

UNIVERSITE CATHOLIQUE DE LOUVAIN  
INSTITUT DE STATISTIQUE



# STATISTICAL TOOLS FOR THE ANALYSIS OF EVENT-RELATED POTENTIALS IN ELECTROENCEPHALOGRAMS.

Thèse présentée en vue de l'obtention du grade de Docteur en Sciences  
(orientation statistique) par:

**Céline Bugli**

Membres du jury:

Jérémie Bigot (*Université Paul Sabatier, Toulouse, France*)

Bruno Boulanger (*Eli Lilly*)

Prof. Paul Eilers (*Leiden University Medical Center, The Netherlands*)

Prof. Bernadette Govaerts

Prof. Philippe Lambert (*Promoteur*)

Prof. Jean-Marie Rolin (*Président du Jury*)

Prof. Léopold Simar

*Louvain-la-Neuve, Juin 2006*



à Christian et à nos projets



# STATISTICAL TOOLS FOR THE ANALYSIS OF EVENT-RELATED POTENTIALS IN ELECTROENCEPHALOGRAMS

Céline Bugli

Since its first use in human in 1929, the electroencephalogram (EEG) has become one of the most important diagnostic tool in clinical neurophysiology. However, their use in clinical studies is limited because the huge quantity of collected information is complicated to treat. Indeed, it is very difficult to have an overall picture of this multivariate problem. In addition to the impressive quantity of data to be treated, an intrinsic problem with electroencephalograms is that the signals are "contaminated" by body signals not directly related to cerebral activity. However, these signals do not interest us directly to evaluate treatment effect on the brain. Removing these signals known as "parasitic noise" from electroencephalograms is a difficult task.

We use data kindly made available by the pharmaceutical company Eli Lilly (Lilly Clinical Operations S.A., Louvain-la-Neuve, Belgium). Particular types of analyses were already carried out on these data, most based on frequency bands. They mainly confirmed the enormous potential of EEG in clinical studies without much insight in the understanding of treatment effect on the brain. The aim of this thesis is to propose and evaluate a panel of statistical techniques to clean and to analyze electroencephalograms.

The first method we propose to apply to electroencephalogram analysis is the alignment of curves named registration before determining the average. Indeed, when monitoring some continuous process on similar units (like patients in a clinical study), one often notices a typical pattern common to all curves but with variation both in amplitude and dynamics across curves. In particular, typical peaks could be shifted from unit to unit. This complicates the statistical analysis of sample of curves. For example, the cross-sectional average usually does not reflect a typical curve pattern: due to shifts, the signal structure is smeared or might even disappear.

Another of the presented approach is based on the preliminary linear decomposition of our signals in statistically independent signals. This decomposition provides on the one hand an effective cleaning method and on the other hand a considerable reduction of the quantity of information to be analyzed. The technique of decomposition of our signals in statistically independent signals is a well-known technique in physics primarily used to unmix sound signals. This technique is named Independent Component Analysis or ICA.

The last topic of EEG analysis presented in this thesis is functional ANOVA. The analysis of longitudinal curve data is a methodological and computational challenge for statisticians. Such data are often generated in biomedical studies. Most of the time, the statistical analysis focuses on simple summary measures, thereby discarding potentially important information. We propose to model these curves using non parametric regression techniques based on splines.

## Remerciements

Mes premiers remerciements vont à mon promoteur, le Professeur Philippe Lambert, qui tout au long de ces 5 dernières années a cru en moi et n'a jamais cessé de m'encourager. Ses conseils judicieux m'ont permis de progresser et de mener à bien cette thèse. Merci également à Bruno Boulanger qui est à l'origine de ce projet et à la firme Eli Lilly pour m'avoir fourni les données analysées. Je désire aussi remercier le Professeur Paul Eilers et Jérémie Bigot pour leur remarques judicieuses sur mon travail. Au cours de ces 5 années, j'ai eu l'occasion de discuter de mon travail avec un bon nombre de personnes. Merci pour ces discussions intéressantes à: Laurent Eysers, Edouard Ledent, le Professeur Jean-Michel Guérit, André Mouraux, le Professeur Pasquale Nardone, Florence Nicol et Alvaro Pereira.

Ma recherche a été rendue possible par une bourse de mécénat financée par Eli Lilly et par une bourse FSR. Ensuite, le Fonds National pour la Recherche Scientifique m'a accordé une bourse FRIA.

Je tiens à remercier le Professeur Jean-Marie Rolin, président de mon jury de thèse, ainsi que les Professeurs Bernadette Govaerts et Léopold Simar qui ont accepté de faire partie de mon comité d'accompagnement et qui ont suivi attentivement l'évolution de ma recherche au cours de ces années.

Enfin, je n'aurais certainement pas pu terminer cette thèse aussi sereinement, surtout lors de cette dernière année, sans le soutien de mes amis et de ma famille. Merci à Astrid, Bianca, Céline, Maria, Nancy, Oana, Réjanne pour leur oreilles attentives. Mon séjour à l'institut de statistique n'aurait jamais pu être le même sans vous. Merci à mes parents, à mon frère Quentin, à Christian, et à Elisa pour m'avoir supporté moralement sans jamais faiblir, pour tout leur amour et pour leur aide "logistique" qui m'a permis de consacrer un maximum de temps à ma recherche.



# Symbols

|                      |                                                    |
|----------------------|----------------------------------------------------|
| $f(\cdot)$           | function                                           |
| $F(\cdot)$           | Fourier transform                                  |
| $j$                  | imaginary symbol                                   |
| $Re(\cdot)$          | real part                                          |
| $Im(\cdot)$          | imaginary part                                     |
| $t_n$                | time points                                        |
| $y_i(t_n)$           | observation of function $y_i$ at time points $t_n$ |
| $h(\cdot)$           | warping function                                   |
| $D^q$                | derivative of order $q$ operator                   |
| $w(\cdot)$           | weight function                                    |
| $\lambda$            | smoothing parameter                                |
| $\tau$               | landmark                                           |
| $\mathcal{P}$        | set of powers                                      |
| $\mathbf{s}(t)$      | column vector                                      |
| $A$                  | mixing matrix                                      |
| $C$                  | separating matrix                                  |
| $E(\cdot)$           | expected value                                     |
| $p(\cdot)$           | probability density function                       |
| $\mathcal{I}$        | mutual information                                 |
| $\mathcal{X}$        | random variable                                    |
| $\mathcal{H}(\cdot)$ | entropy                                            |
| $\phi$               | characteristics function                           |
| $\kappa_k$           | cumulant of order $k$                              |
| $\kappa_4$           | kurtosis                                           |

---

|                             |                                               |
|-----------------------------|-----------------------------------------------|
| $\mu_k$                     | moment of order $k$                           |
| $Q^X(M)$                    | cumulant matrix                               |
| $a_{ij}$                    | element $(i, j)$ of matrix $A$                |
| $\delta$                    | Kronecker symbol                              |
| $\mathbf{E}$                | orthogonal matrix of eigenvectors             |
| $\mathbf{D}$                | diagonal matrix of eigenvalues                |
| $\mathcal{M}$               | set of matrices                               |
| $\phi_{ij}$                 | angle                                         |
| $d_n$                       | sum of the squared difference for $n$ sources |
| $r_n$                       | percentage of reconstruction for $n$ sources  |
| $\mathcal{S}^2$             | estimator of the variance                     |
| $\tilde{c}_{ij}$            | standardized element of the matrix $C$        |
| $\mu$                       | mean                                          |
| $\sigma^2$                  | variance                                      |
| $\phi_s$                    | element of a spline basis                     |
| $\Delta^d$                  | difference operator of order $d$              |
| $\otimes$                   | Kronecker product                             |
| $H$                         | hat matrix                                    |
| $m_{1-\alpha} (1 - \alpha)$ | quantile                                      |

# Contents

|                                                                       |             |
|-----------------------------------------------------------------------|-------------|
| <b>Abstract</b>                                                       | <b>iii</b>  |
| <b>Acknowledgements</b>                                               | <b>v</b>    |
| <b>Symbols</b>                                                        | <b>vii</b>  |
| <b>List of tables</b>                                                 | <b>xiii</b> |
| <b>List of figures</b>                                                | <b>xxii</b> |
| <b>Introduction</b>                                                   | <b>1</b>    |
| <b>1 Motivating study</b>                                             | <b>5</b>    |
| 1.1 The drugs . . . . .                                               | 6           |
| 1.2 Summary of the study set up . . . . .                             | 8           |
| 1.2.1 Study design . . . . .                                          | 8           |
| 1.2.2 The recording . . . . .                                         | 9           |
| 1.2.3 Auditory evoked related potential recording procedure . . . . . | 9           |
| 1.2.4 P300 . . . . .                                                  | 13          |
| 1.2.5 Computerization : the files . . . . .                           | 15          |
| 1.3 Conventional data analysis . . . . .                              | 15          |
| 1.3.1 Artifact removal . . . . .                                      | 16          |

---

|          |                                                                                                       |           |
|----------|-------------------------------------------------------------------------------------------------------|-----------|
| 1.3.2    | Fourier transform and frequency bands . . . . .                                                       | 16        |
| 1.3.3    | Statistical analysis . . . . .                                                                        | 18        |
| 1.3.4    | Results . . . . .                                                                                     | 19        |
| 1.4      | Conclusion . . . . .                                                                                  | 19        |
| <b>2</b> | <b>Independent Component Analysis of electroencephalograms</b>                                        | <b>21</b> |
| 2.1      | Introduction . . . . .                                                                                | 21        |
| 2.2      | Independent Component Analysis . . . . .                                                              | 22        |
| 2.2.1    | The ICA game . . . . .                                                                                | 24        |
| 2.2.2    | Problem statement and assumptions . . . . .                                                           | 28        |
| 2.2.3    | Comparison with Principal Component Analysis . . . . .                                                | 32        |
| 2.3      | Application to dimensionality reduction of electroencephalograms . .                                  | 33        |
| 2.3.1    | Dimensionality reduction . . . . .                                                                    | 34        |
| 2.3.2    | Choice of the dimensionality of the reduced space . . . . .                                           | 35        |
| 2.4      | Application to event-related potential modelling . . . . .                                            | 39        |
| 2.4.1    | Analysis of ERP using PCA <i>vs</i> ICA . . . . .                                                     | 41        |
| 2.4.2    | Analysis of P3a and P3b ICA components . . . . .                                                      | 49        |
| 2.5      | EEG cleaning with ICA . . . . .                                                                       | 51        |
| 2.5.1    | Classical EEG cleaning . . . . .                                                                      | 52        |
| 2.5.2    | ICA components and artifacts . . . . .                                                                | 55        |
| 2.5.3    | Automatic removal of artifactual components . . . . .                                                 | 56        |
| 2.5.4    | Our 2-step cleaning procedure . . . . .                                                               | 60        |
| 2.5.5    | Example . . . . .                                                                                     | 62        |
| 2.5.6    | Choice of the number of components computed in the first step                                         | 69        |
| 2.5.7    | Threshold for the correlation with the four complementary elec-<br>trodes in the first step . . . . . | 70        |
| 2.5.8    | Threshold for the kurtosis in the second step . . . . .                                               | 70        |
| 2.5.9    | Utility of 2 steps . . . . .                                                                          | 72        |
| 2.6      | Comparison of ICA components . . . . .                                                                | 74        |

---

|          |                                                                                                             |            |
|----------|-------------------------------------------------------------------------------------------------------------|------------|
| 2.6.1    | Comparison of components . . . . .                                                                          | 74         |
| 2.6.2    | Standardization . . . . .                                                                                   | 76         |
| 2.6.3    | Application to EEG . . . . .                                                                                | 84         |
| 2.7      | Conclusion . . . . .                                                                                        | 86         |
| <b>3</b> | <b>Registration of event-related potential curves</b>                                                       | <b>89</b>  |
| 3.1      | Introduction . . . . .                                                                                      | 89         |
| 3.2      | Curve registration problem . . . . .                                                                        | 92         |
| 3.3      | Classical curve registration techniques . . . . .                                                           | 94         |
| 3.3.1    | Choice of the template curve . . . . .                                                                      | 94         |
| 3.3.2    | Ramsay and Silverman's non parametric estimation of warping<br>function . . . . .                           | 94         |
| 3.3.3    | Marker registration and landmarks detection using wavelets .                                                | 97         |
| 3.4      | Curve registration using fractional polynomials . . . . .                                                   | 98         |
| 3.5      | Example: Growth acceleration . . . . .                                                                      | 101        |
| 3.6      | Application of fractional polynomials registration to EEG analysis . .                                      | 104        |
| 3.6.1    | Registration of ERP curves . . . . .                                                                        | 104        |
| 3.6.2    | Results of the ERPs registration . . . . .                                                                  | 108        |
| 3.6.3    | Discussion and improvement . . . . .                                                                        | 111        |
| 3.7      | Conclusion . . . . .                                                                                        | 115        |
| <b>4</b> | <b>Functional ANOVA with random patient effect: an application to<br/>event-related potential modelling</b> | <b>117</b> |
| 4.1      | Introduction . . . . .                                                                                      | 117        |
| 4.2      | Spline smoothing and regression . . . . .                                                                   | 118        |
| 4.2.1    | Literature review . . . . .                                                                                 | 118        |
| 4.2.2    | P-spline smoothing and functional ANOVA with P-splines . .                                                  | 119        |
| 4.3      | Results and limitations of a standard analysis . . . . .                                                    | 122        |
| 4.4      | Modelling random patient effects . . . . .                                                                  | 123        |

|          |                                                                         |            |
|----------|-------------------------------------------------------------------------|------------|
| 4.4.1    | Estimation of fixed effects . . . . .                                   | 124        |
| 4.4.2    | Prediction of random effects . . . . .                                  | 126        |
| 4.4.3    | Selection of the penalty parameters . . . . .                           | 126        |
| 4.4.4    | Confidence bands . . . . .                                              | 128        |
| 4.4.5    | Model selection . . . . .                                               | 130        |
| 4.4.6    | Computational details . . . . .                                         | 131        |
| 4.5      | Application to event-related potentials modelling . . . . .             | 133        |
| 4.5.1    | Practical issues and model selection . . . . .                          | 133        |
| 4.5.2    | Computation time and initial conditions . . . . .                       | 135        |
| 4.5.3    | Results . . . . .                                                       | 136        |
| 4.5.4    | Diagnostics . . . . .                                                   | 141        |
| 4.5.5    | Interpretation and discussion . . . . .                                 | 141        |
| <b>5</b> | <b>Software: EEG tool</b>                                               | <b>143</b> |
| 5.1      | Introduction . . . . .                                                  | 143        |
| 5.2      | How to run EEG tool . . . . .                                           | 143        |
| 5.3      | File menu . . . . .                                                     | 144        |
| 5.4      | Basic Operations menu . . . . .                                         | 148        |
| 5.5      | Analyses menu . . . . .                                                 | 153        |
|          | <b>Conclusion and future research</b>                                   | <b>161</b> |
|          | <b>Bibliography</b>                                                     | <b>165</b> |
|          | <b>Appendix</b>                                                         | <b>171</b> |
|          | Appendix A: Jade algorithm . . . . .                                    | 171        |
|          | Appendix B: Variance of the fixed and random effects . . . . .          | 178        |
|          | Appendix C: Computation of the correction factors in F-test . . . . .   | 179        |
|          | Appendix D: Construction of the design matrices for the ERP example . . | 180        |

# List of Tables

|     |                                                                                                                                                                                                                       |     |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 2.1 | Analysis of the amplitude and latency of the frontal component. . . . .                                                                                                                                               | 50  |
| 2.2 | Analysis of the amplitude and latency of the parietal component. . . . .                                                                                                                                              | 50  |
| 2.3 | Averaged correlations between the eliminated components and the 4 complementary electrodes when we computed 32 or 28 independent components. . . . .                                                                  | 69  |
| 2.4 | Percentage of components eliminated regards to different values of the correlation threshold. . . . .                                                                                                                 | 70  |
| 2.5 | Percentage of components eliminated in the first step with kurtosis smaller than 5. We use different threshold for the correlation in the first step and detail the results for each complementary electrode. . . . . | 72  |
| 2.6 | Percentage of increase in mean squared errors using the second proposed solution based on squared elements instead of absolute values. . . . .                                                                        | 83  |
| 4.1 | Mean of the estimations of $m_{0.95}$ for some of the effect curves, standard deviation and approximated ratio between simultaneous and pointwise confidence bands. .                                                 | 137 |



# List of Figures

|     |                                                                                                                                                                                                                                                                                                                                                                    |    |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 1.1 | Lorazepam molecule . . . . .                                                                                                                                                                                                                                                                                                                                       | 7  |
| 1.2 | Rivastigmine molecule . . . . .                                                                                                                                                                                                                                                                                                                                    | 7  |
| 1.3 | Leads implantation scheme : 20 electrodes, 10-20 system . . . . .                                                                                                                                                                                                                                                                                                  | 10 |
| 1.4 | Leads implantation scheme : 28 electrodes . . . . .                                                                                                                                                                                                                                                                                                                | 10 |
| 1.5 | Recording times marked by a cross . . . . .                                                                                                                                                                                                                                                                                                                        | 12 |
| 1.6 | Characteristic peaks in ERP . . . . .                                                                                                                                                                                                                                                                                                                              | 13 |
| 2.1 | ICA Game. . . . .                                                                                                                                                                                                                                                                                                                                                  | 25 |
| 2.2 | Original sources: $\mathbf{s}_1(t)$ and $\mathbf{s}_2(t)$ . . . . .                                                                                                                                                                                                                                                                                                | 26 |
| 2.3 | Observed Mixtures: $\mathbf{x}_1(t)$ and $\mathbf{x}_2(t)$ . . . . .                                                                                                                                                                                                                                                                                               | 27 |
| 2.4 | Components approximated by ICA: $\mathbf{u}_1(t)$ and $\mathbf{u}_2(t)$ . The original signals were very accurately estimated, up to a permutation and a multiplicative constant. . . . .                                                                                                                                                                          | 27 |
| 2.5 | Comparison between ICA and PCA. . . . .                                                                                                                                                                                                                                                                                                                            | 33 |
| 2.6 | Reconstruction without some independent components. . . . .                                                                                                                                                                                                                                                                                                        | 36 |
| 2.7 | (a) Squared difference between the original and the reconstructed data (for 1 EEG): With more than 7 components computed, the square difference becomes close to zero. (b) Percentage of reconstruction performed versus the number of components eliminated: With more 20 components eliminated, the percentage of reconstruction decreases dramatically. . . . . | 38 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 2.8  | (a) Histogram of the percentages of reconstruction performed with 8 components: 8 components reconstruct always more than 80% of the data. (b) The criterion for the choice of the principal components based on the eigenvalues: $p_{n'}$ for $n' = 1, \dots, 28$ (solid line) and the criterion based on the percentage of reconstruction: $r_{n'}$ for $n' = 1, \dots, 28$ (dashed line). According to the value of $p_{n'}$ we would choose only 3 principal components and 6 independent components to achieve a percentage of reconstruction of 80%. . . . . | 40 |
| 2.9  | (a) Averaging of electrode Cz (central area). (b) Averaging of the first principal component: this curve is highly correlated with the P300 curve. . . . .                                                                                                                                                                                                                                                                                                                                                                                                         | 42 |
| 2.10 | (a) Averaging of electrode Cz (central area). (b) Averaging of the independent components selected because they are highly correlated with the P300 curve. . .                                                                                                                                                                                                                                                                                                                                                                                                     | 44 |
| 2.11 | The P300 peak occurs earlier for the frontal component (solid line, left topographic map) than for the parietal component (dashed line, right topographic map). . . .                                                                                                                                                                                                                                                                                                                                                                                              | 45 |
| 2.12 | Topographic map of the first principal component. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 45 |
| 2.13 | (a) Signal from electrode Fz + and - a coefficient $\times$ the "frontal" component: the largest differences in the P3a peak area. (b) Signal from electrode Pz + and - a coefficient $\times$ the "parietal" component: the largest differences in the P3b peak area. . .                                                                                                                                                                                                                                                                                         | 47 |
| 2.14 | The most important difference between ERP curve computed on data (solid line) and on data reconstructed from 8 independent components (dashed line). This difference is still very small. . . . .                                                                                                                                                                                                                                                                                                                                                                  | 48 |
| 2.15 | Extreme values in EEG caused by material problem (like bad electrode). . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 53 |
| 2.16 | Abnormal trend in EEG. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 53 |
| 2.17 | EEG contaminated by electrocardiogram. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 54 |
| 2.18 | Artifact generated by eye blink. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 54 |
| 2.19 | Artifact generated by muscular activity. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 54 |
| 2.20 | An ICA Component (top curve) corresponding to the horizontal movement of the left eye (bottom curve). We have the same perturbation at the same moment. . .                                                                                                                                                                                                                                                                                                                                                                                                        | 56 |
| 2.21 | Component corresponding to eye blink. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 58 |
| 2.22 | Distribution of the artifact compared with the standard normal distribution. . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 59 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |    |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 2.23 | Histogram of the number of components eliminated in the first step (maximum 4 because we have 4 complementary electrodes). . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 61 |
| 2.24 | Histogram of the number of components eliminated in the second step. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 63 |
| 2.25 | The two-step cleaning method. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 63 |
| 2.26 | 4 classical electrodes (named Fp1, Fp2, F7 and F2) with systematic perturbations between 5.5 and 6 sec and between 8 and 8.5 sec. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 64 |
| 2.27 | The four complementary electrodes at the same moment. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 65 |
| 2.28 | Histogram of the correlation of the 32 components with the horizontal movements of the left eye. There is only one component which has correlation larger than 0.7 with the horizontal movement of the left eye. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 66 |
| 2.29 | The 2 first signals of the original data (thin line; electrodes Fp1 and Fp2) and the reconstructed data without the component corresponding to the horizontal movement of the left eye (thick line). There is only a small correction. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 67 |
| 2.30 | The original data (thin line) and the reconstructed data (thick line) after the 2 steps of cleaning: the 2 main perturbations disappeared. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 68 |
| 2.31 | Percentage of components eliminated regards to different values of the correlation's threshold. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 71 |
| 2.32 | Artifacts with kurtosis between 4 and 5. These artifacts are not detected by our 2-steps method. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 73 |
| 2.33 | (a) The 2 independents sources for dataset $A$ : $\mathbf{s}_1^{(A)}(t)$ and $\mathbf{s}_2^{(A)}(t)$ . (b) The 2 mixtures of the sources in dataset $A$ : $\mathbf{x}_1^{(A)}(t)$ and $\mathbf{x}_2^{(A)}(t)$ . (c) The 2 estimated independent components for dataset $A$ : $\hat{\mathbf{s}}_1^{(A)}$ and $\hat{\mathbf{s}}_2^{(A)}$ . (d) The 2 independents sources for dataset $B$ ( $\mathbf{s}_1^{(B)}(t)$ and $\mathbf{s}_2^{(B)}(t)$ , dashed line) compared with the 2 sources for dataset $A$ ( $\mathbf{s}_1^{(A)}(t)$ and $\mathbf{s}_2^{(A)}(t)$ , solid line). (e) The 2 mixtures of the sources for dataset $B$ : $\mathbf{x}_1^{(B)}(t)$ and $\mathbf{x}_2^{(B)}(t)$ . (f) The 2 estimated independent components for dataset $B$ : $\hat{\mathbf{s}}_1^{(B)}$ and $\hat{\mathbf{s}}_2^{(B)}$ . . . . . | 75 |
| 2.34 | (a) The standardized components (dataset $A$ in solid line and $B$ in dashed line). (b) The 2 sources $\mathbf{s}_1^{(B)}$ and $\mathbf{s}_2^{(B)}$ (in dashed lines) generated as the 2 sources $\mathbf{s}_1^{(A)}$ and $\mathbf{s}_2^{(A)}$ (solid line) with rescaling and dephasing. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 80 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 2.35 | (a) Example of frontal sources. (b) Example of parietal sources. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 84  |
| 2.36 | (a) Frontal P3a components under placebo without standardization. (b) Same components as in (a) after standardization. (c) Frontal P3a components under treatment without standardization: before administration (solid line), 5.5 hours (after Lorazepam reached its peak plasmatic concentration, in dashed line) and 25.5 hours after the Lorazepam administration (when Lorazepam concentration in the plasma is almost null, in dot-dashed line). (d) Same components as in (c) after standardization. (e) ERP curves computed directly on electrode CZ: before administration (solid line), 5.5 hours (after Lorazepam reached its peak plasmatic concentration, in dashed line) and 25.5 hours after the Lorazepam administration (when Lorazepam concentration in the plasma is almost null, in dot-dashed line). | 85  |
| 3.1  | (a) Variation in amplitude between curves. (b) Variation in dynamics between curves. (c) Variation in amplitude and in dynamics between curves. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 90  |
| 3.2  | (a) Sample of curves with variation both in amplitude and dynamics. (b) Registered curves. (c) Mean of the curves (dashed line) and of the aligned curves (solid line).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 91  |
| 3.3  | Left panel: 2 warping functions. Right panel: The dashed and dot-dashed curves correspond to the warping functions in the left panel applied on the template curve (solid line). . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 93  |
| 3.4  | Target function $\hat{y}(t)$ evaluated as the mean of the original curves (solid line) and as the mean of the registered curves after one step (dashed) and two steps (dot-dashed lines). . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 95  |
| 3.5  | Some possible shapes of warping functions estimated using fractional polynomials.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 99  |
| 3.6  | The dashed curve corresponds to the average acceleration for boys; the solid curve is the average acceleration curve for girls; (a) the dot-dashed curve correspond to the average acceleration for boys registered using Ramsay and Silverman non parametric estimation of the warping function. (b) the dot-dashed curve correspond to the average acceleration for boys registered using alignment of landmarks (maxima and minima) located using wavelets. . . . .                                                                                                                                                                                                                                                                                                                                                    | 102 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |     |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 3.7  | (a) The dashed curve corresponds to the average acceleration for boys, the solid curve is the average acceleration curve for girls and the dot-dashed curve correspond to the average acceleration for boys registered using our method of alignment based on fractional polynomials. (b) Warping functions for registering the boys' average acceleration to that of the girls (Ramsay and Silverman non parametric estimation in dot-dashed line, landmarks registration in solid line and our method of alignment based on fractional polynomials in dashed line). Because boys mature more slowly, the warping function is above the diagonal, shown as a solid line. . . . . | 103 |
| 3.8  | Two ERP curves to register: target function is the solid line. . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 104 |
| 3.9  | (a) Registered ERP curves using Ramsay and Silverman non parametric method (dot-dashed line). The target function is the solid line and the curve to align is the dashed line. (b) ERP curves registered using alignment of inflection points located using wavelets. The target function is the solid line and the curve to align is the dashed line. . . . .                                                                                                                                                                                                                                                                                                                    | 105 |
| 3.10 | (a) Registered ERP curves using our method of alignment based on fractional polynomials (dot-dashed line). The target function is the solid line and the curve to align is the dashed line. (b) The corresponding warping functions estimated using Ramsay and Silverman non parametric method (dashed line), using alignment of inflection points located using wavelets (dot-dashed line) and using our method of alignment based on fractional polynomials (thin solid line). Because the aligned curves are right shifted compared with the original curve, the warping functions are below the diagonal, shown as bold solid line. . . . .                                   | 106 |
| 3.11 | Comparison of the registered functions using Ramsay and Silverman non parametric method (dashed line), estimated using the alignment of inflection points with wavelets (dot-dashed line) and using fractional polynomials (solid line). . . . .                                                                                                                                                                                                                                                                                                                                                                                                                                  | 107 |

- 
- 3.12 (a) An example of registration of one curve under treatment on the corresponding curve under placebo: the original curve under treatment is in dashed line, the target curve (curve under placebo) in solid line and the registered curve in dot-dashed line. (b) The corresponding warping function (thin solid line). Because the aligned curve is left shifted compared with the original curve, the warping function is above the diagonal (almost everywhere), shown as bold solid line. . . . . 109
- 3.13 Warping functions resulting from the registration of the curves under treatment on the curves under placebo for EEG number 1 (before Lorazepam administration, upper left panel), 6 (2.5 h after administration, upper right panel), 8 (4.5 h after administration, lower left panel) and 12 (25.5 h after administration, lower right panel), each curve in a frame corresponding to one of the 15 subjects. . . . . 110
- 3.14 An example of the bad registration of one curve under treatment on corresponding curve under placebo: the P300 peak under treatment is sometimes aligned to the P200 peak under placebo (The solid line is the curve under placebo, the dashed line is the curve under treatment) . . . . . 112
- 3.15 An example of the bad registration of one curve under treatment on corresponding curve under placebo: the P300 peak under placebo is sometimes aligned with the P200 peak under treatment (The solid line is the curve under placebo, the dashed line is the curve under treatment and the dot-dashed line is the registered curve.) 112
- 3.16 An example of the improved registration of one curve under treatment on corresponding curve under placebo. The solid line is the curve under placebo, the dashed line is the curve under treatment and the dot-dashed line is the registered curve. . 113
- 3.17 Warping functions result of the improved registration of the curves under treatment on the curves under placebo. . . . . 114

- 
- 4.1 (a) Mean curve under placebo (solid line), pointwise confidence bands (light grey) and simultaneous confidence bands (dark grey). (b) Curve representing treatment effect (solid line), pointwise confidence bands (light grey) and simultaneous confidence bands (dark grey). (c) Mean curve under treatment (solid line), pointwise confidence bands (light grey) and simultaneous confidence bands (dark grey). We must still add the concentration effect. . . . . 138
- 4.2 (a) Mean curve under treatment. (b) Concentration effect curves for level 4 (corresponding to the concentration of Lorazepam for period 6 i.e. 2.5 hours after Lorazepam administration, thin solid line) and level 5 (corresponding to the concentration of Lorazepam for period 7 i.e. 3.5 hours after Lorazepam administration, bold solid line) and the corresponding pointwise confidence bands. (c) The sum of the mean curve in (a) and the concentration effect curves in (b) gives the mean curve under Lorazepam for concentration level 4 (thin solid line) and 5 (bold solid line) and the pointwise confidence bands (dark grey for level 4 and light grey for level 5): the P300 peak almost disappears. . . . . 139
- 4.3 (a) Mean curve under treatment. (b) Concentration effect curves for level 1 (corresponding to the concentration of Lorazepam for period 1,2 and 3 i.e. before Lorazepam administration, thin solid line) and level 10 (corresponding to the concentration of Lorazepam for period 12 i.e. 25.5 hours after Lorazepam administration, bold solid line) and the corresponding pointwise confidence bands. (c) The sum of the mean curve in (a) and the concentration effect curves in (b) gives the mean curve under Lorazepam for concentration level 1 (thin solid line) and 10 (bold solid line) and the pointwise confidence bands (dark grey for level 1 and light grey for level 10): the curve is very similar to the mean curve under placebo (pointwise confidence interval in black). . . . . 140
- 4.4 (a) Q-Q plot of the residuals: slight deviation from normality. (b) Plots of the residuals against predicted values for subject 1, 8 10 and 12: no evidence of non homogeneity of variance. . . . . 141

|      |                                                         |     |
|------|---------------------------------------------------------|-----|
| 5.1  | Main window of the EEG tool. . . . .                    | 144 |
| 5.2  | Main window of the EEG tool. . . . .                    | 144 |
| 5.3  | 'Open .MAT dialog window. . . . .                       | 145 |
| 5.4  | Browse window. . . . .                                  | 145 |
| 5.5  | 'Save workspace' dialog window. . . . .                 | 146 |
| 5.6  | 'Import data' dialog window. . . . .                    | 147 |
| 5.7  | 'Export data' dialog window. . . . .                    | 147 |
| 5.8  | 'Basic Operations' menu. . . . .                        | 148 |
| 5.9  | 'ERPs computation' dialog window. . . . .               | 149 |
| 5.10 | 'ERPs visualization' dialog window. . . . .             | 150 |
| 5.11 | An example of ERP. . . . .                              | 151 |
| 5.12 | 'Independent Component Analysis' dialog window. . . . . | 152 |
| 5.13 | 'Topoplot' dialog window. . . . .                       | 153 |
| 5.14 | Example of topoplot. . . . .                            | 154 |
| 5.15 | Analyses Menu. . . . .                                  | 154 |
| 5.16 | 'Cleaning' dialog window. . . . .                       | 155 |
| 5.17 | 'Functional ANOVA' dialog window. . . . .               | 157 |
| 5.18 | 'Smoothing parameter' dialog window. . . . .            | 158 |
| 5.19 | Example of effect curve with confidence bands. . . . .  | 158 |
| 5.20 | 'Registration' dialog window. . . . .                   | 159 |
| 5.21 | JADE algorithm. . . . .                                 | 177 |

# Introduction

Since its first use in human in 1929, the electroencephalogram (EEG) has become one of the most important diagnostic tool in clinical neurophysiology. However, their use in clinical studies is limited because the huge quantity of collected information is complicated to treat. Indeed, it is very difficult to have an overall picture of this multivariate problem.

In addition to the impressive quantity of data to be treated, an intrinsic problem with electroencephalograms is that the signals are "contaminated" by body signals not directly related to cerebral activity. For example, one can locate electric signals corresponding to heart rate or muscular movements such as eyes blinks. However, these signals are not directly interesting to evaluate treatment effect on the brain. Removing these signals known as "parasitic noise" from electroencephalograms is a difficult task. A current practice is to eliminate the parts of the recording presenting too many disturbances. Obviously this is not advisable from a statistical point of view because one is likely to lose significant information on treatment effect. We shall see thereafter a proposal for a more correct method of cleaning.

We use data kindly made available by the pharmaceutical company Eli Lilly<sup>1</sup>. These electroencephalograms were recorded during a cross-over study aiming to observe the effects of a drug known for its positive action on the memory during the treatment of Alzheimer's disease. The goal of this study was to determine the visible effects of a drug on EEG, the long-term effects on memory having already been shown

---

<sup>1</sup>Lilly Clinical Operations S.A., Louvain-la-Neuve, Belgium.

before.

Particular types of analyses were already carried out on these data, most based on frequency bands. They mainly confirmed the enormous potential of EEG in clinical studies without much insight in the understanding of treatment effect on the brain. The aim of this thesis is to propose and evaluate a panel of statistical techniques to clean and to analyse electroencephalograms. These statistical techniques could be classified into 3 groups: registration, Independent Component Analysis and functional ANOVA.

The first method we propose to apply to electroencephalogram analysis is based on the preliminary linear decomposition of our signals in statistically independent signals. This decomposition provides on the one hand an effective cleaning method and on the other hand a considerable reduction of the quantity of information to be analysed. The technique of decomposition of our signals in statistically independent signals is a well-known technique in physics primarily used to unmix sound signals. This technique is named Independent Component Analysis or ICA.

Another of the presented approach is the alignment of curves named registration before determining the average. Indeed, when monitoring some continuous process on similar units (like patients in a clinical study), one often notices a typical pattern common to all curves but with variation both in amplitude and dynamics across curves. In particular, typical peaks could be shifted from unit to unit. This complicates the statistical analysis of sample of curves. For example, the cross-sectional average usually does not reflect a typical curve pattern: due to shifts, the signal structure is smeared or might even disappear.

The last topic of EEG analysis presented in this thesis is functional ANOVA. The analysis of longitudinal curve data is a methodological and computational challenge for statisticians. Such data are often generated in biomedical studies. Most of the time, the statistical analysis focuses on simple summary measures, thereby discarding potentially important information. We propose to model these curves using non parametric regression techniques based on splines.

The thesis is organized as follows.

Chapter 1 is devoted to the presentation of the motivating study and to its analysis using conventional methods.

In Chapter 2, we show that ICA is useful in EEG analysis. We first present the concept of ICA and compare it to Principal Component Analysis (PCA). We present this technique from a statistical point of view and compare the performances of PCA and ICA in 2 aspects of EEG analysis: the first one is the reduction of dimensionality ; the second one is the modelling of an interesting characteristic of EEG signals named event related potential (ERP). We conclude the chapter by proposing a standardization technique of ICA components.

Chapter 3 presents the technique of registration. We first explain the curve registration problem. Different registration techniques are exposed: the non parametric method of Ramsay and Silverman (1997) and marker registration using landmark detection with wavelets (Bigot, 2003). We propose a new registration method based on the parametric estimation of the warping function using fractional polynomials. We illustrate these 3 methods on human growth acceleration curves. We conclude with the registration of EEG using fractional polynomials.

Chapter 4 is devoted to Functional ANOVA. We propose to use functional ANOVA with P-splines to evaluate treatment effects on EEG. After a discussion of the limitations of standard analyses, we introduce a mixed model with random subject effect to analyse the ERP curves. Estimation of the fixed effects, prediction of the random effects and specification of the smoothing parameters are described. Pointwise and simultaneous confidence bands are obtained with model selection. Some computational issues are also discussed. We conclude by applying functional ANOVA with P-splines to the EEG study.

Chapter 5 is devoted to the presentation of a user friendly software named "EEG tool" allowing to use all the methods presented in the previous chapters. EEG tool is a graphical user interface (GUI) with point-and-click features developed using GUIDE, the MATLAB Graphical User Interface Development Environment.

We conclude the thesis with some concluding remarks and possible directions for future research projects.

# Chapter 1

## Motivating study

The goal of our work is to detect and to quantify the effects of a drug on the brain through the analysis of electroencephalograms (EEG). The EEG is a time-varying signal recorded from electrodes attached to the scalp of a human (or sometimes animal) subject. The signal arises from action potentials (short-lasting changes in potential difference) within the neural cells of the brain, and, as such, are a measure of brain activity. Identifiable features of the EEG can be used to differentiate between the brain states of the patient, for example, during sleep, quiet wakefulness, etc. In this work, we shall analyse electroencephalograms provided by Eli Lilly and recorded (by Forenap-pharma<sup>1</sup>) during a placebo-controlled four-way cross-over study. The purpose of this study is to explore the effects of two products on the cognitive functions. These two products are Rivastigmine and Lorazepam. Rivastigmine has a positive effect on the memory whereas high concentrations of Lorazepam cause disorders of the memory.

Many psychiatric and neurological disorders involve significant or disabling cognitive impairment. Marketed products for the treatment of these disorders typically provide at best modest improvements in cognition when they are used. Well-tolerated

---

<sup>1</sup>Centre Hospitalier de Rouffach, France

and efficient drugs to improve the state of all the patients or to prevent his/her cognitive decline are desperately needed. Unfortunately, it is presently difficult to ascertain the potential efficacy of experimental drugs except by the construct of expensive and time-consuming studies in patients with cognitive deficits. The present study is motivated by the desire to validate clinical experimental methodology and instrumentation for application in normal volunteers to assist in the selection of experimental drugs for further evaluation in efficacy studies. We hope that the analysis of electroencephalograms will allow to detect a treatment effect directly after an injection (or just some hours after) whereas, generally, the effect on cognition is only visible in the long run.

## 1.1 The drugs

Lorazepam (see Figure 1.1) is extensively used as a sedative and anti anxiety agent in clinical practice. Peak plasma levels are attained 3 hours after oral administration (in most studies, the peak effect of Lorazepam occurred approximately 3 hours after oral dose intake) and the elimination half-life is 14 hours after administration. Sedation as well as impaired performance and cognition have been largely documented, using pharmacoelectroencephalogram, evoked potential recording and neuropsychological tests, in healthy volunteers after single oral administration. Lorazepam's impact on cognition, behaviour and performance are temporary, and disappear with time, as the drug is eliminated from the body.

Rivastigmine (see Figure 1.2) is being marketed for the symptomatic treatment of Alzheimer's disease. Early clinical studies in healthy male subjects have shown that Rivastigmine is rapidly absorbed : peak plasma concentrations are reached after approximately 1 hour. The elimination half-life is approximately 1.5 hours. Beneficial effects have not been shown to persist beyond the end of treatment with Rivastigmine and as such it is believed that the drug's effects are only temporary.

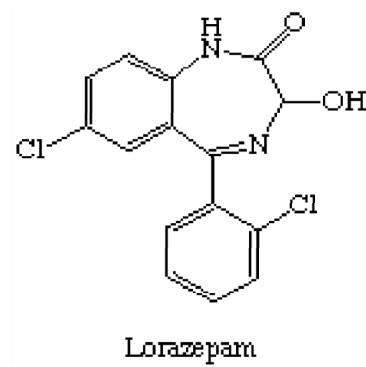


Figure 1.1: Lorazepam molecule

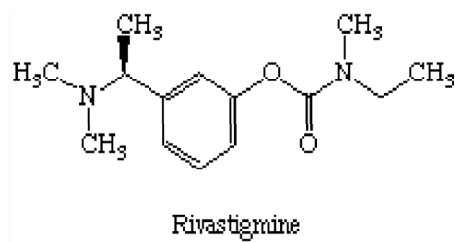


Figure 1.2: Rivastigmine molecule

## 1.2 Summary of the study set up

### 1.2.1 Study design

This is a randomised, double-blind, placebo-controlled four-way cross-over study performed with 16 healthy male subjects (4 subjects per sequence). The study is designed to assess and to compare the effect of Rivastigmine and Lorazepam versus placebo, on some selected neuropsychological test, EEG and evoked potential brain mapping. However, when we will analyse the data in the following, we will use data for only 15 out of the 16 subjects because one of them has too many missing data.

Four periods of 2.5 days are scheduled, separated by a wash-out period of at least 7 days: in each period, study medication will be randomly administered once a day to each volunteer according to following cross-over design:

| Sequence | Period |   |   |   |
|----------|--------|---|---|---|
|          | 1      | 2 | 3 | 4 |
| 1        | A      | B | C | D |
| 2        | B      | D | A | C |
| 3        | C      | A | D | B |
| 4        | D      | C | B | A |

In each period, Rivastigmine 3 mg or placebo will be administered as a single oral dose at 9:00 am followed by Lorazepam (2mg) or placebo one hour later as described below:

| Treatment   | Drugs                            |
|-------------|----------------------------------|
| Treatment A | Rivastigmine 3mg - Placebo       |
| Treatment B | Placebo - Placebo                |
| Treatment C | Rivastigmine 3mg - Lorazepam 2mg |
| Treatment D | Placebo - Lorazepam 2mg          |

The impact of Lorazepam on cognition allow to simulate effects of the Alzheimer's disease. The combination of Lorazepam and Rivastigmine will then allow to simulate

effects of Rivastigmine on a patient with Alzheimer's disease even if we work with healthy patients.

### 1.2.2 The recording

Any recording system for the EEG requires the following components :

1. Electrodes : Attached to the scalp of the subject.
2. Amplifiers : The amplitude of the input signals from the electrodes is usually in the range 10-100  $\mu\text{V}$  and high input impedance differential amplifiers are used to boost this level.
3. Recording unit : Used to keep a permanent record of the EEG signal.

The same setup and the same reference electrodes were always used. Twenty-eight EEG leads are recorded using an ear linked reference as well as 4 artifacts channels (Jasper, 1958). These four signals correspond to the heart rate, the horizontal movements of the left eye and the vertical movements of both eyes. These four channels are used for the detection of eye movements, muscle activity and other potential causes of artifacts.

Generally, an EEG is recorded from scalp electrodes placed according to the 10-20 International System. In this method, 20 electrodes are placed to cover the scalp evenly. Position of the 20 electrodes is showed in Figure 1.3. Here, eight electrodes were added to obtain 28 electrodes. One can see the position of all electrodes in Figure 1.4.

### 1.2.3 Auditory evoked related potential recording procedure

The EEG measures the electric cerebral activity. That electric activity is present in a spontaneous way. It is affected by external stimuli (e.g. tone or light flash). Consequently, any modification of the cerebral activity involves a modification of the

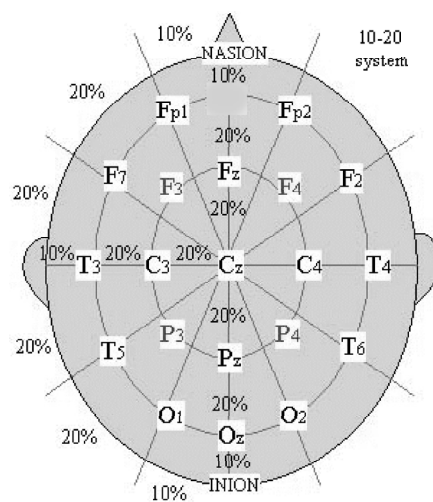


Figure 1.3: Leads implantation scheme : 20 electrodes, 10-20 system

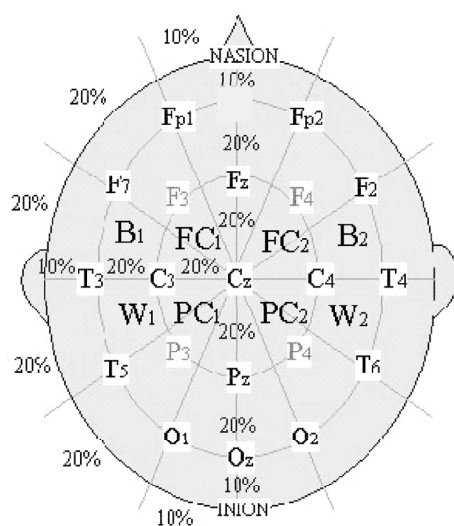


Figure 1.4: Leads implantation scheme : 28 electrodes

EEG. EEGs are usually measured with the subject sitting quietly not performing any specific task (the so-named resting state). When stimuli are presented to the subject, such as a flashing light, the recorded EEG is named an evoked potential (EP); when the subject is asked to perform some task in response to the stimuli, such as recalling a series of words<sup>2</sup>, the recorded EEG is named an Event Related Potential (ERP). The changes in the EEG are then induced either by the perception of the sensory impulses at the cerebral level, or by the preparation of a movement, or by the cognitive response of the brain to these stimuli. ERP can be visualised during a short period following the stimulation time, with a response pattern which is more or less predictable under similar conditions. We name an ERP episode, the EEG signals observed during the seconds following a stimulation. The amplitude of ERP is low compared to the ongoing EEG. Hence, it is common practice to take the average of several ERP episodes in order to increase the signal to noise ratio merely enabling to visualize the evoked activity. The reason for averaging is that ERP can be visualised during a short period following the stimulation time, with a response pattern which is more or less predictable under similar conditions (Quiroga, 1998).

There are mainly three modalities of stimulation :

1. Auditory : stimuli are single tones of a determined frequency.
2. Visual : stimuli are produced by a single light or by the reversal of a pattern.
3. Somatosensory : stimuli are elicited by electrical stimulation of peripheral nerves.

Sequences of stimuli are organised according to paradigms in order to study the responses under different tasks. The most widely used paradigms are :

- No-task evoked potential : Subjects are relaxed and instructed to perceive the stimuli without performing any task.

---

<sup>2</sup>Here, the subject count the number of stimuli tones

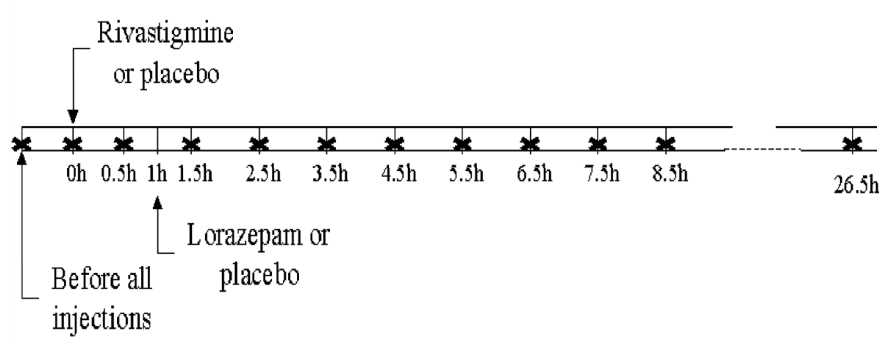


Figure 1.5: Recording times marked by a cross

- Oddball paradigm : Two different stimuli are presented in a pseudo-random order : a frequent non-target stimulus and a deviant stimulus named the target. Subjects are instructed to pay attention to the appearance of the target stimulus.

Here, we use the data from an auditory evoked related potential experiment. This means that the EEG were recorded while the subjects were submitted to auditory stimuli and is asked to perform some task in response to the stimuli. The 12 records were obtained before and during each injection of Rivastigmine (or placebo) and 0.5, 1.5, 2.5, 3.5, 4.5, 6.5, 7.5, 8.5 and 26.5 h after the Rivastigmine (or placebo) administration. Note that Lorazepam (or the placebo) is administered 1 hour after the Rivastigmine (or placebo) administration (Figure 1.5). Each EEG is recorded during 3 minutes at a frequency of 256Hz. This frequency could seem high, involving a huge quantity of data. However, signals recorded at lower frequency would not allow to detect specific peaks (for example the P300 peak presented in Section 1.2.4): maximum of the peak should then be difficult to identify because the peak should be displayed as a plateau.

The standard auditory "oddball" paradigm is used. Subjects have to listen to

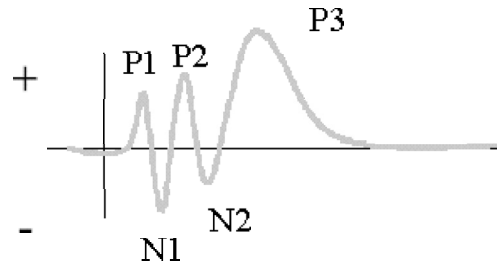


Figure 1.6: Characteristic peaks in ERP

a series of two tones, with a frequency of 500Hz for frequent tones and a frequency of 2000Hz for infrequent tones. Subjects are asked to count infrequent tones. The tones are presented through earphones with a duration of 50 ms at 85 db. The tones are presented in a randomised way for intervals ranging from 1s to 1.9s and with the frequent (infrequent) tones presented in 85% (15%) of the record duration (130 on average in order to have 20 infrequent tones for which the subjects have to count). Each EEG is recorded with a sampling frequency of 250 Hz for the 28 electrodes.

### 1.2.4 P300

The averaged ERP episodes present some well-known peaks. The ones usually pointed are the P100 or P1 (peak latency approximately 100 ms after stimulation), the P200 or P2 ( $\sim 200$  ms), and the P300 or P3 ( $\sim 300$  ms) peaks (Figure 1.6). The P100 peak can be observed after non-target and target stimulation. Since this peak does not depend on the task, it has relatively short delay ( $\sim 100$ ms). This delay is named latency. P200 and P300 are typically only found after the target stimulation. Since these responses are task dependent and have long latency, they are traditionally related to cognitive processes such as signal matching, decision making, attention, memory updating, etc. The P300 peak has the highest amplitude and, hence, is easier to detect.

The P300 peak is a good indicator of brain performance. It is often studied by neurophysiologists as amplitude changes or delay in the occurrence of the peak are signs of memory problem like with Alzheimer's disease or indication that a drug is affecting the brain. We shall focus on the analysis of the P300 peak to determine a treatment effect.

The P300 component of the event-related brain potential (ERP) is considered as a "cognitive" neuroelectric phenomenon generated during physiological tasks during which subjects wait and discriminate stimuli that differ from one another in some way. Such a discrimination produces a relatively large (10 - 20  $\mu\text{V}$ ), positive-going waveform with a modal latency of about 300 ms in young adult elicited with auditory stimuli. P300 is related to cognitive processes such as attention allocation and activation of immediate memory. Hence, interest in P300 has expanded dramatically because of its relevance to assess cognitive function in a variety of basic and applied circumstances.

The theoretical interpretation of P300 is based on neurophysiological investigations of the brain mechanisms underlying its generation, evidence from psychometric experiments and biological influences on central nervous system (CNS) function. A major theoretical interpretation of P300 amplitude is that it indexes brain actions stemming from tasks that are required in the maintenance of working memory when the mental model or context of the stimulus environment is updated. P300 can be considered as a manifestation of the CNS activity involved with the processing of new information when attention is solicited to update memory representations.

Under the oddball paradigm, there are probably two components in the P300 wave (Baudena et al., 1995). These two components are merged so that we generally cannot detect the two corresponding peaks : we only observe the peak of the mixture named P300 until now. The first one of these components presents a peak around 250 ms after stimulus. This component named P3a has its maximum amplitude in the frontal area. The second component presents a peak around 350 ms after stimulus. This component named P3b has its maximum amplitude in the parietal area. P3a corresponds to the stimulus detection. It can be linked up to attention

allocation brought by an unexpected stimulus. P3b is associated with discrimination, classification, selection and decision (Polish and Kok, 1995).

In the following, we will analyse ERP curves and more specifically the P300 peak. For each of the 15 subjects<sup>3</sup>, each of the 2 considered treatments<sup>4</sup> and each of the 12 period of recording of the subject i.e. for each of the 360 EEG records<sup>5</sup>, we compute for each of the 28 electrodes an ERP curve as the average of the EEG signal during 400 ms after each auditory stimuli. Because of missing EEG records, we have only 161 ERP curves for each of the 28 electrodes.

### 1.2.5 Computerization : the files

The files containing the data were directly recorded by the NeuroScan monitor used in this study. We cannot open these files (extension '.cnt') directly without an ad-hoc software. We must use an algorithm to convert the files in ASCII format. To do that we use a Matlab package. You can find this package and more details about this on the web site :

<http://eeg.sourceforge.net>.

## 1.3 Conventional data analysis

In this section, we shall present techniques conventionally used to analyse that kind of data. We shall motivate the need for data cleaning. The Fourier transform and its usefulness to analyse EEG data will be determined. Finally, one will find a description of the conclusions of the statistical analysis already performed for this study.

---

<sup>3</sup>One of the 16 subject had too many missing values and was removed from the data.

<sup>4</sup>We are only interested by the comparison between placebo and Lorazepam i.e. treatment B and D defined in Section 1.2.1.

<sup>5</sup> $15 \times 2 \times 12 = 360$

### 1.3.1 Artifact removal

As explained in detail in Chapter 2, EEG data are corrupted by electrical signals such as heart rate or muscles movements. Due to the very low amplitude of the EEG signals, artifacts<sup>6</sup> often contaminate the recordings, thereby restricting or making impossible any direct analysis or interpretation. These artifactual signals can hide the treatment effect. Hence, we want first to remove these artifacts before performing the EEG analysis. Usually and for this study in particular, EEG analysts use a first filtering: only the part of the signal between 0.5 and 70 Hz is kept. After this filtering, they use a visual removal artifacts procedure. That means that the parts of recording presenting visually too much perturbations are discarded leading to a substantial data loss. An alternative automatic filtering technique will be proposed in Chapter 2. It makes use of the 4 artifact channels (see section 2.5).

### 1.3.2 Fourier transform and frequency bands

The Fourier transform is the mathematical translation of time-varying signals into frequency-varying signals. This transformation has been found especially useful for problem simplification in many fields of scientific interest. The Fourier transform of a function  $f(t)$  is defined by the expression:

$$F(\omega) = \int_{-\infty}^{\infty} f(t)e^{-j\omega t} dt$$

where  $e^{-j\omega t}$  is the negative imaginary exponential defined by:

$$e^{\pm j\omega t} = \cos \omega t \pm j \sin \omega t$$

with  $j^2 = -1$ . The inverse Fourier transform is defined by:

$$f(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} F(\omega)e^{j\omega t} d\omega.$$

---

<sup>6</sup>Artifacts are alterations of the EEG due to head movements, blinking, muscle and heart activity, etc.

This expression state that  $f(t)$  can be decomposed in an infinite sum (integral) of complex exponentials (i.e. sine waves).

We can construct a low-pass filtering process by using the properties of the Fourier transform. To keep the part of a signal  $f(t)$  with frequency smaller than  $x$ , one only has to transform the temporal signal  $f(t)$  into its Fourier transform  $F(\omega)$  and truncate the Fourier transform at the frequency  $x$ . The filtered signal is the inverse Fourier transform of the truncated Fourier transform (Van Loan, 1992).

EEG analysts usually rely on the decomposition of the Fourier transform of the signals into frequency bands to interpret EEG data recorded during sleep. It allows to decompose the sleep into several phases well-known by neurologist. Seven frequency bands are considered : the delta (0.5 - 3.5 Hz), the theta (4 - 7.5 Hz), the alpha1 (8 - 9.5 Hz), the alpha2 (10 - 12.5 Hz), the beta1 (13 - 17.5 Hz), the beta2 (18 - 20.5 Hz), and the beta3 (21 - 32 Hz) phases.

These frequency bands have been related with different brain states or pathologies:

- Delta rhythms (0.5 - 3.5 Hz) : They are characteristic of deep sleep stages. Furthermore, delta oscillations with certain specific morphologies, localizations and rhythms are correlated with different pathologies.
- Theta rhythms (4 - 7.5 Hz) : They are enhanced during sleep and they play an important role in infancy and childhood. In the awake adult, high theta activity is considered abnormal and it is related with different brain disorders.
- Alpha rhythms (8 - 12.5 Hz) : They appear spontaneously in normal adults during wakefulness, under relaxation and mental inactivity conditions. They are best seen with eyes closed.
- Beta rhythms (13 - 20.5 Hz) : They are enhanced upon expectancy states or tension.

To analyse the frequency bands, the following spectral parameters were extracted for each electrode:

- The absolute energy<sup>7</sup>
- The relative energy (% of the energy of each frequency band versus the total EEG band).
- The mean frequency of the total EEG bands.
- The alpha slow wave index (ASI)<sup>8</sup>.
- Some ratio of powers<sup>9</sup> (for example,  $\alpha/\delta + \theta$ ).

The main drawback of this method is that each electrode is analysed separately.

Usually, the analysis of the P300 peak focuses on its amplitude and latency. A conventional method to compare the amplitude and latency is the ANOVA model with random effect to account for subject heterogeneity (see e.g. Brown and Prescott, 2003).

### 1.3.3 Statistical analysis

For this particular study, statistical analyses were carried out on available data from all randomised subjects and separately for each electrode. Treatment groups were compared at each time point separately (Figure 1.5). Mean responses of the subjective assessment and neuropsychological tests were compared at each time of measurement between treatments with a mixed-effect ANOVA adapted to the 4-way cross-over design. The model included fixed effects for the period and the treatment and variance components for the variability between- and within- subjects. All four treatments were then compared with an overall F-test and pair wise comparisons were made using

---

<sup>7</sup>The total energy of a signal is defined as the sum of squared moduli ( $\mu\text{V}$ ) of the frequency bands and for the total studied EEG band (0.5 - 32 Hz):  $E = \sum |F(\omega)|^2$  and  $|F(\omega)|^2 = \text{Re}(F(\omega))^2 + \text{Im}(F(\omega))^2$ .

<sup>8</sup>The alpha slow wave index is computed as the ratio of powers alpha/(delta+theta).

<sup>9</sup>The power is the amplitude squared.

single degree of freedom contrast t-test at the unadjusted 5% level. In a secondary analysis, changes from baselines were also summarized and compared at each time post-dosing with the same procedure.

### 1.3.4 Results

We only report the results of the comparison of Lorazepam with placebo. With Lorazepam alone, decreases in mean energy (in latency range 260-460 msec), latency and amplitude of P300 were detected when compared to placebo. Mean energy (260-460 msec) and mean amplitude were lower from 0.5 to 8.5h after placebo (instead of Rivastigmine) injection with a peak effect at 3.5h. A decrease in mean latency was also detected between 1.5 and 6.5h with a peak effect at 5.5h.

## 1.4 Conclusion

In the following, we propose and evaluate a panel of statistical techniques to clean and to analyse electroencephalograms. These methods are applied on the data of the study presented in this chapter. The aim is to overcome limitations of the conventional data analysis presented above. Classical cleaning techniques are not automated, either lead to a substantial data loss. In Chapter 2, we propose an alternative automatic filtering technique. For the statistical analysis of the P300 peak, conventional approach consists in comparing the amplitude and latency using an ANOVA model with random effect to account for subject heterogeneity. This analysis focuses on simple summary measures, thereby discarding potentially important information. In Chapter 3 and 4, we propose techniques allowing to bring information about the modification in shape of the peak and not only about some specific characteristics like amplitude or latency.

