this makes it a movement-related potential [26]. Its role, however, is not totally clear. Originally the RP was thought to be a measure of motor preparation, but many experimental studies showed that its waveform is modulated by factors that imply other processes. It is possible that its presence does not indicate "voluntariness" of movement, but a set of brain processes related to the genesis of movement, including movements interpreted as voluntary [23]. It is also demonstrated that the RP is involved in mechanisms of working memory and has a role in the selection of attentional resources [2].

The potential starts about 2 s before movement onset, is maximal at the midline centro-parietal area, symmetrical and widely distributed over the scalp no matter the site of the movement [53]. A typical maximum height for averaged waveforms is usually about -5μV [8].

The Readiness Potential is the result of two different components: an early and a late component, called Early BP (also called simply Bereitshaftspotential or BP1) and Late BP (also called Negative Slope or BP2). These have clearly different functions since their amplitude, slopes and onsets are modulated by factors that often leave the other unchanged, are generated in different brain locations and thus reflect different processes.

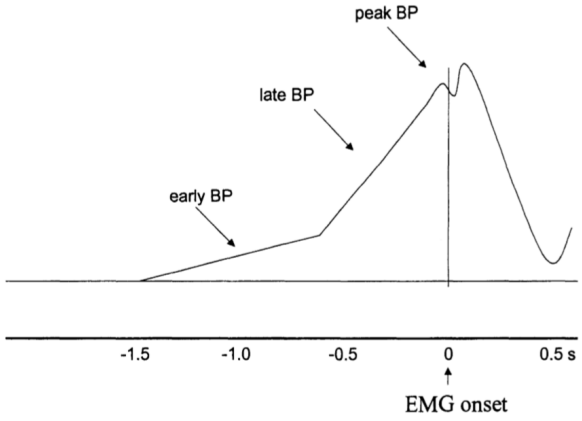


Figure 3.1: Schematic representation of the early and late component of the RP [26]

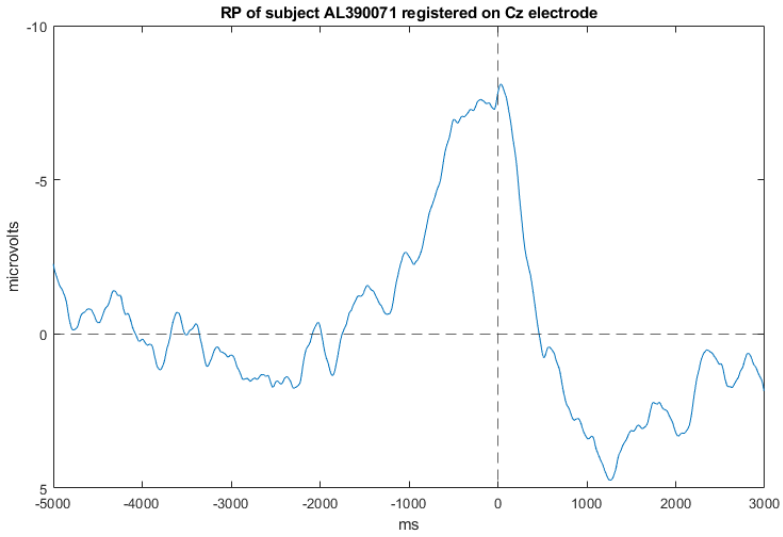


Figure 3.2: Readiness Potential recorded at electrode Cz

The Readiness Potential is part of the broader Motor-Related Cortical Potential (MRCP) [53], elicited by free movements, that includes the following components:

- Early BP
- Late BP
- Pre-motion positivity (PMP or P-50)
- Motor Potential (MP or N-10)
- N+50
- P+90
- N+160
- P+300

Apart from the first two, it's possible to refer to the other elements of the MRCP using a common ERP name convention [39]: the name begins with the letter P or N to indicate the polarity of the wave (Positive or Negative), then a number with the sign + or – indicates the time in milliseconds where the component peak is located, with the event that time-locks the readiness potential at time 0. The Readiness potential can be very different among subjects in both amplitudes and onsets but shows good repeatability within subjects [8]. Not all components are always visible in all subjects and in some cases, probably due to anatomical differences, the potential appears even absent [6].

3.1.1 Factors influencing RP amplitude

In this section we are going to discuss the general factors that influence the RP amplitude in literature. In the following sections the focus will be on the single early and late components, but many changes of the waveform must be attributed to the whole potential and do not belong to single components.

Generally, the RP is found to be higher in subjects with higher levels of intention [35]: when the person performing the movement gets bored, the amplitude decreases. The force is also an important factor: movements that require more force will elicit a larger RP [6] [36] and also movements that require more effort for anatomical reasons (e.g. middle-finger respect to index movements) elicit a RP with larger amplitude [34]. Comparing a single movement with a sequence that starts with the movement previously referred to, the sequential task will elicit a larger RP [55]. When two or more movements are performed simultaneously the observed potential exhibits higher amplitude respect to the potential recorded in the same single movements alone [3] and more "complex" movements (e.g. movement of index immediately followed by middle finger respect to the two fingers simultaneously) also will elicit a larger RP over the midline vertex and over the bilateral central regions [33].

Regarding pathologic conditions, the potential is found to be generally smaller in schizophrenia patients with respect to controls by a number of studies [5] [56]. Patients affected by cerebellar lesions also show a smaller RP amplitude, and in some cases it can be totally absent [34] [54] [17]. Lastly, for tics (involuntary movements) in Tourette syndrome patients the RP is absent, while it is found before a voluntary action mimicking the tics [46].

RP (whole) amplitude

Factor	Influence
Higher level of intention	Larger
More force required	Larger
More effort required	Larger
Sequential task respect to single movement	Larger
Simultaneous movements respect to single movements	Larger
More "complex" movements	Larger over the midline vertex and bilateral central regions
Schizophrenia patients	Smaller
Cerebellar lesions patients	Smaller or absent
Tics in Tourette syndrome	Absent

Table 3.1: Factors influencing RP amplitude

3.2 Early BP

The first component of the RP is the early BP, or BP1, or simply Bereitshaftspotential. This is an initial slow rising phase that lasts from about 1500 ms to about 400 ms before movement, but because of the high variability of the subject these values can be very different in different conditions. The early BP is topographically characterized by a vertex maximum and the main areas contributing to the early BP are the premotor cortex and the supplementary motor area (SMA), both bilaterally [23]. This component is influenced by cognitive functions such as level of intention, preparatory state and movement selection in both amplitude and onset. One hypothesis is that the early BP reflects in part nonspecific preparation processes for the following movement [6].

3.2.1 Factors influencing early BP amplitude

The amplitude of the early RP is modulated by a number of factors. One of these regards the choice of the direction of the movement to make: when the subject gets to choose the direction of the movement, and is therefore given the freedom to influence a parameter of the experiment, the elicited early RP has a recorded larger amplitude respect to situations where the same movement has to be repeated over and over in the same direction [61]. Another situation where the early BP amplitude is higher is during learning [65]: when given a task (e.g. playing the G major scale on the guitar) the amplitude increases during the training period, but when the subject becomes skilled with the movement the early BP becomes smaller.

As already mentioned, voluntary muscle relaxation produces a RP, but the difference between the potential elicited by a contraction and the one elicited by a relaxation is in the early BP amplitude, that is smaller when the subject voluntarily relaxes muscles at a certain time [60]. Many pathological conditions also alter the early BP amplitude. Parkinson's disease is a pathology known for altering the early BP amplitude [11]. This abnormality consists in a generally smaller amplitude in patients. The levodopa treatment, the most common for Parkinson's disease, increases the early BP amplitude in both patients and controls [6] while the opposite effect is given by dopamine antagonists: both patients and controls elicit a smaller early BP when given these kind of drugs [6]. Studies reveal that also patients suffering sensory motor area (SMA) lesions show a smaller amplitude, especially for electrodes Cz and Fcz, in contralesional respect to ipsilesional movements [17]. Finally, schizophrenia affects the amplitude of early BP: reduced amplitude is observed in patients that never underwent medication respect to the rest of the patients [64].

Early BP amplitude

Factor	Influence
Direction of the movement freely chosen	Larger
During learning	Larger
After becoming skilled in the task	Smaller
Muscle relaxation respect to contraction	Smaller
Parkinson's disease patients	Smaller
Levodopa administration (for both patients and controls)	Larger
Dopamine antagonists administration (for both patients and controls)	Smaller
SMA lesions patients	Smaller especially in Cz and Fcz in contralesional respect to ipsilesional movements
Schizophrenia Patients that never underwent medication respect to other schizophrenia patients	Smaller

Table 3.2: Factors influencing early BP amplitude

3.2.2 Factors influencing early BP onset

Benjamin Libet in a famous study demonstrated that the onset of the first component of the RP, that is the onset of the RP itself, happens earlier when subject preparation for the movement to perform is enhanced, while the "urge to move" is correlated with a later onset [38]. Movements repeated at a self-paced rate with intervals of 5 seconds or longer elicit an early BP with earlier onset with respect to movements to be repeated at fixed intervals [53]. In sequential motor tasks starting with a simple movement the onset happens earlier respect to the potential elicited by the single movement alone [33], while for faster movements the onset is delayed [53].

Regarding pathological conditions, many authors report a delayed onset for patients affected by schizophrenia [20] [14].

Early BP onset

Factor	Influence
Enhanced preparation for the movement	Earlier
Self-paced movements (intervals of minimum 5 s) respect to fixed intervals	Earlier
Sequential motor tasks respect to simple movements	Earlier
Faster movements	Later
Schizophrenia patients	Later

Table 3.3: Factors influencing early BP onset

3.3 Late BP

The second component of the RP is the late BP, or BP2, or Negative slope (NS'). This is distinguished from the other component from the abrupt increase in the gradient of the signal recorded by the central electrode corresponding to the movement, happening around 400 ms before movement onset [53]. The negativity begins to shift to the central region contralateral to the hand that is moving, and while the early BP was generated in the premotor cortex and in the SMA, in the late BP the contribution of the primary motor cortex (M1) becomes prominent [23].

The late BP is maximal over the contralateral central area for hand movements (corresponding to electrodes C1 and C2 following the 10-20 standard) but for foot movements the maximum is found in the midline (Cz electrode). This difference is probably due to the different cortical locations of the portion controlling the hand and the portion controlling the foot in the primary motor cortex and is evidence of the involvement of M1 in the generation of this component. The late BP is influenced by features of the movement itself such as precision, discreteness and complexity.

3.3.1 Factors influencing late BP amplitude

The precision of the movement to perform affects the amplitude of this component of the RP. Actions that require a higher degree of precision in terms of force production will be preceded by a higher late BP [40]. Another factor influencing the amplitude is the perceived effort: there is a positive correlation between the amplitude of the potential in the last 100 ms and the effort that the subject perceives during the trial [57]. Movements whose direction is freely selected by the subject produce a larger late BP than movements in a fixed direction [50] [12], movements that are self-initiated are preceded by a larger late BP than externally triggered ones [27] and self-paced movements of proximal parts of the upper extremity of the body produce a higher late BP than distal parts [28]. As stated in the previous section the discreteness of the movement influences the late BP waveform. In fact, more discrete unilateral movements produce larger amplitudes over the central contralateral region (e.g. larger amplitude in middle finger alone respect to two fingers simultaneously) [34]).

Some pathological conditions affect the late BP: patients with tardive dyskinesia will elicit a larger late BP than controls [1], while patients affected by dystonia will elicit a smaller late BP [9]. Treatments of some diseases also affect the amplitude of this component, particularly a higher amplitude is found during motor recovery in patients with hemiparesis stroke [25] and in Parkinson's disease patients after pallidotomy [18].

Late BP amplitude	
Factor	Influence
More precise movements	Larger
Higher perceived effort	Larger amplitude in the last 100 ms
Free selection of the direction	Larger
Self-initiated movements respect to externally triggered ones	Larger
Proximal parts of the upper extremity respect to distal parts	Larger
More discrete unilateral movements	Larger over the central contralateral region
Tardive dyskinesia patients	Larger
Dystonia patients	Smaller
During motor recovery in patients with hemiparesis stroke	Larger
Parkinson's disease patients after pallidotomy	Larger

Table 3.4: Factors influencing late BP amplitude

3.3.2 Factors influencing late BP onset

The onset of the late component of the RP is found to be delayed for central electrodes (Cz and C3 in the 10-20 standard) in catatonic patients respect to healthy controls. This probably reflects the difficulties that these people find in the execution and the termination of movements. The use of Lorazepam on catatonic subjects is correlated with a significantly later onset of the late BP in left fronto-parietal electrodes (corresponding to C3, P3 and F3 in the 10-20 standard) respect to controls [45].

Late BP onset	
Factor	Influence
Catatonic patients	Later for central electrodes
Lorazepam on catatonic subjects	Later in left fronto-parietal electrodes

Table 3.5: Factors influencing late BP onset

3.4 Lateralized readiness potential

In 1988 two groups introduced in literature the Lateralized Readiness Potential (LRP), one in Groningen [7] and one in Illinois [19]. As already discussed, while the first part of the RP is equally distributed on right and left hemisphere, and early BP is therefore measured at the midline, the later part of the potential becomes lateralized, with larger amplitudes found in electrodes contralateral to the movement. A simple method for obtaining the LRP is subtracting the ipsilateral electrode signal from the contralateral one. In case of right-hand movements, the LRP is obtained subtracting the ERP elicited in electrode C3 (contralateral) to the one elicited in electrode C4 (ipsilateral):

Instead of C3 and C4 it is possible to put the electrodes in the C3' and C4' sites, located 1 cm anterior of C3 and C4, obtaining a more precise electrode position for the LRP recording [43]. Another method for calculating the LRP is the double subtraction method. The method is called double subtraction because two subtractions are performed in sequence.

The first subtraction is, for both hands movements:

$$Subtraction1 : C3 - C4$$

Then we have a second subtraction where the right-hand result of subtraction 1 is subtracted from the left-hand result of subtraction 1:

$$Subtraction2 : (C3 - C4)(L) - (C3 - C4)(R)$$

The last step is averaging:

$$Averaging : \frac{(C3 - C4)(L) - (C3 - C4)(R)}{2}$$

The LRP should be interpreted as a measure of the difference between the contralateral RP with respect to the ipsilateral: negative LRP values mean that for those time-points the contralateral side has a more negative values, and since the RP is a negative potential more negative values are larger signals. One of the studies that first assess the existence of the LRP also demonstrates the relation between the LRP and the onset of a peripheral motor response: EMG activity begins when the signal reaches a fixed threshold value, regardless of response accuracy or latency [19].

The LRP reaches the maximum amplitudes for hand movements, and due to the shape of the primary motor cortex for foot movements the polarity of the signal is reversed: the side where the highest voltage value is reached is the ipsilateral one to the movement instead of the contralateral.

There are two ways in which we can obtain the LRP:

1. Averaging using the stimulus as the time-locking phenomenon (*s-LRP*)
2. Averaging using the response as the time-locking phenomenon (*r-LRP*)

The interval between the stimulus and the s-LRP onset is influenced by alterations in processes preceding response selection, while pure motor execution is reflected in the interval between r-LRP onset and the reaction time [62].

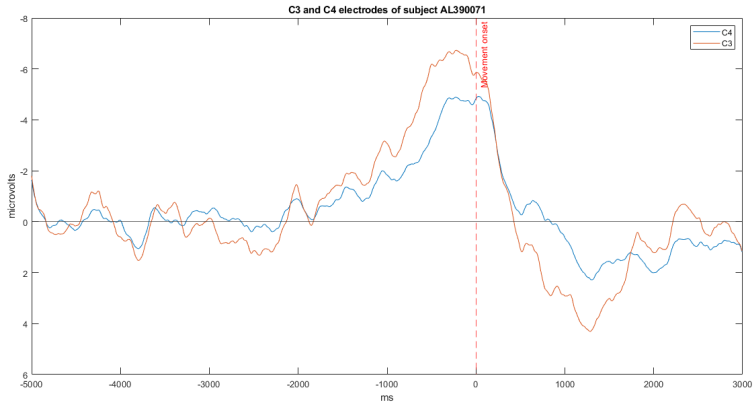


Figure 3.3: RP recorded at electrodes C3 (red) and C4 (blue)

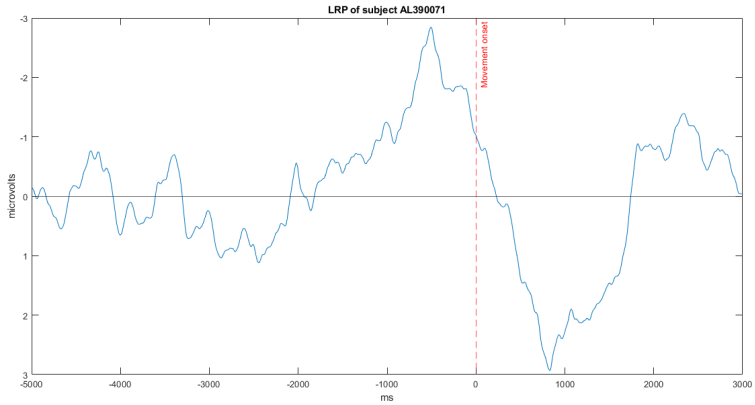


Figure 3.4: Lateralized readiness potential

3.4.1 Factors influencing LRP amplitude

A factor that affects LRP amplitude, and thus the lateralization of the last part of the RP, is the complexity of the response. For more complex responses to certain stimuli the amplitude will be larger with respect to simple responses (e.g. if the subject needs to perform three key presses when a certain event happens with respect to one single key press) [21]. The amplitude of the potential also increases when a shift of the side of movement initiation takes place between trials [36]. In the Libet's experiment one of the parameters is the so called "W judgment", that is the subjective experience of earliest awareness of the wish to move when a free movement is executed. There is a positive correlation between the W judgment value and the amplitude of the LRP [22].

The RP, and thus the LRP, are elicited by both performed and imagined movements. For actual movements the elicited LRP has larger amplitude than for imagined movements [4].

While the RP gets larger for movements that require more force, this is not the case for the LRP: response force and rate of force production are not factors that influence the LRP amplitude [59].

LRP amplitude

Factor	Influence
More complex response	Larger
Shift of the side of movement between trials	Larger
Earlier W judgment	Larger
Performed movement respect to imagined movements	Larger
Response force	Unchanged
Rate of force production	Unchanged

Table 3.6: Factors influencing LRP amplitude

3.4.2 Factors influencing LRP onset

The onset of the LRP is thought to reflect the activation of central motor processes [63].

Falkenstein et al. (1994) [15] found that the complexity of the task affects the onset in a way that more complex movements (e.g. when there are more alternatives to respond with) produce a LRP with delayed onsets (about 63 ms). The peak of the LRP in the experiment, in contrast, was delayed by a higher amount (about 85 ms). In the study was concluded that the LRP onset is closely related to central decision processes, while the peak latency is correlated with other mechanisms.

When looking at r-LRP, Li et al. (2017) [37] obtained a delayed onset for visual-auditory targets respect to auditory signals alone. This probably reflects the prioritization of the motor system for visual stimuli when the subject is given multisensory information.

LRP onset	
Factor	Influence
More complex task	Later
Visual-auditory stimulus respect to auditory stimulus alone	Later (r-LRP)

Table 3.7: Factors influencing LRP onset

Chapter 4

Materials

4.1 Experimental protocol

In every experimental session the subjects had to perform three different tasks:

1. **Voluntary**: in this first task the subjects were instructed to bend the index finger in a single, firm movement whenever they wanted during an interval of about 10 seconds after an acoustic signal. This experiment aims to give the subjects the ability to choose the timing and not to feel the urge to move, in order to make the movement "self-paced".

2. **Semi-voluntary**: the difference compared to the first task is that the subject must flex the finger as soon as the acoustic signal is heard. The trigger is external, and the subject cannot choose the timing of the movement, that is "cue-based".

3. **Involuntary**: in the last task the patellar reflex is elicited stimulating the tendon with a reflex hammer. In this case the acoustic signal is only heard by the experimenter through headphones and the subject is blinded, so that the subject does not expect the stimulation to happen.

   Every session is composed of 40 trials for each task and the intervals between the acoustic signals are random to avoid adaptation by the brain. In many sessions the involuntary task could not be accomplished because of the impossibility to correctly elicit a patellar reflex in the subject.

4.2 Experimental materials

- Acquisition device: Galileo Suite, EB Neuro, Brain Explorer amplifiers
- PC with Galileo software installed for elaboration and visualization
- PC with OpenSesame for the acoustic signal and the use of Labjack
- Labjack and optocoupler circuit
- 64 electrodes EEG cap
- 4 adhesive electrodes for EOG recording
- 2 adhesive electrodes for EMG recording
- Ground electrodes for the wrist
- 2 earlobe reference electrodes
- NUPREP abrasive paste
- TEN20 conductive paste
- EEG conductive gel

4.3 Session preparation

Before each session the materials are checked and cleaned, if needed, because traces of dry gel on the electrodes can be source of noise. Earlobes and wrist electrodes are cleaned using alcohol, while, as for the cap, only water is used. After signing the consent, the subject is placed on a chair facing away from the computer where the recording traces are visualized, the earlobes and the wrist electrode are mounted using the TAN20 paste, and the cap is set on the head. The electrodes for EOG and EMG recordings are then placed and the impedance of each electrode of the cap is checked using the Galileo software.

The goal is to have impedance lower than 10 $k\Omega$ for all electrodes, using NUPREP abrasive paste first and then EEG conductive gel to reach the objective, as described by Steven J. Luck. Unfortunately, not in all experiment an optimal impedance has been reached, leading to frequent rejections in our data due to noisy records. The last step before the recording is to check for noisy channels and, if the problem cannot be solved, to remove them from the visualization panel.

4.4 MATLAB

MATLAB is the environment used for data analysis. It is a powerful programming language based on C that allows with simple commands the manipulation of matrices, the creation of graphics and, generally, data manipulation for a large number of applications due to the numerous toolboxes available.

4.5 EEGLAB

EEGLAB is a MATLAB toolbox, a useful program for EEG analysis and visualization maintained by the Swartz Centre for Computational Neuroscience (SCCN). EEGLAB contains a variety of functions for filters application, data rejection, averaging, data visualization and other complex applications like time-frequency analysis and independent component analysis (ICA).

Figure 4.1: MATLAB logo

Chapter 5

Methods

In this section we describe the amplitude and onset measures derived from literature about the RP. These are implemented in MATLAB and applied to our data, to evaluate the script performance and verify the literature findings about voluntary, semi-voluntary and involuntary movements. We described some important techniques used to extract the ERP from the continuous EEG recording.

5.1 ERP extraction

The used techniques for ERP extraction from EEG continuous recording are:

- **Epoching**: it is a necessary step for averaging, and consists in the division of the continuous EEG signal in fixed-length windows, time-locked to a certain event (e.g. a stimulus). In our experiments, epochs are time-locked to the muscle activation detected in the EMG track. Each epoch contains a baseline period, prior to the event, and a period following the event. Our epochs start 5 seconds prior to movement onset and end 3 seconds after movement onset.

- **Baseline correction**: since many factors could bias the signal amplitude [39], after extracting the epochs a correction procedure is implemented, consisting in subtracting to the whole signal the mean value of the baseline, that is a period where no signal is supposed to exist and where no signal is present. In our case, we consider as the baseline the period from 4,5 s prior to movement onset to 3,5 s prior to movement onset. High-pass filtering the signal also helps reducing the biases, but it is a blunt technique compared to baseline correction, which is the best way to remove the offsets given by, for example, skin potentials or static electrical charges on the electrodes [39].

- **Averaging**: it consists in summing all the epochs and then dividing the obtained signal for the number of epochs. This sums all the time-locked signal of the epochs (in our case the ERP) and not the non-time-locked signals, that we consider as noise. Thus, the goal of averaging is to increase the SNR, since the signal, assumed to be almost identical in each

trial, has the same phase for each epoch, while noise has random phase. A typical number of epochs needed to compute an ERP through averaging in our study is between 30 and 40. An important step between baseline correction and averaging is the artifact rejection.

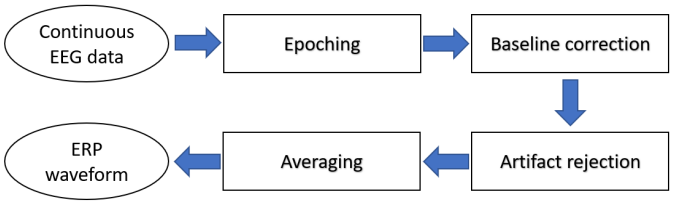


Figure 5.1: Workflow for the extraction of the ERP waveform from EEG continuous data

5.2 Amplitude measures

When measuring signals, one of the main and more intuitive approaches is measuring the peak amplitudes. The "peak amplitude" in a certain window is defined as the maximum voltage value reached in that window, meaning the most positive or the most negative point in that time period. Since we are talking about slow negative cortical potentials, we will be looking for negative peaks. Amplitude measures are typically related to the average signal value in a period where only noise is considered to be present. A typical window where this can be done in experiments is the prestimulus period, namely the period preceding the stimulus. The analysis of the amplitude of a component by looking at peaks can, though, be misleading since peak measures are influenced by a number of factors totally unrelated to the brain activity, such as high frequency noise and latency variability [39]. To overcome the high-frequency noise problem a possible approach is to low-pass filter the data, smoothing the signal. A more reliable way to measure the amplitude of a certain component is the "mean amplitude". This measure consists in computing the average value of the signal in a certain window. In the majority of cases this technique overcomes the problems that arise in peak amplitude measures, since "there is nothing special about the point at which the voltage reaches a local maximum" [39] and components are not instantaneous events but events extended over time. Moreover, the sensitivity to high-frequency noise is reduced for mean amplitudes and, as long as the measurement window is large enough, the latency variability is not a problem.

Despite the positive aspects, mean amplitude measures have some disadvantages. One of the biggest ones is the problem of overlapping components, especially if these components have different latencies in different conditions. The other problem (related to mean amplitudes) is the definition of the measurement window. The best way to overcome this problem is to base the window on previous studies, although this solution does not assure perfect results.

A study that uses peaks to measure the early BP and the late BP amplitude is the work from Dick et al. [11], also addressed in a more recent study by Karaman et al. [31]. The method by Dick et al. involves measuring the peak negativity (N1) in the whole averaged epoch. In this case, the components are not measured as the peak in a certain time window. In fact, the early component of the RP (NS1 in the study) is simply measured as the amplitude of the signal at the time -650 ms, where time zero is the movement onset. Instead, the late component (NS2 in the study) is derived subtracting NS1 from N1. This amplitude measure has been used to asses the impaired amplitude of the RP in patients affected by schizophrenia by a number of studies.

To summarize, *the method proposed by Dick et al. for the measure of the components of the RP is the following:*

- Negative peak (N1): measured as the most negative point
- Early BP (NS1): measured as the signal amplitude 650 ms prior to movement onset
- Late BP (NS2): measured as $NS1 - N1$

Mean amplitudes have also been used for the same purpose; an example is the work from Singh et al. [56], which studied the case of schizophrenia patients using mean amplitude measurements. The measured components are three. The first one is the early BP, referred to as RP in the paper, measured as the mean value in the window from 1000 ms prior to movement onset to 500 ms prior to movement onset; the second is the late BP, referred to as the NS', measured as the mean value in the window from 500 ms prior to movement onset to 100 prior to movement onset; the last component mentioned is the MP, measured as the mean value of the signal in the last 100 ms preceding the onset. The findings of this work confirm the literature findings about schizophrenia, since amplitudes are generally found to be lower in patients respect to controls.

Summarizing, *this is the method proposed by Singh et al.:*

- Early BP (RP): mean amplitude in the interval [-1000 -500] ms
- Late BP (NS'): mean amplitude in the interval [-500 -100] ms
- Motor potential (MP): mean amplitude in the interval [-100 0] ms

The problem with Singh method is that the RP components onset suffer a very high variability, and while for specific experiments the use of the same time windows for all subjects and all conditions could be not problematic, in situations where we want to compare RP components amplitudes that arise at different times this technique leads to errors. To solve this problem Wright et al. [65], instead of computing the mean value of fixed time windows, computed the mean amplitude value of the early BP singularly for each subject by first detecting their onsets. After the detection of the onsets of both components, the early component has been calculated as the mean value in the interval between the early BP onset and the late BP onset, while the late component has been calculated as the mean value between the late BP onset and the peak of the registered MP.

This method is also used in previous studies [16] [32] [66] and, summarizing, consists in the following measures:

- Early BP: measured as the mean amplitude in the interval between the early BP onset and the late BP onset
- Late BP: measured as the mean amplitude in the interval between the late BP onset and the MP peak.

Each measure is repeated for each electrode and then put into a table for further analysis.

5.3 Onset measures

In their work Mordkoff et al. [44] described the most used methods for onset detection of the LRP, and clustered them in three groups, that will now be described.

5.3.1 Criterion-based methods

Criterion-based methods are the simplest ones. The onset is considered to be the first time-point where the signal exceeds an arbitrary value chosen by the experimenter. Studies that chose this approach are, for example, that by Osman & Moore (1993) [48] or the one by Smulders et al. (1996) [58]. There are two ways in which the threshold can be chosen:

1. "Fixed-criterion": a fixed threshold value is used in all conditions
2. "Relative-criterion": a certain proportion of the maximum value of the signal is chosen as the threshold (e.g. 20% of the amplitude of peak)

5.3.2 Baseline-deviation methods

This method is based on the distinction between signal and noise: we consider the point in time where the signal first "emerges" from noise for a significant number of samples as the onset. To do this we consider the baseline period, where is assumed to be only noise and no signal. Similarly to the criterion-based method we set a threshold value, that is the sum of the mean value of the baseline and the standard deviation of the baseline multiplied for an arbitrary factor (e.g. 2.5 SDs above the mean baseline value). Differently of the criterion-based method, the onset is not the first time-point where the threshold is crossed. There is another condition that needs to be satisfied: the signal needs to be consistently over the threshold. The onset, then, is the first point in time after which, in an arbitrary window, the amplitude values are over the threshold (e.g. 50 ms). This method is used in another study by Osman et al. (1992) [47] and appears to be more consistent than the criterion-based ones.

5.3.3 Regression-based methods

They are the most recently developed and the most sophisticated methods. Regression-based methods are based on linear regression lines fitting the data to obtain the onset. There are two main studies that apply these methods, and they do it in different ways.

The *regression-based method used by Masaki et al. (2004) [41]* for the detection of LRP onset considers the onset as the first point where the line fitted to the signal slope crosses the baseline mean value. The line is found by first taking an "anchor" point; in our case, that is the signal at the negative peak. After defining the anchor point, series of least squares linear regressions based on the anchor point and an arbitrary number of data points preceding it are calculated, finding a possible regression line, and checking the mean squared error between the line and the data. The process is iterative, and the next iteration consists in taking a higher number of points preceding the anchor point using least-squares technique and calculating the best fitting line for the data and the consequent mean squared error. The algorithm stops when the error does not decrease anymore for a certain amount of iterations, the final line is considered to be the last one before the error stopped decreasing and then the onset is the intersection between the final line and the baseline value. In our study we applied this regression method to calculate both the LRP onset and the early BP onset. The only difference between them is that while for LRP the anchor point is the negative peak, for the early BP the considered anchor point is the movement onset.

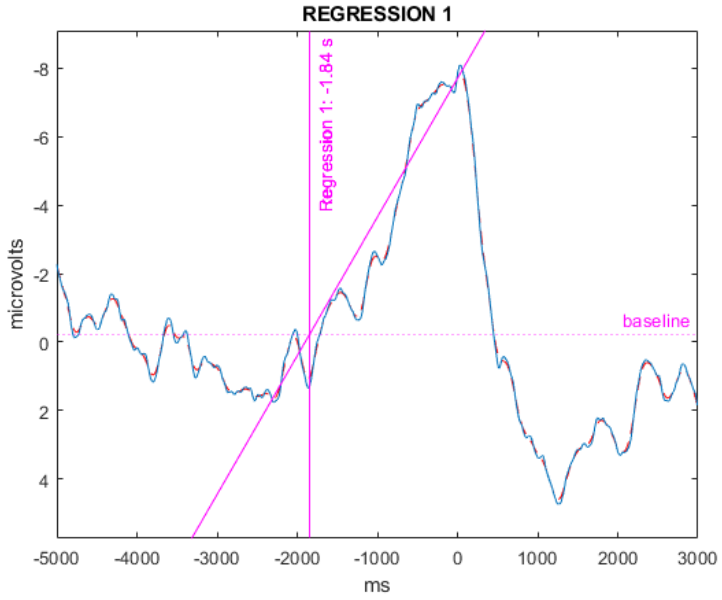


Figure 5.2: Regression-based method proposed by Masaki et al. for onset detection

The other study that proposes a regression-based method for the detection of LRP onset is the *work from Schwarzenau et al. (1998) [52]*, in which the "segmented regression" (SR) technique is used. In this case, the onset is defined as the "break-point" between two lines computed by fitting the points of the waveform. First, the boundaries where the LRP onset can be found are set. From literature, the LRP onset is supposed to be possibly found in an interval between 3 s before the movement onset and 0.25 s before its peak. The algorithm is iterative and, for each iteration, a different time-point between these limits is chosen, leading to the identification of two different time intervals:

- Interval A: between the first data sample and the considered time-point
- Interval B: between the considered time-point and 250 ms prior to LRP peak

For each iteration two lines are fitted: one using the data in interval A, where the preonset is supposed to be, and the other for the data in interval B, where the LRP slope is supposed to be. The mean squared error for each line is calculated, considering only data in interval A for the first line and data in interval B for the second line; the sum of the errors is computed and compared to the minimum value obtained in previous iterations. We can consider this an optimization algorithm where the sum of the mean squared error of the two lines is the cost function to minimize. The lines are considered as valid solutions only if the one fitting the data in interval B has negative slope, and this slope is steeper than the line that fits data in interval A. Once a valid solution with a minimum in the cost function is found, the intersection between the lines is calculated and, if it is in an interval between 3000 ms prior to movement onset and 250 ms prior to LRP peak, is then considered valid.

This method is also used in our study to find the onset of both early and late BP. The differences are in the definitions of intervals A and B and in the acceptability criteria for new solutions. For the early BP onset we consider two time-points for each iteration: the first point (i) is chosen in the interval in which the early BP onset is possible to find, that is in literature between -3 s and -0.8 s before movement onset; the second point (j) is chosen in the interval where the late BP onset is possible to find, that is between -650 ms and -300 ms before movement onset. The intervals are now defined this way:

- Interval A: between the first data sample and the time-point i
- Interval B: between the time-point i and the time-point j

Similarly to the LRP onset case, the interval A is supposed to be the preonset period and the interval B is supposed to be the window where the early BP slope is. The acceptability criteria are the following: the lines are considered as valid if the line fitting interval B has negative slope and is steeper than the line fitting interval A, and the early BP onset is considered a valid solution only if the intersection of the lines happens inside the interval between -3 s and -0.8 s. For the late BP only one time-point is considered for each iteration. This time-point is chosen in the interval where the late BP onset is considered to be possibly found, that is between the early BP onset + 250 ms and the negative peak – 250 ms. The intervals are now the following:

- Interval A: between the early BP onset and the time-point for the considered time-point
- Interval B: between the considered time-point and the negative peak

Interval A is supposed to be the one where the slope of the early BP happens, while in interval B we suppose to find the late BP steeper slope. The acceptability criteria for the late BP onset are the following: the lines must have both negative slope and the line in interval B has to be steeper than the line in interval A. The late BP onset is considered valid if it falls in the interval between -1 s and the movement onset.

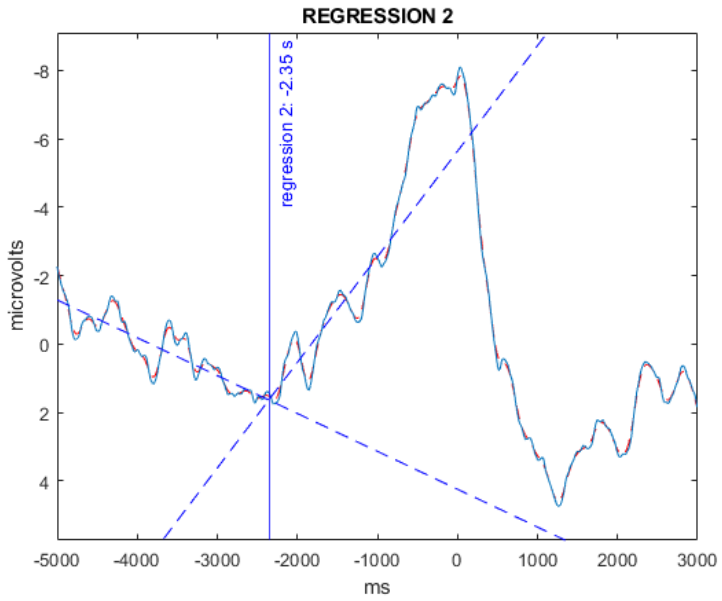


Figure 5.3: Regression-based method proposed by Schwarzenau et al. for onset detection

Chapter 6

Results

We applied data with different quality levels to the algorithms to test their robustness. The features that have been observed to evaluate the data quality are the following:

- Noise and biases presence, especially in the baseline period
- Peak amplitude latency (should be around the movement onset)
- Signal clearly arising from noise where early BP onset is supposed to be
- Increase of the signal slope corresponding to the late BP onset

In accordance to these criteria we divided our dataset into three different groups:

1. High-quality data
2. Medium-quality data
3. Low-quality data

The data classification is made by visual inspection.

Some data are voltage measures and because of this the used unit measure is μV, while some data are expressed in current density, and their unit measure is then μA.

6.1 High-quality data

The best quality recordings are the ones that own all the features described in the previous list. We expect these data to be correctly analyzed and the results to be plausible. One of the subjects that produced data classified as high-quality is subject AL390071 during the voluntary protocol. The waveform produced by the EEG signal processing owns all the characteristics necessary for the algorithm to perform at its best, and the amplitude measures produced the following results:

Amplitude measures of subject AL390071 at electrode Cz

Source	Amplitude	
Dick et al. [11]	Component	Measure
	N1	$-8.10\mu V$
	Early BP	$-4.96\mu V$
	Late BP	$-3.14\mu V$
Singh et al. [56]	Component	Measure
	Early BP	$-4.16\mu V$
	Late BP	$-7.26\mu V$
	MP	$-7.44\mu V$
Wright et al. [66]	Component	Measure
	Early BP (onset calculated using the criterion method)	$-2.11\mu V$
	Early BP (onset calculated using the baseline method)	$-2.18\mu V$
	Early BP (onset calculated using the regression 1 method)	$-1.70\mu V$
	Early BP (onset calculated using the regression 2 method)	$-0.96\mu V$
	Late BP	$-6.97\mu V$

Table 6.1: Amplitude measures of subject AL390071 at electrode Cz (high-quality data)

The onset measures for the same subject are the following:

Onset measures of subject AL390071

Component	Onset
RP	

Method	Measure
Criterion-based	$-1.61s$
Baseline-based	$-1.54s$
Regression-based 1 (Masaki et al.) [41]	$-1.84s$
Regression-based 2 (Schwarzenau et al.) [52]	$-2.35s$

Late BP

Method	Measure
Regression based 2 using criterion-based RP onset	$-0.66s$
Regression based 2 using baseline-based RP onset	$-0.66s$
Regression based 2 using regression-based 1 RP onset	$-0.65s$
Regression based 2 using regression-based 2 RP onset	$-0.68s$

LRP

Method	Measure
Criterion-based	No plausible onset detected
Baseline-based	$-1.18s$
Regression-based 1 (Masaki et al.) [41]	$-1.42s$
Regression-based 2 (Schwarzenau et al.) [52]	No plausible onset detected

Table 6.2: Onset measures of subject AL390071 (high-quality data)

6.2 Medium-quality data

Unlike high-quality data, these lack one or two features from the list in the beginning of this chapter. When the software applies its measurement algorithms to "dirty" data some results will most likely be implausible or impossible, particularly for measurements following the protocol described by Wright et al. where the onsets of the early BP and the late BP are necessary to compute their amplitude. The subject that will be an example of medium-quality data is subject AL858070 during the voluntary protocol. These are the results of the algorithm:

Amplitude measures of subject AL858070 at electrode Cz

Source	Amplitude
Dick et al. [11]	Component: Measure N1: $-58.29\mu A$ Early BP: $-54.26\mu A$ Late BP: $-4.03\mu A$
Singh et al. [56]	Component: Measure Early BP: $-51.82\mu A$ Late BP: $-50.02\mu A$ MP: $-43.62\mu A$
Wright et al. [66]	Component: Measure Early BP (onset calculated using the criterion method): Impossible Early BP (onset calculated using the baseline method): Impossible Early BP (onset calculated using the regression 1 method): Impossible Early BP (onset calculated using the regression 2 method): Impossible Late BP: Impossible

Table 6.3: Amplitude measures of subject AL858070 at electrode Cz (medium-quality data)

The onset measures for the same subject are the following:

Onset measures of subject AL858070

Component	Onset
RP	Method: Criterion-based — Measure: No plausible onset detected Method: Baseline-based — Measure: No plausible onset detected Method: Regression-based 1 (Masaki et al.) [41] — Measure: $-2.30s$ Method: Regression-based 2 (Schwarzenau et al.) [52] — Measure: No plausible onset detected
Late BP	Method: Regression based 2 using criterion-based RP onset — Measure: No plausible onset detected Method: Regression based 2 using baseline-based RP onset — Measure: No plausible onset detected Method: Regression based 2 using regression-based 1 RP onset — Measure: $-0.89s$ Method: Regression based 2 using regression-based 2 RP onset — Measure: No plausible onset detected
LRP	Method: Criterion-based — Measure: No plausible onset detected Method: Baseline-based — Measure: $-2.86s$ Method: Regression-based 1 (Masaki et al.) [41] — Measure: No plausible onset detected Method: Regression-based 2 (Schwarzenau et al.) [52] — Measure: $-1.97s$

Table 6.4: Onset measures of subject AL858070 (medium-quality data)

6.3 Low-quality data

These recordings lack most of the features necessary for the correct data analysis. From these data we expect many failures by the algorithm, meaning that the onsets will be impossible to detect for most of the used methods and the amplitudes value will probably be biased by noise. We chose subject OB896971 and the recording made during the voluntary experiment to represent low-quality data in this chapter. These are the results:

Amplitude measures of subject OB896971 at electrode Cz

Source	Amplitude	
Dick et al. [11]	Component	Measure
	N1	$-25.66\mu A$
	Early BP	$28.22\mu A$
	Late BP	$-53.88\mu A$
Singh et al. [56]	Component	Measure
	Early BP	$26.17\mu A$
	Late BP	$41.85\mu A$
	MP	$64.24\mu A$
Wright et al. [66]	Component	Measure
	Early BP (onset calculated using the criterion method)	Impossible
	Early BP (onset calculated using the baseline method)	Impossible
	Early BP (onset calculated using the regression 1 method)	Impossible
	Early BP (onset calculated using the regression 2 method)	Impossible
	Late BP	Impossible

Table 6.5: Amplitude measures of subject OB896971 at electrode Cz (low-quality data)

Onset measures of subject OB896971

Component	Onset
RP	

Method	Measure
Criterion-based	No plausible onset detected
Baseline-based	No plausible onset detected
Regression-based 1 (Masaki et al.) [41]	No plausible onset detected
Regression-based 2 (Schwarzenau et al.) [52]	$-2.04s$

Late BP

Method	Measure
Regression based 2 using criterion-based RP onset	No plausible onset detected
Regression based 2 using baseline-based RP onset	No plausible onset detected
Regression based 2 using regression-based 1 RP onset	No plausible onset detected
Regression based 2 using regression-based 2 RP onset	No plausible onset detected

LRP

Method	Measure
Criterion-based	No plausible onset detected
Baseline-based	No plausible onset detected
Regression-based 1 (Masaki et al.) [41]	No plausible onset detected
Regression-based 2 (Schwarzenau et al.) [52]	No plausible onset detected

Table 6.6: Onset measures of subject OB896971 (low-quality data)

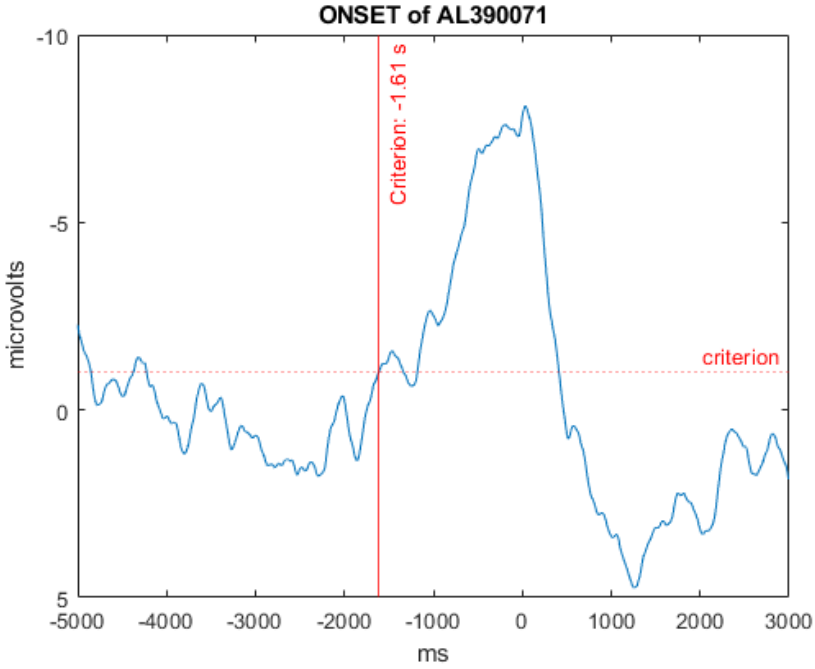


Figure 6.1: RP onset of subject AL390071 measured using the criterion-based method

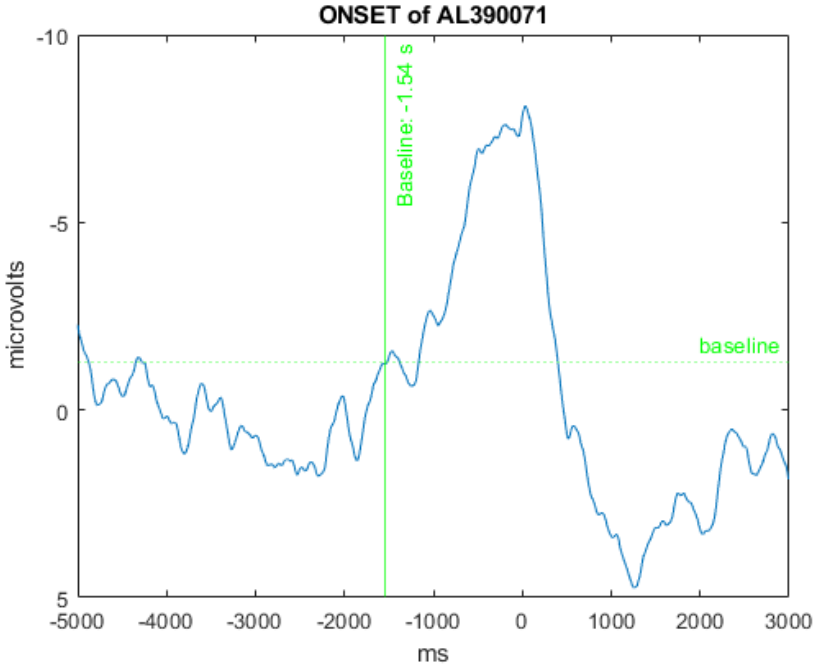


Figure 6.2: RP onset of subject AL390071 measured using the baseline-based method

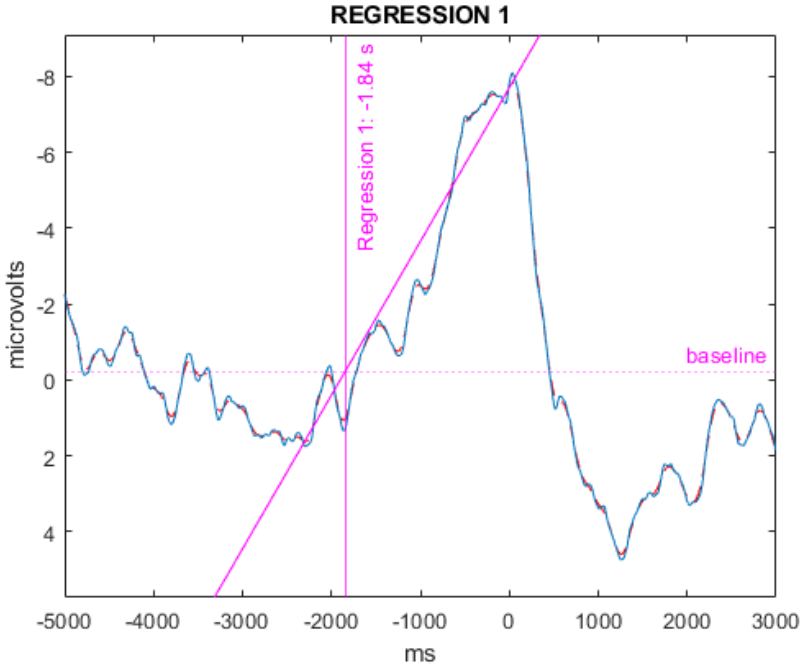


Figure 6.3: RP onset of subject AL390071 measured using the regression-based 1 method

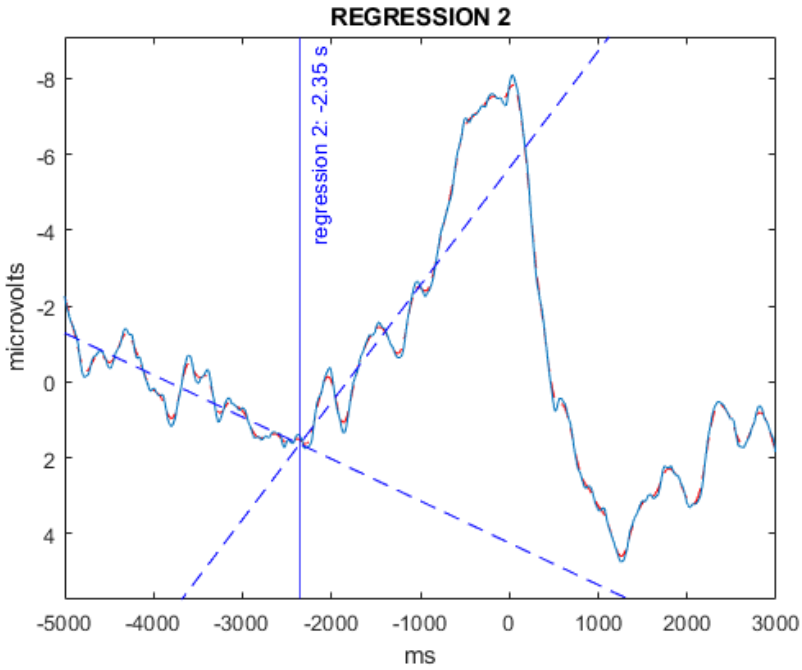


Figure 6.4: RP onset of subject AL390071 measured using the regression-based 2 method

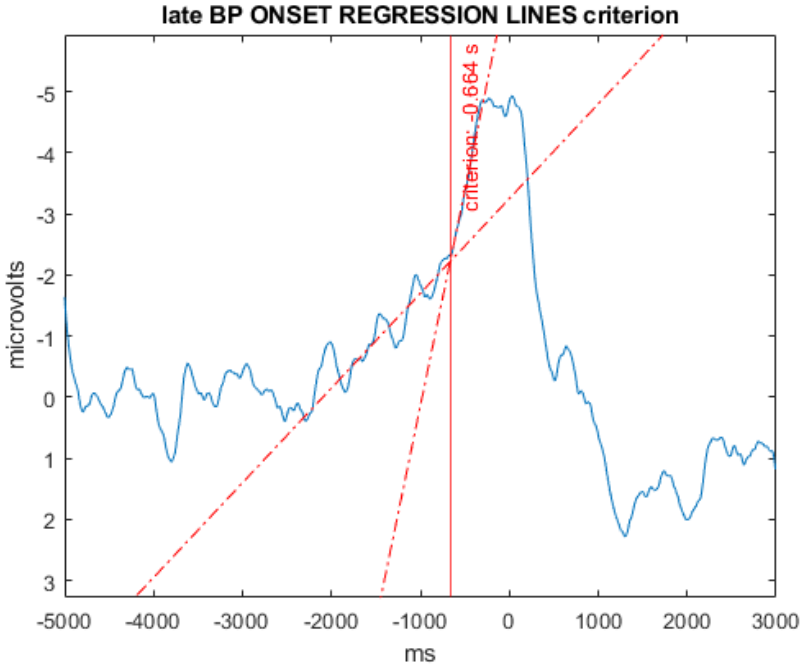


Figure 6.5: Late BP onset of subject AL390071 measured using the regression-based 2 method with criterion-based calculated RP onset

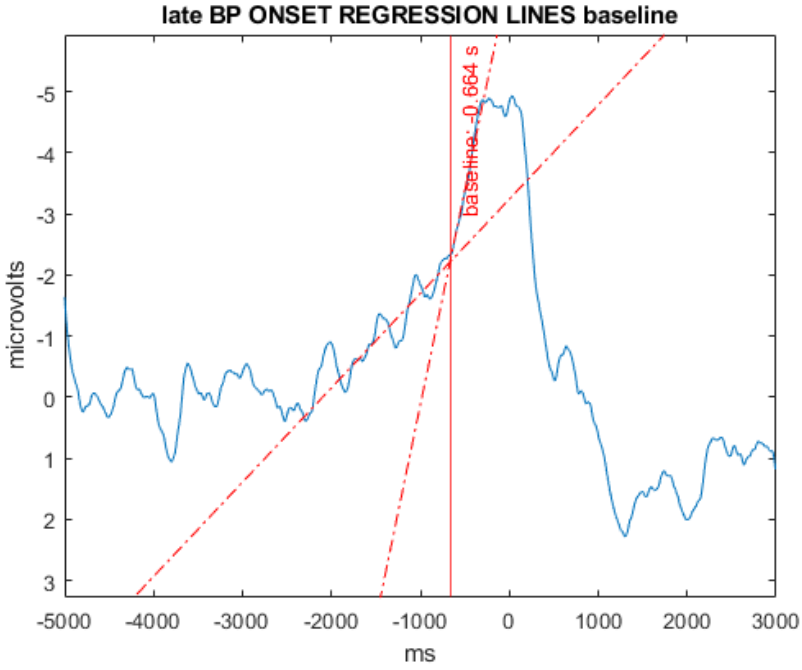


Figure 6.6: Late BP onset of subject AL390071 measured using the regression-based 2 method with baseline-based calculated RP onset

Figure 6.7: Late BP onset of subject AL390071 measured using the regression-based 2 method with regression-based 1 calculated RP onset

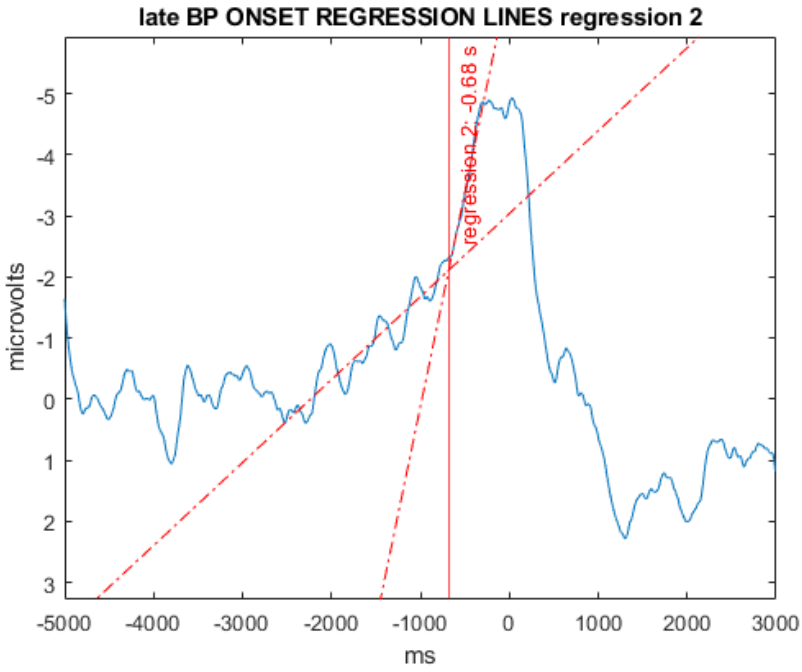


Figure 6.8: Late BP onset of subject AL390071 measured using the regression-based 2 method with regression-based 2 calculated RP onset

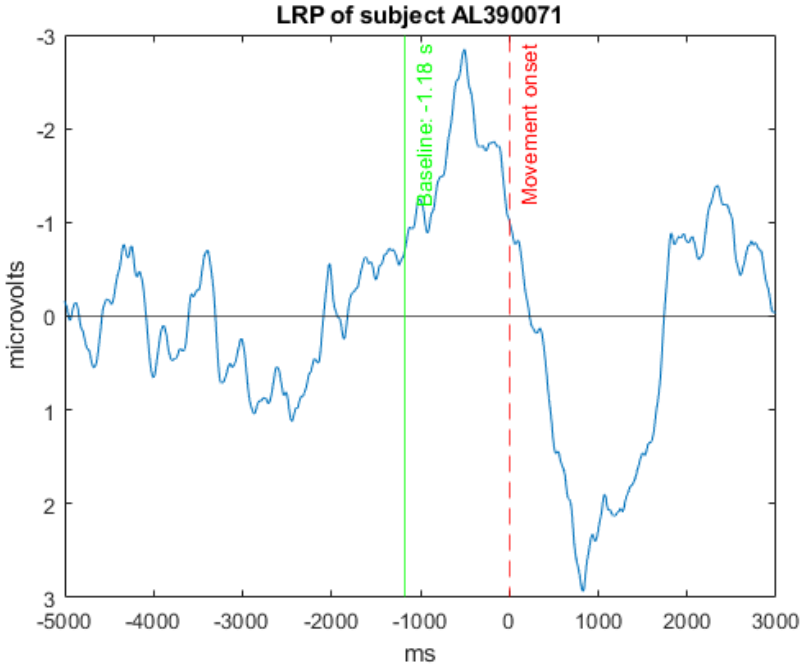


Figure 6.9: LRP onset of subject AL390071 measured using the baseline-based method

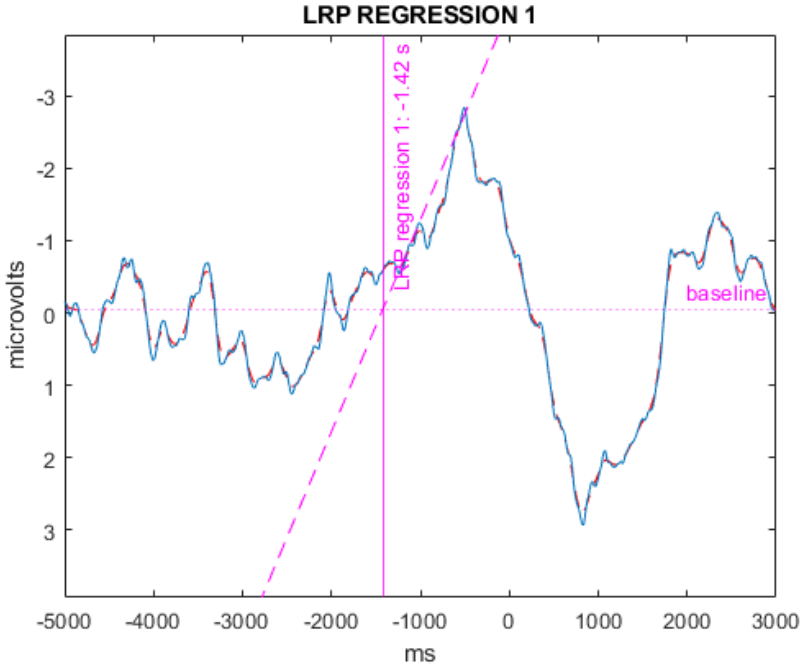


Figure 6.10: LRP onset of subject AL390071 measured using the regression-based 1 method

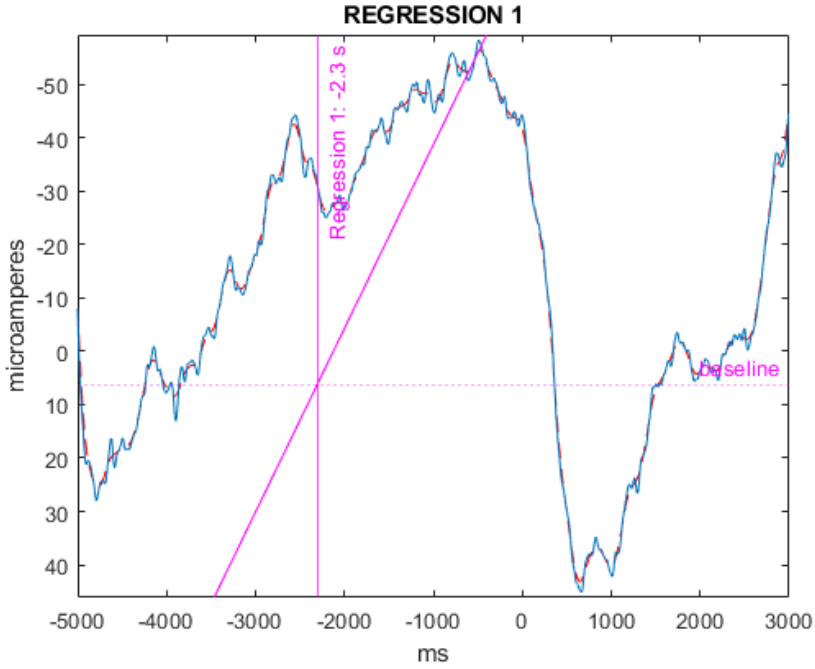


Figure 6.11: RP onset of subject AL858070 measured using the regression-based 1 method

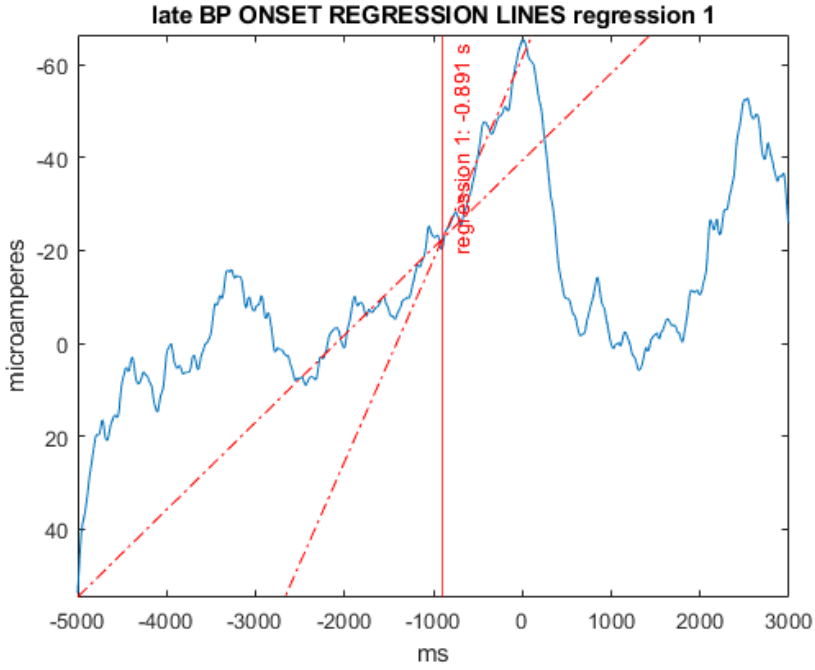


Figure 6.12: Late BP onset of subject AL858070 measured using the regression-based 2 method with regression-based 1 calculated RP onset

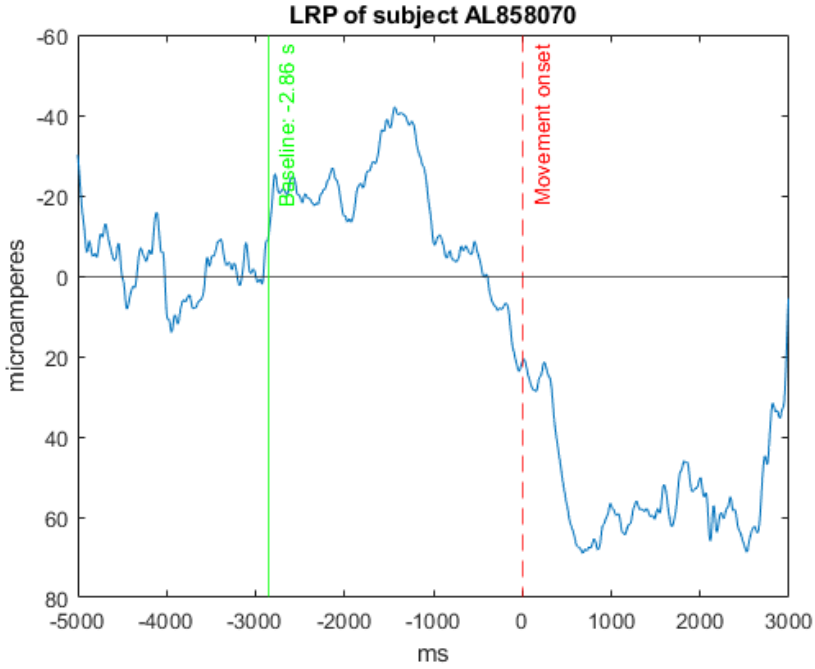


Figure 6.13: LRP onset of subject AL858070 measured using the baseline-based method

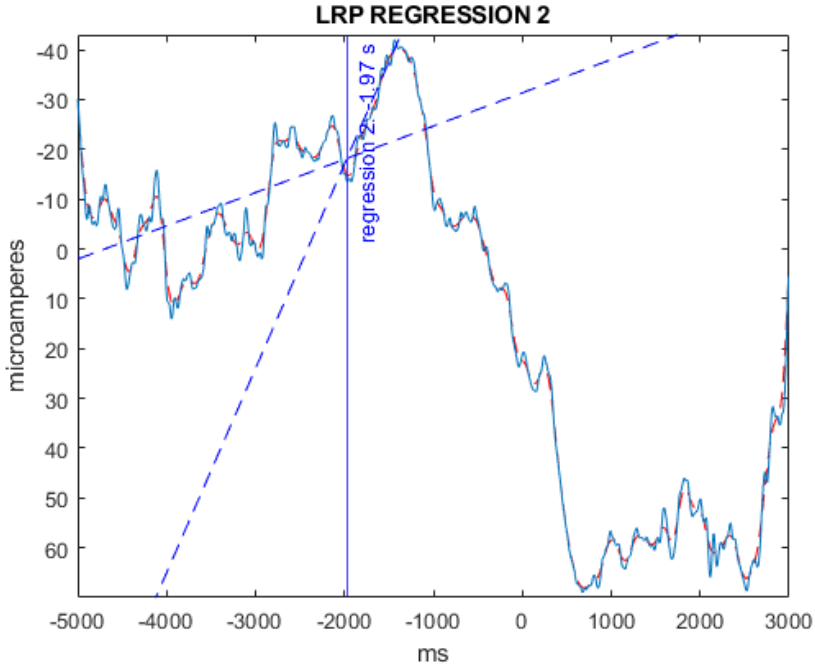


Figure 6.14: LRP onset of subject AL858070 measured using the regression-based 2 method

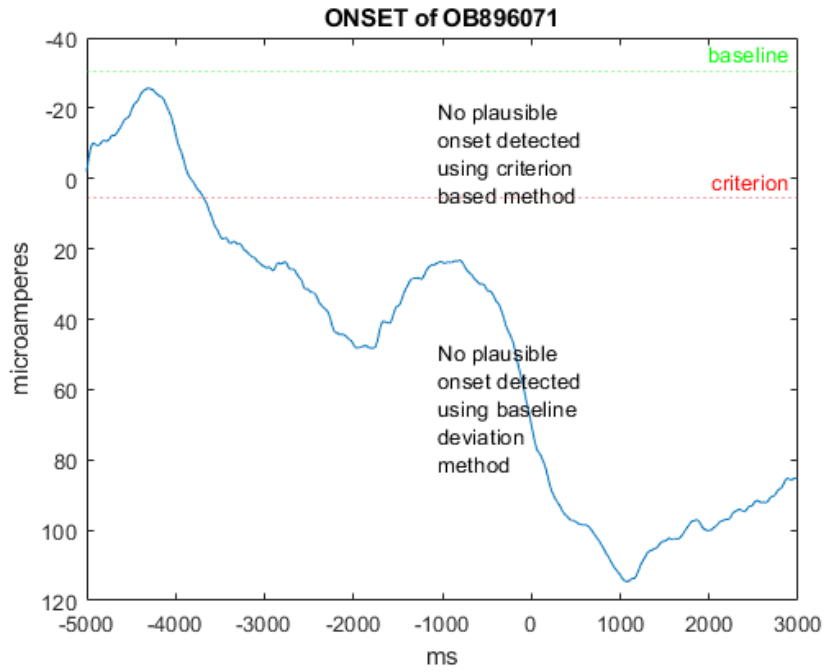


Figure 6.15: RP onsets of subject OB896071 measured using the criterion-based and the baseline-based method (the dotted lines show the theshold levels)

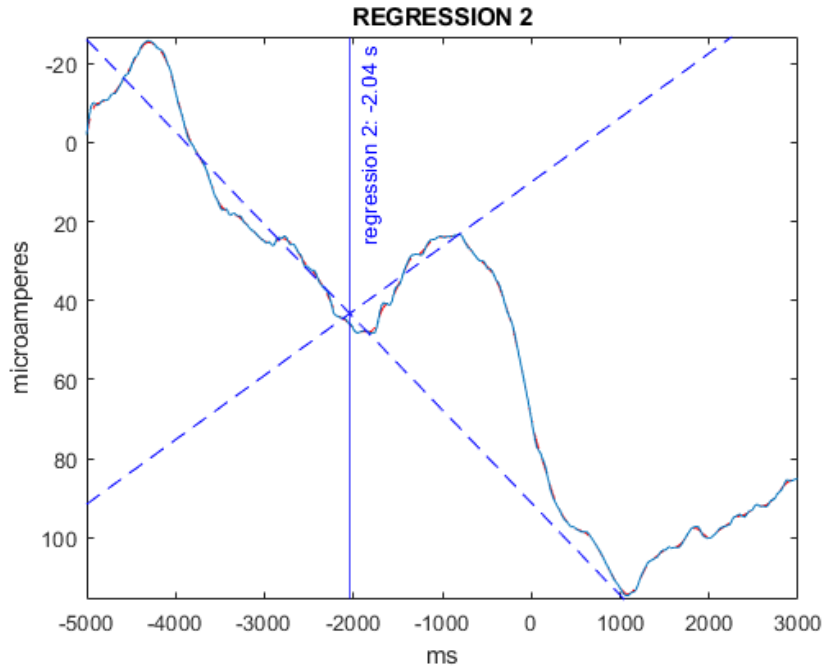


Figure 6.16: RP onset of subject OB896071 measured using the regression-based 2 method

Chapter 7

Conclusions

The results show that the quality level of the input data is extremely important for the software performances.

When high-quality data is processed, the vast majority of the outputs is correctly computed and the measures are inside the range of possible results. The onsets correctness can also be appreciated by visual inspection. The only problematic measures for these data are LRP onset measures. This problem arises because of the used method to compute LRP: while the standard for LRP computing is the double subtraction method, our protocol only includes right-hand movements and the double subtraction is then impossible. The LRP we applied our measures to is computed with a single subtraction, the signal quality is significantly lower and the measures are then unreliable. This statement about LRP is true for all quality-level data.

Using medium-quality data many measures are not computed because of the noise and the biases present in the waveform. These problems make some onsets impossible to detect, and thus make Wright et al. [66] method impossible to be applied. Regression-based methods proved to be the most reliable. While the criterion-based and the baseline-based methods that rely respectively on the peak amplitude and the baseline cleanliness are heavily affected by noise and interference with other brain processes, the regression-based methods have proven to be a more robust way to obtain onset measures.

With low-quality data almost all the onset measurements are impossible to perform. The most robust method is the regression-based one, following the work of Schwarzenau et al. [52]. This method proved to be less affected by problems in the baseline than the rest of the measure techniques.

To solve some of the problems that emerged from the results, we now propose some adjustments to the acquisition protocol. Because of the sensibility that the algorithm has for biases and superposition with other brain activities, data quality could improve asking the subject to maintain eyes fixation in a certain point, avoiding eye-movement artifacts, and also asking the subject to avoid talking and swallowing during the movement. These are common countermeasures to avoid noise and superposition problems in EEG recordings. The usage of a lower number of electrodes is also a factor that can contribute to better data quality [39]. Another problem linked to the electrodes is the impedance: it was very difficult to obtain values under 10 $k\Omega$ and this problem probably arises because of the equipment quality.

Finally, to improve the reliability of LRP measurements we propose to include left-hand movements in the experimental protocol, so that the double-subtraction method is possible to apply.

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