Research and Clinical Methods for Investigating Brain Processing I & II

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Objectives:

**Lecture I**

- General Introduction
- Basic knowledge on Electroencephalography
  - Advantages and Limitations
- EEG rhythms and behaviors
- Introduce ERPs – experimental findings and their use to assess pathophysiological conditions

**Lecture II**

- Laboratory Experience – working on real oddball paradigm to produce P300 and ERP responses
Introduction

- Neuropsychology is a discipline that investigates the relationship between behavior, mind and brain using the experimental method.

- Clinical neuropsychology is concerned with understanding the mental functions of the brain in a broad sense and with putting this knowledge to use in diagnosis and prognostic evaluation of neurological patients, as well as in rehabilitation of patients in whom reduced quality of life is caused by problems of language, memory, or other cognitive, motivational or emotional domain.
Introduction

- The field of neuropsychology stood alone until 1960s as the only method for investigating the relationship of cognitive functions to the living human brain (using prominently the behavioral method).

- Since then, an accelerating processes has resulted in a range of new tools for functional brain imaging.

- Today, we can say that neuropsychology is an interdisciplinary science a convergence of: neurology, neuroanatomy, neurophysiology, neurochemistry, psychology, artificial intelligence, engineering, etc.
Behavioral method

Functional Imaging
Introduction

- The real advantage for both clinical and research neuropsychology is to have normative data available that allow evaluation of individual performance with reference to age and demographic variables.
Introduction

- Brain is a complex system and trying to discover how it works is a real challenge

- It has been sad that the brain is the most complex system of the entire Universe (Rita Levi Montalcini, 2001; Eric Kandel, 2000; Vilayanur S. Ramachandran, 2004)

The adult human brain contains app. 100 billion neurons
Although the anatomical substrate of the brain is well known, we still do not know how the brain works (XXI century).

[Kolb and Wishaw, 2009]
Although the anatomical substrate of the brain is well known we still do not knowing how the brain works (XXI century) [Kolb and Wishaw, 2009]

“the most fascinating thing nowadays is to assist how the brain tries to understand itself”
Introduction

For more than half century the modern neuroscience have used the method of REDUCTIONISM (one the dogma of empirism/materialism)

The ideas that support this position are:

1. everything that exists can be explained as the interactions of a small number of simple things

2. breaking up things in smaller parts could help to understand complex system
The opposite view is the **HOLISM** (ὅλος = all, entire) or **CONNESSIONISM**

The ideas that support this position are:

1. **All the properties of a given system cannot be explained by the sum of its component-parts alone**

2. **Instead, the system as a whole determines in an important way how the parts behave**

**Aristotle (Metaphysics):**
«The whole is more than the sum of its parts»
He was a recipient of the 2000 Nobel Prize in Physiology and for his research on the physiological basis of memory storage in neurons.

«The ultimate aim is to use reductionism, not only to take things apart, but to put them together again. You have to be a reductionist and a holist at the same time». 
Brain Imaging

Direct methods

EEG

MEG

TMS

Indirect methods

PET

fMRI
FUNCTIONAL IMAGING

METABOLIC SIGNAL (indirect method)

- PET (Positron Emission Tomography)
- fMRI (functional Magnetic Resonance Imaging)

ELECTRIC and MAGNETIC SIGNALS (direct method)

- EEG (Electroencephalography)
- MEG (Magnetoencephalography)
fMRI measures regional cerebral blood flow in relation to oxygen consumption.

PET measures the accumulation of glucose (2-deoxyglucose) in the neural cells.

2-deoxyglucose has a slow metabolism and is detected

**Ratio**

\[
\frac{\text{oxyemoglobin}}{\text{deoxyemoglobin}} \quad \text{(BOLD response)}
\]

**Genesis of fMRI and PET signals**

**Neuroimaging:**

- High spatial resolution (1 - 2 mm)
- Low temporal resolution (1 - 2 s)
• The principle assumption is that **neurons** as the other cells of the human body require energy in the form of **oxygen** and **glucose** for their cellular integrity and to perform specialized functions

• The Brain is extremely metabolic demanding organ
Dendrite rather than axon ionic currents are associated with recordable extracranial electromagnetic signals.

EEG and MEG signals are mainly generated by postsynaptic potentials of cortical pyramidal neurons.

Dendrite postsynaptic potentials:
- 10-100 ms duration
- $1/r^2$ attenuation

Axon action potentials:
- 1 ms duration
- $1/r^3$ attenuation

Good summation

Poor summation

Dendrite rather than axon ionic currents are associated with recordable extracranial electromagnetic signals.
The neurons of the cerebral cortex produce electrical activity and this activity can be easily measured by placing electrodes on the surface of the scalp.

Thousands of neurons generate an EEG signal that can be recorded.

EEG measures the current flow of post-synaptic excitation/inhibition of the dendrites of pyramidal cells just under the skull.

[Bear, Connors and Paradiso 2001]
Neural basis of the EEG

Pyramidal neurons are spatially aligned and perpendicular to the cortical surface.

Thus, EEG represents mainly the postsynaptic potentials of pyramidal neurons close to the recording electrode.

(Picture of pyramidal neurons in the cerebral cortex, Nolte 1991)
High Temporal Resolution
Poor Spatial Resolution

High Temporal Resolution
High Spatial Resolution
What EEG can tell us about the relationship between brain, mind and behavior?

The cerebral cortex produces a range of rapid electrical rhythms that are closely correlate with different mental state or behaviours.
Electroencephalography (EEG)

- EEG patterns are well established and consistent among healthy individuals.
- EEG provides many clinical applications since it can detect abnormalities in brain functions.
The character of the waves is highly dependent on the degree of activity of the cerebral cortex and the waves change markedly between the states of wakefulness and sleep and coma.

EEG rhythms *correlate* with behaviors and cognitive processing.

- The intensities of the brain waves on the surface of the scalp range from 0.1 to 100 µV.
- Their frequencies range from 1 every few seconds to 50 or more per seconds.
Event-Related Potentials (ERP)

Frequency range

3D Topographic Maps

Source Localization
ERP-components
For identifying the time

Frequency components
Eyes open  Eyes closed
For identifying the frequency

Brain Topography
For identifying the scalp location

Dipole source localization
For identifying the brain areas
EEG frequency potentials are good indicators of global brain state. They often display rhythmic patterns at characteristic frequencies.
Electroencephalography (EEG)

In 1929 Hans Berger published “On electroencephalogram of man” in this paper he pointed out to many scientific questions (that I would say in some extent are still valid today)

How is the EEG affected:
- by sensory stimulation?
- by sleep,
- by drugs
- by other mental state and intellectual ability?

Berger distinguished two patterns of brain activity:

Alpha rhythm at 8-13Hz “passive EEG”
Typically recorded on the occipital electrodes with eyes closed

Beta rhythm at frequencies > 13Hz “active EEG”
Accompanying mental exertion
Electroencephalography (EEG)

- EEG is a direct method to study brain activity
- Recording EEG is relatively simple
- The method is not invasive

It can also be done on children

EEG experiment at EEG laboratory (SMI)
(Aalborg University)
Electroencephalography (EEG)

Different regions of the brain can be measured by selecting the appropriate electrodes.
Electroencephalography (EEG)

**Electrodes:** Silver-silver chloride Ag/AgCl

**Active electrodes:** Attached to the scalp by conductive gel
Electroencephalography (EEG)

The International 10-20 System of Electrode Placement

The International 10-20 System of Electrode Placement is the most widely used method to describe the placement of electrodes at specific intervals along the head. Each electrode site has a letter to identify the lobe, along with a number or another letter to identify the hemispheric location.

The letters used are:

F - Frontal lobe
T - Temporal lobe
C - Central lobe
P - Parietal lobe
O - Occipital lobe

"Z" refers to an electrode placed on the mid-line.

Even numbers (displayed in blue in the image above) refer to the right hemisphere and odd numbers (displayed in red in the image above) refer to the left hemisphere.
Electrodes Maps

High-density **128** electrodes

**10-5** System

**21** electrodes Classical montage

**10-20** System
Small voltage fluctuations, usually few tens of microvolt (µV) in amplitude are measured by selected pair of electrodes (measured as potential difference)

**Monopolar montage:** include to choose one “active” electrodes (place on a brain area of interest, i.e. visual areas O1, Cz) and one “reference” electrode (on an inactive area, i.e.: mastoids, earlobe, tip of the nose)
Example of continuous EEG recording
EEG Rhythms

**Delta** $\delta$ (0.1 - 3.5Hz)

**Theta** $\theta$ (4 - 7.5Hz)
slow (4-6 Hz) and fast (6-7.5 Hz)

**Alpha** $\alpha$ (8 - 13Hz)
slow (8-9Hz) middle (9 -11.5Hz) fast (11.5-13Hz)

**Beta** $\beta$ (14 - 30 Hz)
slow (14-18 Hz) and fast (18.5-30 Hz)

**Gamma** $\gamma$ (30-70Hz)

[1 sec. sample]

[Bear, Connors and Paradiso 2001]
Beta Rhythm

- Characteristics:
  - frequency: 14-30 Hz
  - amplitude: 2-20 µV

- The most common form of brain waves
- Are present during mental thought and activity
Delta Rhythm

- Characteristics:
  - frequency: 0.5-3.5 Hz
  - amplitude: 20-200µV

- Found during periods of deep sleep in most people
- Characterized by slow wave patterns
- Also useful in detecting tumors and abnormal brain behaviors
Alpha Rhythm

- Characteristics:
  - frequency: 8-13 Hz
  - amplitude: 20-60 µV

- Easily produced when quietly sitting in relaxed position with eyes closed (few people have trouble producing alpha waves)
  - Ask a subject to close his/her eyes and relax this will produce an immediate increase in alpha activity in the occipital areas

- Alpha rhythm can be greatly diminished or abolished by eye opening, sudden alerting, and mental concentration or a strong sensory stimulation, a phenomenon known as “alpha blockage” or “alpha desynchronization”
When the **eye are open** – the frequency of the brain increases greatly but the synchronization of the signal decreases so that the brain waves decrease to weak waves called **beta waves**

When the **eye are closed** – synchronous discharge of many neurons in the cerebral cortex at a frequency of about 12/sec. - producing **alpha waves**
In recent years, the long-held belief that alpha rhythms are strongly influenced by the thalamus has been confirmed in several animal models and, in humans, is well supported by numerous non invasive imaging studies.
Modulation of the alpha

- We have also conducted several studies where we have demonstrated a suppression (or desynchronization) of the alpha activity by attentional processes when healthy individuals are involved in pain perception.

- Successively, we observed opposite phenomena: a synchronization of alpha from distraction.
Anticipation of pain triggers top-down attentional processes that enhance neural firing and modulate synaptic activity.

Alpha activity decreases (alpha blocking) in somatotopic fashion over the body regions corresponding where the subjects is expecting the stimulus.

(Babiloni et al., 2003; 2004; 2008)
• Alpha activity can be dynamically modulated with cognitive and motor tasks used as distractors

Compared to the Pain condition, the maps of Pain+Movement and Pain+Cognition conditions showed an occurrence of alpha 3 ERS at medial frontal and central areas.
Klimesch’s hypothesis of inhibitory function of alpha synchronization

- Synchronization of the alpha frequency range is considered to be a marker of active inhibition of sensory information, or a means of inhibition of non-task relevant cortical areas.

- Klimesch’s hypothesis proposes alpha as a mechanism for increasing signal to noise ratios within the cortex by means of inhibition of unnecessary or conflicting processes to the task in hand.

- This proposal is compatible with the notion of “surround inhibition” wherein active cortical areas, indexed by alpha desynchronization are surrounded by a “doughnuts” of synchronization or inhibition.

(Klimesch, 1999; 2000)
Theta Rhythm

- Characteristics:
  - frequency: 4-7Hz
  - amplitude: 20-100µV

- Believed to be more common in children than adults

- Theta rhythms can also occur during hypnagogic state, or imagery, hypnosis, and meditation
Gamma Rhythm

- Characteristics:
  - frequency: 36-44Hz
  - amplitude: 3-5µV

- Occur with sudden sensory stimuli

- Fast brain waves, at about 40 cycles per second (Hz), Gamma rhythms appear to be involved in higher mental activity, including perception and consciousness

- It seems to be associated with consciousness, since it disappears with general anesthesia
Large scale neural synchrony

- The relationship between gamma band synchronization and conscious awareness remains debated however this relationship has always provoked large interest.

- Large scale neural synchrony is a good candidate model for conscious cognition.

(Varela et al. 2001)
Neuronal synchronization in the gamma band is considered important for the transient functional integration of neural assemblies across brain areas to achieve various cognitive functions (Crick 1994; Singer 1999; Varela et al. 2001).

Different neuronal assemblies need to be in phase synchronization to allow the communicative exchange of information.
Both “Visible” and “Invisible” stimuli caused an increase of gamma activity in the EEG. However, only the “visible” words induced a transient long-distance synchronization of gamma oscillations across widely separated regions of the brain.

(Melloni et al., 2007)
This might suggest that:

Consciousness would emerge from large scale coordination of neural activity
Event-Related Potentials (ERP)

Frequency range

3D Topographic Maps

Source Localization
What Issues can ERP analysis address?

- ERPs have helped to delineate psychiatric and neurological conditions such as schizophrenia and ADHD, or how attention or working memory normally work.

- ERPs have been also of a great help in identify perceptual processes such as vision, audition, somatosensation, or pain.

- ERPs have also been used to study the effects of pharmacological manipulations.
Characteristics of the ERPs:

Another measure of the brain activity, derived from EEG recordings, is the event-related potentials (ERP).

The ERPs are regarded as manifestations of brain activities that occur in preparation for, or in response to, discrete events, be they internal or external to the subjects.

At the present, ERPs are one of the most established methods in cognitive neuroscience and are considered the “gold standard” in terms of temporal resolution among non-invasive imaging methods.

*Fabiani et al., Event-Related Brain Potentials: Methods, Theory and Applications (2000)*
Unlike the EEG, which represents spontaneous brain activity, the ERP is generated as response to specific stimuli. The ERP is derived from the electroencephalogram (EEG) by repeated stimulus presentation which is later averaged.
Event-Related Potentials (ERP): characteristics

- ERPs reflect activity **TIME-LOCKED** to particular sensory and/or cognitive events
- ERPs provide a very fine scale determining the **TIME** and temporal sequencing of particular events
Event-Related Potentials (ERP)

Average is made on the EEG continuous trace on a large number of trials

• Noise is cancelled out
Event-Related Potentials (ERP)

- Specific sensory modality (visual, auditory, somatosensory) or basic cognitive processing (attention, working-memory) produce unique components in the event-related waveform.

- These components are traditionally labeled according to their polarity (positive or negative peak) and timing with respect to the stimulus, either in order of appearance (e.g., P1, P2, P3 or N1, N2, N3) or in milliseconds (e.g., N200, P300).
Event-Related Potentials (ERP)
ERPs are on-line processing measures that reflect information-processing stages in a time window extending continuously from sensory processing to complex cognitive events.

Andreassi, 2007
Somatosensory Evoked Potentials (SEPs)

**P1-N1**: Peaks time between **50-60ms** are generated in the post-central gyrus (Primary Somatosensory Cortex (SI) *contralateral to the stimulation*).

*Time variable*: depending of the body part stimulated.
Example of SEP responses to painful laser (CO2) stimulations of different body parts

[Kakigi et al, 2003]
Primary Somatosensory Cortex SI

Contralateral hemisphere activation

[Image of brain scans]

[Image of brain diagram with areas labeled]

(Kakigi et al. 2003)
Secondary Somatosensory Cortex SII

- P2 component is generally originated in the secondary somatosensory cortex (SII)
- Bilateral activity

[Kakigi et al. 2003]
P300

- No other component has received as much attention as the P300

- The P300 was discovered over 40 years ago and has provided much fundamental information on normal and dysfunctional cognition (Bashore & van der Molen, 1991; Sutton et al., 1965)

- *It is considered to be an endogenous potential as its occurrence links not to the physical attributes of a stimulus but to a person's reaction to the stimulus*
P300 functional significance

- P300 is thought to reflect processes involved in stimulus evaluation or categorization
- Memory and Context Updating Theory
- Attentional Resources Allocation Theory
In this framework, P300 indexes brain activity underlying revision of the mental representation induced by the incoming stimuli (Donchin, 1981)
Resource allocation and P300

- When task conditions are undemanding:
  - P300 amplitude is large and peak latency is short

- For tasks that require greater amounts of attentional resources:
  - P300 amplitude is smaller and peak latency is longer as processing resources are used for task performance
The **P300** wave is elicited by infrequent, task-relevant stimuli.

It is usually elicited using the **oddball paradigm** in which low-probability target items are inter-mixed with high-probability non-target (or "standard") items.
The oddball task presents two different stimuli in a random sequence, with one occurring less frequently than the other does (target=T, standard=S).

Subject is instructed to respond mentally or physically to the target stimulus and not respond otherwise.
The three-stimulus task is similar to the oddball with a compelling distracter (D) stimulus that occurs infrequently. In each task, the subject is instructed to respond only to the target and otherwise to refrain from responding. The distracter elicits a P3a, and target elicits a P3b (P300).
Where are the generators of the P300?

- Superior temporal sulcus and the posterior superior parietal cortex are involved in generating the effortful P300 (P3b)

- The dorsolateral prefrontal cortex, supramarginal gyrus and cingulate gyrus may be involved in generating the automatic P300 (P3a)
Figure 8.
Schematic representation of brain activation patterns underlying P3a and P3b generation (after Gazzaniga et al., 2000). The model suggests that stimulus information is maintained in frontal lobe working memory and monitored by anterior cingulate structures. When focal attention for the standard stimulus is disrupted by the detection of a distracter or a target (stimuli that garner attention automatically or purposefully from task demands), the P3a is perhaps generated by the activation pattern of the anterior cingulate and related structures. The attention-driven neural activity signal may be transmitted to temporal-parietal areas. Memory-related storage operations are engaged and P3b is generated via temporal/parietal cortical structures. As indicated by the ERP waveform and arrow to the right, every “P300” is composed of the P3a and P3b subcomponents, but the resulting ERP scalp topographies vary with the stimulus and task conditions that elicit them. Reprinted with permission from W.W. Norton & Company (Copyright, 2000).
P300 in Pathological Conditions

- The P300 has been applied in a wide array of clinical research settings

- However, data from a large-scale, blinded, randomized, prospective studies of ERP-guided therapy is still missing

- However, due with the decreasing costs of signal acquisition and data processing such research may soon be practical
ERPs in Neuropsychological Assessment

- Nowadays, there is a growing interest in the application of ERPs analyses for disease screening and as index of progression.
- For clinical purposes, they are elicited most commonly by auditory stimuli (it is strongest to avoid forced attention).
P300 in Schizophrenia

- Beginning in the 1970s attempts have been made to objectify various aspects of schizophrenia and its pathogenesis via analysis of the P300

- It has been proposed that the observed ERP abnormalities may reflect the observed defects in mnemonic binding and account in part for symptoms of reality-distortion (Guillem et al., 2003)
P300 in Schizophrenia

- P300 amplitude has been studied as a possible biological marker for or liability to schizophrenia (e.g., Duncan, 1988; Ford, 1999; Friedman & Squires-Wheeler, 1994; McCarley, Faux, Shenton, Nestor, & Adams, 1991)

- Roth and Cannon (1972) initially reported that component amplitude in patients with schizophrenia was smaller than in controls
Reduction of P300 in schizophrenia

Ford 1999 “Schizophrenia: The broken P300 and beyond”

P300 amplitude is lower in persons with schizophrenia
Reduction of P300 in schizophrenia

Figure 1. Grand-average event-related potentials (ERPs) elicited by a startling noise (105 dB SPL) are shown for three groups of subjects, normal age- and sex-matched controls, patients with schizophrenia, both medicated and unmedicated. The P300 at Pz is reduced in both groups of patients. Reprinted with permission from Pfefferbaum et al., 1989.

Ford 1999 “Schizophrenia: The broken P300 and beyond”
Relationship between P300 and clinical symptoms

P300 amplitude at Pz is plotted against Brief Psychiatric Rating Scale negative symptoms (motor retardation, blunted affect, mannerisms and posturing, and emotional withdrawal) in an auditory oddball paradigm.

Patients with more negative symptoms have smaller amplitude auditory P300 (this is also visible for visual stimuli).

Patients with greater thinking disturbances have smaller P300.

Ford 1999 “Schizophrenia: The broken P300 and beyond”
Fluctuations of P300 amplitude are associated with fluctuations in clinical severity

Figure 8. Event-related potentials (ERPs) at Fz, Cz and Pz to auditory target stimuli are shown for two patients with schizophrenia, studied at two times in their illness characterized by relatively good (lower Brief Psychiatric Rating Scale [BPRS] scores) and relatively bad (higher BPRS scores) clinical state. Even when his symptoms were relatively good, Mr. A had smaller P300s than did Mr. B when his symptoms were relatively severe. Nevertheless, P300 reflected clinical state in both patients, becoming larger when symptoms improved.
What does a small P300 mean?

- Is P300 small because of psychological and behavioral limitations?

Or..

- Is P300 small because of a neuroanatomical or neurochemical deficit that underlies any psychological manifestations?
Psychological and Neuroanatomical explanations of P300

- There are evidences that sustained attention is not consistent as in the controls indicating that a this reduction may be due to a limitation in the level of resources available or allocated to the task.

- Frontal and temporal gray matter volumes deficits may account for automatic P300 reduction.
P300 latency may also be applied clinically as a diagnostic tool and prognostic marker for recovery after cortical insult.

- A small study of patients with ischemic stroke has shown that changes in P300-latency correlated with subclinical damage to the right parietal lobe.

- Magnitude of alterations of P300 correlated with functional recovery after several months.
ERPs and Dementia

- They have been used to distinguish dementia from pseudodementia.
- More specifically, a prolongation in P300 latency is helpful in establishing the diagnosis of dementia with confidence.
- It is also possible to distinguish between different types of dementia by the pattern of electrophysiologic abnormalities and in particular by which components of the event-related potentials are delayed.
Pain Assessment in Patients with Impaired Cognition, especially Dementia

Objectives:

- The main objective of the Action is the development of a comprehensive and internationally agreed-on toolkit for assessing pain in adults with cognitive impairment, especially with dementia.

Secondary objectives:

- preparing appropriate dissemination strategies for both toolkit and guidelines
- analyzing and, if possible, correcting scientific, social and political barriers against dissemination
- encouraging cross-national learning and consideration of cross-national differences in this process
- increasing the overall awareness for the deleterious situation of pain sufferers with cognitive impairment in the public and in bodies of experts

Working Group 1 - Psychometrics and Algesimetry:
This WG will be responsible for evaluating the formal qualities of the existing scales and propose alternatives where necessary

Working Group 2 - Nursing and Care:
This WG will assess the clinical/practical usability and usefulness of the tools for preparing and monitoring pain management.

Working Group 3 - Clinical Evaluation and Epidemiology:
In this WG colleagues experienced in large-scale research and knowledgeable in the epidemiology of pain, dementia and similar conditions will participate. They will initiate and run the necessary clinical multi-centre and international population-based studies.

Working Group 4 - Experimental Evaluation:
In this WG neuroscientists, physiologists, pharmacologists and neuropsychologists will participate and together they will provide experimental tests for the validity of the tools and for physiological markers of pain, which do not solely rely on self-report.

Working Group 5 - Palliative Care:
This WG will focus on the particular challenge of assessing pain at the end of life when dementia is only one of many complicating factors for the quality of life.

Main Achievements:

- The assembled tools will cover pain in general as well as the most prevalent specific forms of pain (toothache, headache, joint and back pain, etc.).
- The various stages of the disorders will be considered; particularly, specific tools for palliative care will be integrated into the toolkit
- Publication of guidelines for assessment by use of the toolkit and of clinical and experimental validation studies
- Development of training programs for nursing and medical staff