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# PREMASCOL-EEG : corrélation entre l'EEG néonatal et la scolarité à 5 ans chez les prématurés nés avant 33 SA

Céline Bruneau

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PRETERM CHILDREN BORN BEFORE 33 WEEKS

THÈSE  
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE  
SPÉCIALITÉ :

Pédiatrie, option Neuropédiatrie

Par Mme Céline Bruneau Biboulet

*[Données à caractère personnel]*

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le 22/09/2021

DEVANT LE JURY COMPOSÉ DE :

Président du jury :

Mr le Professeur Thierry Debillon

Membres :

Mme le Docteur Alexa Garros (directrice de thèse)

Mme le Docteur Cécile Sabourdy

Mr le Docteur Guillaume Mortamet

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## **Liste des abréviations**

AUDIPOG: Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie.

BLR: Brunet-Lézine Révisé

EEG: Electroencephalogram

EOS: Early Onset Sepsis

DQ: Developmental Quotient

GA: Gestational Age

IVH: Intraventricular Haemorrhage

LIFT: Loire Infants Follow-Up Team

MRI: Magnetic Resonance Imaging

NICU: Neonatal Intensive Care Unit

PMA: Post Menstrual Age

PRS: Positive Rolandic Sharp

PVL: Periventricular Leukomalacia

SD: Standard Deviation

## **Abstract**

**Context:** Preterm infants represent a large population (11% of birth every year worldwide), they are at high risk of neurodevelopmental sequelae and learning disabilities. A recent study has shown a correlation between neonatal EEG and neurodevelopmental outcome at 2 years old evaluated by Brunet-Lézine test.

**Objective:** To study the correlation between neonatal EEG grading and schooling at 5 years old, in very preterm infants born before 33 weeks of GA.

**Methods:** The study was monocentric and retrospective, it included children born before 33 weeks of GA between 01.01.2010 and 01.01.2014 in Grenoble Alpes University Hospital and followed in the local network "Naître et Devenir". Neonatal EEGs were performed at 28 and 32 weeks of GA and could be controlled at full term or if there were abnormalities. Depending on the result of each EEG (normal, moderately abnormal, or severely abnormal) children were classified in three categories: normal, transient moderately abnormal and very abnormal. Schooling was assessed at age 5 and classified in two groups: normal (unassisted age-appropriate schooling) and not normal.

**Results:** 420 EEGs were performed in 208 infants. EEG following was normal in 55%, transiently moderately abnormal in 23% and very abnormal in 22%. At the age of 5, 71% had a normal schooling. In univariate analysis schooling at age 5 was associated with neonatal EEG grading ( $p = 0,02$ ). The relationship was no longer significant after adjustment on confounding factors (gestational age, maternal education level, bronchopulmonary dysplasia, and sex).

Conclusion: Neonatal EEG surveillance could add information to help predicting neurodevelopmental outcome at age 5 in preterm newborns when associated with other predictors.

Key words: EEG, preterm, neurodevelopmental, schooling



## **Résumé**

**Contexte** : Les prématurés représentent une grande population (11% des naissances chaque année à travers le monde), ils ont un risque accru de trouble du neurodéveloppement et de difficultés scolaires. Une étude récente montre une corrélation entre les anomalies de l'EEG néonatal et le score neuro développemental de Brunet-Lézine à 2 ans.

**Objectif** : Etudier la corrélation entre la surveillance EEG en période néonatale et la scolarité à 5 ans chez les prématurés nés avant 33 SA.

**Méthodes** : Cette étude monocentrique et rétrospective a inclus les enfants prématurés nés avant 33 SA entre le 01.01.2010 et le 01.01.2014 hospitalisés au CHU de Grenoble Alpes et suivis dans le réseau « Naître et Devenir ». Les EEG néonataux ont été réalisés à 28 et 32 SA et ils pouvaient être contrôlés à terme ou s'ils étaient anormaux. En fonction des résultats de chaque EEG (normal, modérément anormal ou sévèrement anormal) les enfants ont été classés en 3 catégories (0 : normal, 1 : anormal modéré et transitoire, 2 : très anormal). La scolarité a été évaluée à 5 ans et classée en 2 catégories : normale (classe appropriée à l'âge sans aide) et anormale.

**Résultats** : 420 EEG ont été réalisés chez 208 enfants. La surveillance EEG était normale dans 55% des cas, anormale de façon modérée ou transitoire chez 23% et très anormale chez 22%. A l'âge de 5 ans, 71% des enfants avaient une scolarité normale. En analyse univariée, la scolarité à 5 ans était associée avec la surveillance EEG néonatale ( $p=0,02$ ). La relation n'était plus significative après ajustement sur les facteurs de confusion (âge gestationnel, dysplasie bronchopulmonaire, niveau d'éducation maternel et sexe).

Conclusion : La surveillance EEG néonatale peut apporter des informations pour aider à prédire le neurodéveloppement à 5 ans chez les enfants prématurés quand elle est associée aux autres facteurs prédictifs.

Mots clés : EEG, prématurité, neuro développement, scolarité

## **Introduction**

Despite improvements in obstetric and neonatal care, there are 15 million preterm newborns worldwide each year, representing 11% of birth (1). Among those babies, more than 1 million die before the age of five due to prematurity and its complications (1). In France in 2011, preterm births represented between 5 to 12% of births and the mortality rate was lower than worldwide, around 16% for children aged 24-31 weeks of gestational age (GA) (2).

Whereas the survival rate improves, preterm children remain at high risk of neurodevelopmental disorders (3–5). Indeed, at the age of 2 years, neuromotor and sensory disabilities represent 19,8% of children born between 24 and 31 weeks of GA, 4,6% have neuromotor sequelae (cerebral palsy), and less than 1% present severe sensory sequelae (2). Moreover, 40,7% have neurodevelopmental sequelae (2).

In the EPIPAGE study (which studied births before 33 weeks of GA in France to evaluate their outcome and to analyse the role of different factors causing sequelae) with follow up at 5 and 8 years old, preterm children needed more specialised care such as physiotherapists, speech therapists, occupational therapists, psychiatrists or psychologists, and more special care at school than in the reference group (born at 39 or 40 weeks of GA). At the age of 8, only 41% of very preterm children were in the age-appropriated class in an ordinary school without support at school and/or special care (6,7). In a meta-analysis published in 2010 preterm children presented more difficulties in academic achievement such as executive functioning, complex conceptual tasks and language processing or mathematical skills, but also had attention problems (8). These difficulties became more evident when children begin academic learnings,

around 6 years old. Detecting cognitive or motor impairment as soon as possible is a challenge because early intervention improves the outcome (9).

Neurodevelopmental outcome remains a particularly important issue. Children born in Grenoble agglomeration before 33 weeks of GA are followed up in « Naître et Devenir », the regional network of neonatologists which includes outpatient and inpatient monitored until the age of 7 old to identify as soon as possible neurodevelopmental disabilities to provide an earlier management.

To ensure individualised follow-up, the aim is to identify premature children at high risk of neurodevelopmental sequelae and schooling difficulties. In neonatal intensive care units, brain imaging (ultrasound), clinical examination and neurophysiological methods are used to assess premature infants. Numerous risk factors for a poor cognitive prognosis have already been identified such as low gestational age (<32 weeks of GA), low birth weight (<1500g), male sex, socioeconomic status, intraventricular haemorrhage (IVH) with ventricular dilatation or with parenchymal damage (IVH 3 and 4) white matter abnormalities (2,4,7,10,11).

EEG is a useful and non-invasive tool that can be performed in neonatal intensive care unit (NICU). Recent studies have shown that EEG can predict early neurodevelopmental outcomes (12,13). In these two studies only early neurodevelopmental outcome was assessed at 12, 18 and 24 months of age. In the most recent study, non-optimal development at 2 years old was significantly associated with more severe EEG abnormalities in children born before 32 weeks of GA, and in the other study EEG abnormalities significantly predicted unfavourable neurodevelopmental outcome at 12 and 18 months corrected age in preterm children born before 34 weeks of GA (12,13). Another study, assessed the prognostic value of EEG in predicting psychomotor outcome at 6 years old, and showed that infants having

EEG dysmature patterns at the neonatal period were more likely to develop moderate or severe neuromotor and cognitive impairment at age 6 (14).

The first objective of this study was to assess the relationship between neonatal EEG classification and schooling at 5 years old.

Secondary objectives were to investigate the relationship between maternal, prenatal, perinatal, and neonatal characteristics and neonatal EEG. We have also investigated the relationship between neonatal EEG and the Brunet-Lézine test at 2 years old.

## **Methods**

### **Study design and population**

This retrospective study included children born before 33 weeks of GA between 01.01.2010 and 01.01.2014 and hospitalized in the NICU of the University Hospital of Grenoble and followed up in the « Naitre et Devenir » network, who had available data for neonatal EEG grading and schooling at 5 years old.

In the analysis, we included children who had complete data for EEG grading and schooling at 5 years old.

Clinical data collected during the neonatal period are described in table 1 and table 2. It included maternal characteristics: maternal age, maternal education level in 2 categories (high (university degree) versus low (secondary school level or lower and/or professional degrees)), multiple pregnancies, obstetrical vascular pathology, chorioamnionitis and newborn characteristics: gestational age, birth weight, small for gestational age (according to French AUDIPOG curves (15)), sex, Apgar score, antenatal corticosteroids administration, bronchopulmonary dysplasia (according to Jobe and Bancalari classification (16)), using of post-natal corticosteroids, IVH (according to Papile Classification (17)) and periventricular leukomalacia, early onset sepsis (defined as the detection of bacteria or fungus from a blood or placenta culture associated with ongoing clinical and/or laboratory abnormalities, occurring  $\leq$  72 hours of life), necrotizing enterocolitis (defined by Bell Classification (18)), breastfeeding, length of parenteral nutrition, length of hospital stay.

EEGs were performed for at least 40 minutes and included both active and quiet sleep, with 8 electrodes placed at FP1, FP2, C3, C4, O1, O2, T3, and T4, using the

international 10–20 system. For children born before 28 weeks of GA, at least one EEG was performed in the first two weeks of life, and another one around 32 weeks of GA. After that, it was not systematically repeated. For children born between 28 and 32 weeks of GA, only one EEG was performed in the first two weeks of life, and it was not systematically repeated. For these children, EEG was controlled if there were abnormalities around full term (37 weeks of GA). For children born after 32 weeks of GA, EEG was not systematically performed. Children who were transferred in other hospitals after 32 weeks of GA did not have systematically a control of the EEG, so EEG grading was not always available.

EEG were classified using the French Glossary and were classified in three categories using a recent study: normal (normal background activity for the corrected age and no abnormal features), moderately abnormal (increased discontinuity with maximal inter-burst interval during less than 1.5 of the maximal value for the age group, abnormal delta brushes, dysmature patterns, positive temporal sharp waves and positive rolandic sharp waves less than 1/min, disorganised patterns) or severely abnormal (excessive discontinuity with maximal inter-burst interval duration above one and a half of the maximal value for the corrected age, seizures, the absence of sleep cycles and positive rolandic sharp waves more than 1/min) (12,19). Neonatal EEG was therefore classified in three categories in accordance with the LIFT study: 0: normal if all the recordings were normal, 1: transient moderately abnormal if there were moderate abnormalities that disappeared before the third recording, 2: very abnormal if severe abnormalities were recorded or moderate abnormalities were recorded in more than two EEGs.

Follow-up at 5 years old is included in the regular evaluation performed within the “Naitre et Devenir” network using detailed evaluation of schooling conditions (Appendix 1).

Schooling at age 5 was classified into five categories: unassisted age-appropriate schooling, age-appropriate schooling with assistance and health interventions outside school (speech therapy or physiotherapy or psychomotricity or psychology), age-appropriate schooling with assistance within the school (life support), grade repetition or specialized establishment and no schooling. The last 4 categories were grouped into “not normal schooling”. (Appendix 1).

At 2 years of corrected age, revised Brunet-Lézine (BLR) test was conducted by a specialised psychologist (20). BLR test is a French developmental test, validated in the literature (21) that provides a developmental quotient (DQ). Psychomotor development was considered non optimal when the BLR test DQ was below 85, optimal when  $DQ > 100$  and at risk when DQ between 85-100.

The study was approved by the hospital’s Delegation for Clinical Research and Innovation on 29.09.2020 and by the committee for the protection of persons.

Informed and written consent was obtained from the families when signing their participation in the network charter, which stated that anonymized data obtained from regular follow-up could be used for evaluation, according to the European GDPR.



## Statistical analysis

To perform descriptive analyses, mean and standard deviation (sd) were used for continuous variables, and percentage for categorical variables.

For univariate analysis, Mann-Whitney and Student tests were performed for continuous variables.  $\chi^2$  tests were performed for categorical variables, Fisher tests if the  $\chi^2$  hypothesis was not validated.

A multivariate logistic regression was performed with adjustment on factors selected either from the univariate analysis and from factors identified from the literature and clinically relevant factors which were gestational age, bronchopulmonary dysplasia, maternal education level and sex.

A p-value < 0.05 was considered statistically significant.

No imputation was performed on missing data.

Statistical comparisons were performed in R4web 1.2 (UGA & CHUGA with EIT Health support, Grenoble, France) for univariate tests, and Stata (StataCorp, CollegeStation, TX, USA) for multivariate analysis.

## **Results**

Among 456 children born before 33 weeks of GA between 01.01.2010 and 01.01.2014 and hospitalized in Grenoble NICU, 427 had inclusion criteria, 13 died and 16 refused follow up.

At least one EEG was performed in 359 infants. For 68 infants no EEG was performed, these preterm newborns were mostly born between 32 and 32 + 6 weeks of GA (except for 8 infants born before 32 weeks and who had no EEG performed). EEG grading was available for 304 children, among whom schooling at age 5 was available for 208 infants, that represent the population included in this study. For 55 infants, the EEG grading was not realizable because they had only one or two EEG which were abnormal without new control because they were transferred in non-university NICU.

The flow chart is shown in figure 1.

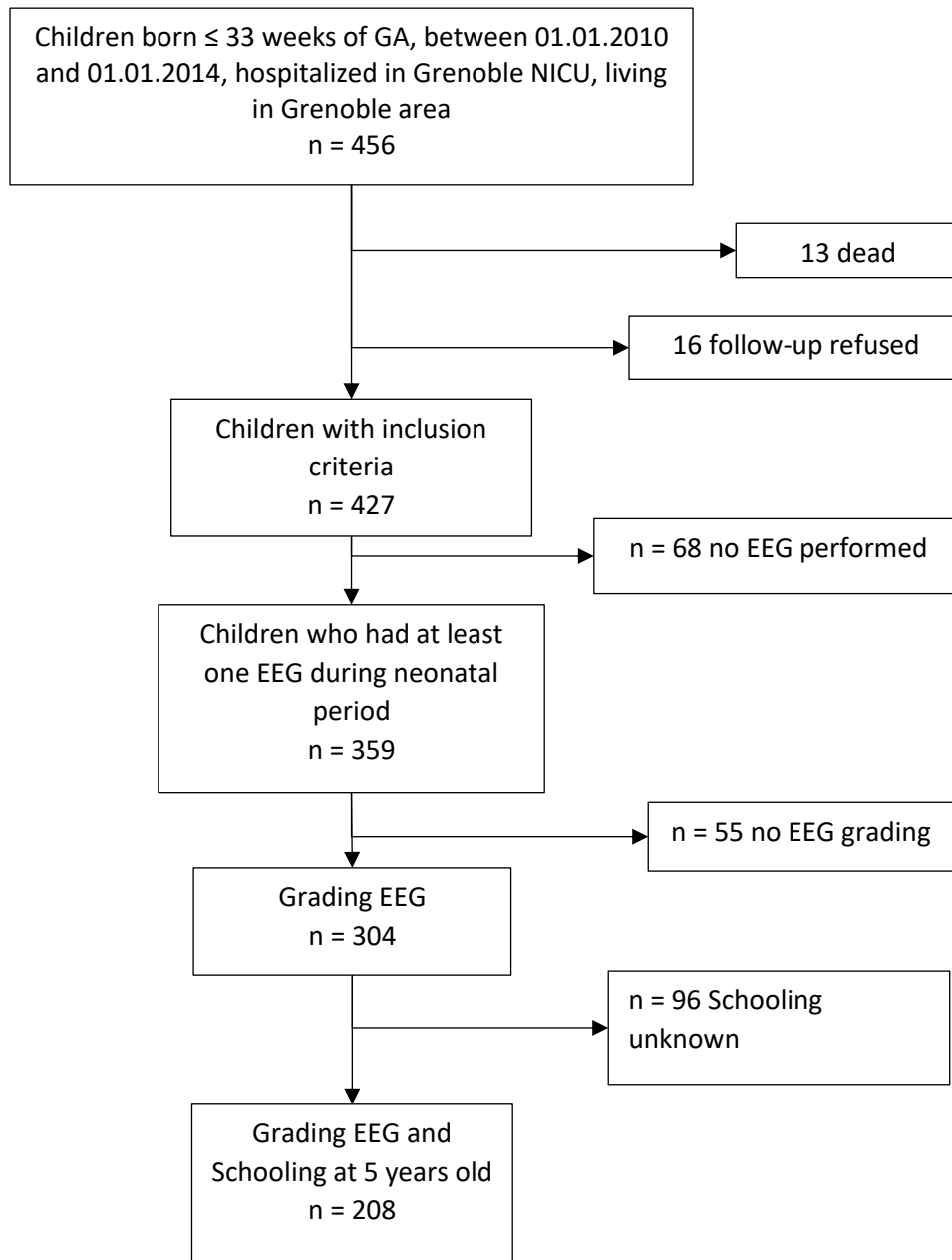


Figure 1. Flow Chart.

## Participant Characteristics

Table 1 shows the comparison of perinatal and socio-demographic data between the group of 208 patients included in the study and 219 non included because of lack to follow-up or missing data. Included children were more immature, had lower birth weight, more bronchopulmonary dysplasia, longer hospital stays and were more frequently breastfed than non-included children. Severe cerebral lesion (IVH 3-4 and periventricular leukomalacia) accounted for 4,9% of the study population and 1,9% of the non-included population. However, the difference was not statistically significant.

Regarding GA, 22%, 25% and 53% of the children were born between 24-27, 28-29 and 30-32 weeks respectively.

In the study population missing data did not exceed 5%, except for maternal education level (22%).

**Table 1. Comparison of maternal and neonatal characteristics between included and not included infants.**

	Study Population n=208	Not included n=219	p
<b><u>Maternal characteristics</u></b>			
Maternal age (years), mean +/- sd	30,4 +/- 5	29,7 +/- 5,1	0,179
High maternal education level <sup>a</sup> , n (%)	79 (49%)	65 (48,1%)	0,294
Multiple pregnancy, n (%)	77 (37%)	87 (36,7%)	>0,99
Chorioamnionitis, n (%)	19 (9,1%)	23 (9,7%)	0,966
Obstetrical vascular pathology <sup>b</sup> , n (%)	77 (37,6%)	83 (41%)	>0,99
<b><u>New-born characteristics</u></b>			
Gestational age (weeks), mean +/- sd	29,2 +/- 2,1	30,6 +/- 1,9	<0,001
Birthweight (g), mean +/- sd	1276,7 +/- 382	1503 +/- 380,3	<0,001
Boy, n (%)	92 (44,2%)	115 (48,5%)	0,418
Apgar test (5 min), mean +/- sd	8,4 +/- 2,1	8,7 +/- 1,9	0,143
Antenatal corticosteroids, n (%)	33 (16,2%)	47 (21,8%)	0,351
Small for gestational age <sup>c</sup> , n (%)	28 (13,5%)	29 (13,4%)	0,819
Bronchopulmonary dysplasia, n (%)	82 (40,8%)	46 (22,6%)	<0,001
Postnatal corticosteroids, n (%)	10 (4,9%)	4 (1,9%)	0,102
IVH 3-4 or periventricular leukomalacia, n (%)	10 (4,9%)	4 (1,9%)	0,102
Early onset sepsis <sup>d</sup> , n (%)	14 (6,8%)	21 (9,8%)	0,497
Breastfeeding, n (%)	59 (29,3%)	79 (40,7%)	<0,001
Length of hospital stay (days), mean +/- sd	65,5 +/- 43,8	46,8 +/- 21,8	<0,001

Abbreviation: sd = standard deviation

Mann Whitney or Student test for continuous variables.

Fisher or  $\chi^2$  test for categorical variables.

<sup>a</sup> High maternal education level: university studies. <sup>b</sup> Obstetrical vascular pathology: vascular intrauterine growth restriction, maternal high blood pressure, or preeclampsia. <sup>c</sup> small for gestational age: birthweight < 3e percentile. <sup>d</sup> early onset sepsis: isolation of bacteria or fungus from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring  $\leq$  72 hours of life.

## Factors associated with schooling

At age 5, 148 (71%) children had normal schooling (unassisted age-appropriate schooling) and 60 (29%) had abnormal schooling. Among these 60 children, 42 (20,3%) had received health intervention outside of school, 14 (6,7%) had received support in school, 1 (0,5%) had attended a special school and 3 (1,5%) were unschooled.

Normal schooling at 5 years old was significantly associated with high maternal education level ( $p < 0,001$ ), higher gestational age ( $p = 0,003$ ), sex ( $p = 0,015$ ) (boys had a lower proportion of normal schooling), lower rate of bronchopulmonary dysplasia ( $p = 0,021$ ) and shorter length hospital stays ( $p = 0,02$ ). It was also associated with lower rate of periventricular leukomalacia ( $p = 0,035$ ). There was no significant difference for IVH (table 2).

**Table 2. Factors associated with normal schooling.**

	Normal schooling n = 148	Abnormal Schooling n = 60	p
<b>Maternal characteristics</b>			
Maternal age (years), mean +/- sd	30,5 +/- 5	30,1 +/- 5,1	0,552
High maternal education level, n (%)	72 (60%)	7 (17,1%)	<0,001
Multiple pregnancy, n (%)	61 (41,5%)	16 (26,7%)	0,065
Chorioamnionitis, n (%)	15 (10,2%)	4 (6,7%)	0,593
<b>New-born characteristics</b>			
Gestational age (weeks), mean +/- sd	29,5 +/- 1,9	28,5 +/- 2,4	0,003
Boy, n (%)	74 (50,3%)	42 (70%)	0,015
Apgar test (5 min), mean +/- sd	8,5 +/- 1,9	8,4 +/- 2,5	0,813
Antenatal corticosteroids, n (%)	126 (86%)	45 (77,6%)	0,189
Small for gestational age, n (%)	17 (11,6%)	11 (18,3%)	0,286
Bronchopulmonary dysplasia, n (%)	51 (35,4%)	31 (54,4%)	0,021
Postnatal corticosteroids, n (%)	6 (4,1%)	4 (6,9%)	0,629
IHV	6 (4,1%)	5 (8,6%)	0,34
Severe IHV (3-4)	4 (2,7%)	3 (5,2%)	0,657
Periventricular leukomalacia, n (%)	0	3 (5,1%)	0,035
Necrotising Enterocolitis, n (%)	7 (4,8%)	1 (1,7%)	0,528
Early onset sepsis, n (%)	10 (6,8%)	4 (6,8%)	>0,99
Breastfeeding, n (%)	101 (70,6%)	38 (69,1%)	0,969
Duration of parenteral (days), mean +/- sd	18,9 +/- 14,8	22 +/- 13,1	0,185
Length of hospital stay (days), mean +/- sd	59,6 +/- 28,9	80 +/- 66,1	0,002
<b>EEG surveillance</b>			
<b>Grade 0</b>	89 (60,2%)	25 (41,7%)	0,02
<b>Grade 1</b>	32 (21,6%)	16 (26,7%)	
<b>Grade 2</b>	27 (18,2%)	19 (31,6%)	

Abbreviation: sd = standard deviation

Mann Whitney or Student test for continuous variables.

Fisher or  $\chi^2$  test for categorical variables.

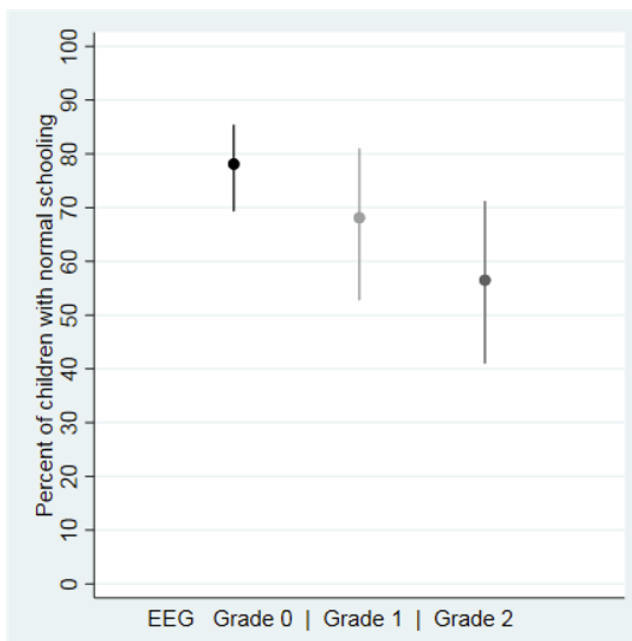
<sup>a</sup> High maternal education level: university studies. <sup>b</sup> Small for gestational age: birthweight < 3e percentile. <sup>c</sup> Necrotising enterocolitis:  $\geq$  Bell's stage 2. <sup>d</sup> Early onset sepsis: isolation of bacteria or fungus from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring  $\leq$  72 hours of life.

## Univariate analysis

EEG categories were statistically associated with schooling at 5 years old (figure 2). Among children with normal EEG surveillance (Grade 0), 78% had a normal schooling at 5 years old, among children with EEG grade 1, 68% had normal schooling and among preterm with EEG grade 2, only 57% had a normal schooling at 5 years ( $p < 0,05$ ) (figure 2).

The positive predictive value of a grade 0 EEG for normal schooling was 77.0%, with a sensitivity of 60,5% and a specificity of 58%.

**Figure 2. Rate of normal schooling at 5 according to neonatal EEG grade.**



Grade 0: normal EEG surveillance, Grade 1: transient moderate abnormalities, Grade 2: permanent moderate or severe abnormalities. Circles indicated the percentage of children with optimal outcome. Intervals indicate the 95% IC



### Multivariate analysis

Multivariate analysis was adjusted for gestational age, bronchopulmonary dysplasia, maternal education and sex (table 3).

In the multivariate analysis, normal schooling remained significantly associated with maternal education level but was no longer statistically associated with neonatal EEG surveillance (p=0,095).

**Table 3. Odds Ratios of univariate and multivariate analysis for schooling.**

	Univariate analysis		Multivariate analysis	
	Normal Schooling		Normal Schooling	
	OR [95% CI]	p-value	aOR [95% CI]	p-value
<b>Grade EEG</b>				
0	1		1	
1	0.60 [0.28-1.28]	0.185	0.67 [0.24-1.87]	0.439
2	0.37 [0.18-0.76]	0.007	0.42 [0.15-1.16]	0.095
<b>Bronchopulmonary dysplasia, n (%)</b>				
Non	1		1	
Oui	0.46 [0.25-0.86]	0.015	0.67 [0.18-2.44]	0.539
<b>Maternal education level</b>				
Low <sup>a</sup>	1		1	
High <sup>b</sup>	7.29 [2.99-17.77]	< 0.001	9.56 [3.55-25.71]	< 0.001
<b>Gestational age, mean +/- sd</b>	1.23 [1.07-1.42]	0.004	1.29 [0.96-1.74]	0.094
<b>Sex</b>				
Girl	1		1	
Boy	0.43 [0.23-0.82]	0.011	0.55 [0.23-1.34]	0.188

Grade 0: normal EEG surveillance, Grade 1: transient moderate abnormalities, Grade 2: permanent moderate or severe abnormalities.

<sup>a</sup> Low maternal education level = secondary school level or lower and/or professional degrees. <sup>b</sup> High maternal education level: university studies.

## Factors associated with EEG

For children born before 28 weeks of GA, the mean number of EEGs was 2,3 (1-10), for children born at 29 and 30 weeks of GA it was 2 (1-5) and 1,7 (1-5) for 31-32 weeks of GA resulting in 420 neonatal EEG recordings.

Among these 208 preterm infants, 115 (55%) had normal EEG grading (Grade 0), 47 (23%) had transient moderately abnormal EEG and 46 (22%) had very abnormal EEG.

In univariate analysis, normal EEG grading was statistically related to higher GA ( $p=0,006$ ), less necrotising enterocolitis ( $p=0,027$ ), shorter hospital stays ( $p=0,002$ ) and shorter duration of parenteral administration ( $p=0,001$ ) but not to the presence of IVH and periventricular leukomalacia (table 4).

**Table 4. Factors associated with EEG classification.**

	EEG Grade 0 n = 115	EEG Grade 1 n = 47	EEG Grade 2 n = 46	p
<b><u>Maternal characteristics</u></b>				
Maternal age (years), mean +/- sd	30,4 +/- 5,1	31,6 +/- 4,8	29,1 +/- 4,8	0,095
High maternal education level <sup>a</sup> , n (%)	41 (49,4%)	19 (48,2%)	19 (48,7%)	0,531
Multiple pregnancy, n (%)	43 (37,7%)	17 (36,2%)	17 (37%)	0,982
Chorioamnionitis, n (%)	10 (8,8%)	2 (4,3%)	7 (15,2%)	0,183
<b><u>New-born characteristics</u></b>				
Gestational age (weeks), mean +/- sd	29,6 +/- 1,9	28,9 +/- 2	28,4 +/-2,4	0,006
Boy, n (%)	59 (51,8%)	28 (59,6%)	29 (63%)	0,367
Apgar test (5 min), mean +/- sd	8,7 +/- 1,7	8,5 +/- 2,2	7,4 +/-2,4	0,191
Antenatal corticosteroids, n (%)	93 (83%)	40 (87%)	38 (82,6%)	0,805
Small for gestational age <sup>b</sup> , n (%)	14 (12,3%)	6 (12,8%)	8 (17,4%)	0,683
Bronchopulmonary dysplasia, n (%)	37 (33,9%)	20 (43,5%)	25 (54,3%)	0,056
Postnatal corticosteroids, n (%)	3 (2,7%)	3 (6,4%)	4 (8,7%)	0,248
IVH, n (%)	4 (3,5%)	2 (4,3%)	5 (11,1%)	0,21
Severe IVH (3-4), n (%)	3 (2,7%)	1 (2,1%)	3 (6,7%)	0,391
Periventricular leukomalacia, n (%)	1 (0,9%)	1 (2,1%)	1 (2,2%)	0,59
Necrotising Enterocolitis <sup>c</sup> , n (%)	3 (2,6%)	0	5 (10,9%)	0,027
Early onset sepsis <sup>d</sup> , n (%)	6 (5,3%)	4 (8,5%)	4 (8,7%)	0,605
Breastfeeding, n (%)	75 (68,8%)	30 (68,2%)	34 (75,6%)	0,669
Duration of parenteral (days), mean +/- sd	17,1 +/- 13,8	20,7 +/- 12,8	24,8 +/-16,1	0,002
Length of hospital stay (days), mean +/- sd	55,9 +/- 21,8	74,7 +/- 70,6	80,1 +/- 44,7	0,001

Abbreviation: sd = standard deviation

Mann Whitney or Student test for continuous variables.

Fisher or  $\chi^2$  test for categorical variables.

<sup>a</sup> High maternal education level: university studies. <sup>b</sup> Small for gestational age: birthweight < 3e percentile. <sup>c</sup> Necrotising enterocolitis:  $\geq$  Bell's stage 2. <sup>d</sup> Early onset sepsis: isolation of bacteria or fungus from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring  $\leq$  72 hours of life.

### Factors associated with Revised Brunet-Lézine test

In this study, the BLR Test at 2 years old was also associated with a normal EEG surveillance. In the population we have obtained the BLR Test for 143 children, 25 (17%) had a score < 85, 91 (64%) had a score between 85 and 100 and 27 (19%) had a score > 100. For 65 children (31%), BLR Test was not available. The BLR Test at 2 years old was associated with neonatal EEG surveillance, children with normal EEG had more frequently BLR score > 100 at 2 years old ( $p=0,032$ ). (Appendix 2).

## **Discussion**

Assessing the neurological prognosis of preterm neonates remains an important challenge. While neonatal intensive care techniques have fundamentally changed the outcome of very premature babies with fewer neuromotor and neurosensory sequelae leading to severe handicaps, there are still many children with academic learning difficulties. EPIPAGE cohort described more than half of the premature babies born before 32 weeks of GA who needed specific help to stay in appropriate grade level school (7).

In France, the follow-up of premature babies born before 32 weeks of GA is organised in each region up, generally up to 7 years in most cases within a network of neonatal follow up. Preterm are followed up by several health professional specialised in the management of premature babies to detect as soon as possible any difficulties. Neuromotor and neurosensorial difficulties may appear early in childhood but cognitive difficulties may appear later.

In the neonatal period, EEG is a tool to follow maturation changes in the white matter and to detect cerebral abnormalities widely used in NICUs. Between 24 and 41 weeks of GA, neonatal EEG undergoes major changes, these changes occur in the organization of behavioural states, in background activity, in EEG features and in spatial and temporal organization (19). It is possible to accurately assess the term of neonates: every two weeks of GA, organization of behavioural states evolves until having a difference between active wakefulness, active sleep, quiet sleep, and quiet wakefulness. Each physiological feature is also unique for each two weeks of GA. (Appendix 3).

In French recommendations in 2004, if the child is born before 28 weeks of GA, EEG records are to be acquired systematically between day 2 and day 3, between day 7 and day 8, at 31–32 weeks of GA and at 36 weeks of GA. For children born between 29 weeks of GA and 32 weeks of GA, EEG records are to be acquired systematically between day 2 and day 3 and between day 7 and day 8. The 36 weeks of GA EEG must be repeated when the 32 weeks of GA EEG is abnormal (22). In fact, these recommendations are difficult to apply because of the patient instability especially in the first week of life and new comfort-based care methods named NIDCAP (23). Moreover there is a development of increasingly effective non-invasive tools to detect cerebral abnormalities (intracranial haemorrhage and white matter injury) which are cranial ultrasound and MRI (11,24,25). Furthermore, in preterm children, background EEG abnormalities and positive rolandic sharp (PRS) are correlated to periventricular leukomalacia (PVL) and these brain lesions are linked to motor outcome (26). For PRS, their density (number per minute) and their persistence are associated with poorer motor outcome, they are mostly seen before 34 weeks of PMA (26,27). Cerebral ischaemia, infection and inflammation are principal factors known in PVL so it supports the importance of following the evolution of EEG and to control it also when an infection occurs.

This study aimed to show a correlation between neonatal EEG monitoring and cognitive outcome at 5 years old. It was based on two recent studies the first one LIFT cohort showing a correlation between EEG grading in neonatal period and BLR test at 2 years old, the second one PREMASCOL showing a correlation between BLR at 2 years old and cognitive outcome at 5 years old (12). No significant correlation was found between EEG surveillance and schooling in multivariate analysis, only maternal education level remained significant. In previous studies, the role of high maternal

education in child neurodevelopment (cognitive, language and motor) has already been investigated and was related to multiple interrelated factors, such as maternal intelligence quotient, home environment and socio-economic level (28,29). In comparison to LIFT cohort, there were less normal EEG surveillance (Grade 0) (56% versus 72,5%) and more Grade 2 EEG (22% versus 7,5%), the proportion of Grade 1 EEG was close (23% versus 22%). This difference in EEG monitoring grade 2 was not explained by the term or by the presence of brain damages, indeed there was a close proportion of infants born between 24 and 27 weeks (22,3% versus 22%), born after 30 weeks (47,9% versus 53%), and born between 28 and 29 weeks (29,8% versus 25%). Moreover, the proportion of infants with severe cerebral lesion (IVH 3-4, white matter disease or IVH and white matter disease) was close (7,6% in LIFT cohort and 4,9% in this study) and IVH 1-2 were present in 6,9%. In another study of 2015 (24), prevalence of severe IVH (III and IV) and PVL is also close to this study (9,7%). In comparison with EPIPAGE cohort, at 5 years old there was a close proportion of children who needed special care (29% in our study and 33% in EPIPAGE study), but at 8 years old in EPIPAGE study, the number of children who needed special care had increased, only 41% were in the appropriate grade level without any support.

Limitations of this study were being monocentric and retrospective, moreover, there was an important rate of our population which was lost to follow up at age 5 years or who did not have EEG or less than 2 EEG in neonatal period. Children lost to follow-up had higher birth weight and GA, less bronchopulmonary dysplasia, shorter hospital stay, and were more breastfed. In the literature (2,4,7), these factors are associated with better neurodevelopment. Moreover, assessment at age 5 may underestimate the learning difficulties that may appear later with reading, writing, mathematic skills and

attention difficulties. Indeed, it might be interesting to follow this study up to 7 years of age because the cognitive assessment might be more accurate.

In this study, EEG grading was based on a very precise analysis, including the duration of discontinuity periods, term-specific physiological patterns, and the presence and repetition of pathological patterns. In this study and in LIFT cohort, neonatal EEG was correlated to neurodevelopment at the age of 2, in both of these studies BLR test and Ages and Stages Questionnaire (ASQ) were used to assess neurodevelopmental outcome at the age of 2, these tests have shown their validity to evaluate children (21). However, in this study, the 5-year-old assessment was based on the schooling in the age-appropriate class without help, which is not very accurate for the assessment of cognitive impairments in children. Moreover, neuropsychological assessment with standardised test like Wechsler scale was not carried out in all children at age 5.

In previous studies, in full-term children or in children with congenital heart disease, EEG background changes may reflect brain damage and neuronal network dysfunction (30,31). In premature newborns, white matter maturation is delayed compared to term newborns. These alterations have been demonstrated using tractography and are correlated with neurodevelopmental outcome (32,33). These studies have shown that the alteration of corticospinal and callosal tracts are delayed in premature children because they are myelinated later in the third trimester, these tracts are very important for learnings (32). Extra uterine development of this tracts is close but not the same than intra utero, maybe we should use tractography in preterm children to assess those who are more at risk of learning disabilities. It could be interesting to study more specifically the executive functions of these children and their corollary in terms of functional imaging using tractography.



This study had shown factors which are associated with schooling at the age of 5 so it would be interesting to develop a composite score with all factors known to determine preterm babies with a cognitive risk outcome to reduce « hidden » disabilities.

## **Conclusion**

In preterm infants, normal EEG surveillance, in association with perinatal factors like high maternal education level, high gestational age, female sex and no bronchopulmonary dysplasia tends to predict a good cognitive outcome at 5 years especially with high maternal education level which seems to be the most important factor.

It would be interesting for each premature born before 32 weeks of GA to define a composite score at the end of the neonatal period to assess his neurological risk and propose a personalized follow-up and standardized cognitive evaluation. Moreover, it could be interesting to use neonatal EEG monitoring data by performing standardized cognitive tests, especially for executive and attentional functions from the age of 6.

## DOSSIER DE SOUTENANCE DE THESE

### CONCLUSION (Annexe 4)

**THÈSE SOUTENUE PAR:**

Céline BRUNEAU BIBOULET

**TITRE:**

PREMASCOL-EEG: CORRELATION BETWEEN NEONATAL EEG AND SCHOOLING AT AGE 5 IN PRETERM CHILDREN BORN BEFORE 33 WEEKS

**CONCLUSION:**

In preterm infants, normal EEG surveillance, in association with perinatal factors as high maternal education level, high gestational age, female sex and no bronchopulmonary dysplasia tends to predict a good cognitive outcome at 5 years especially high maternal education level which seems to be the most important factor.

It would be interesting for each premature born before 32 weeks of GA to define a composite score at the end of the neonatal period to assess his neurological risk and propose a personalized follow-up and standardized cognitive evaluation. Moreover, it could be interesting to use neonatal EEG monitoring data by performing standardized cognitive tests, especially for executive and attentional functions from the age of 6 years.

**VU ET PERMIS D'IMPRIMER**

Grenoble, le :

LE DOYEN

LE PRÉSIDENT DE LA THÈSE



Pr. Patrice MORAND  
Le Doyen de l'UFR de Médecine



Pr. Patrice MORAND



Pr. *Th. Debillon*  
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Hôpital Couple Enfant  
Clinique de Néonatalogie  
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Pr Th. DEBILLON

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# Appendix

## Appendix 1 : Examen spécifique à 5 ans

### Examen spécifique 5 ans – page 1

NOM :

Prénom :

Date de naissance :

AG :

Examen réalisé par :

Mode d'exercice: Libéral  Salarié : hospitalier  PMI  CAMSP

Date d'examen :

Age lors de l'examen :          ans          mois


	Mesure	DS ou percentile
Poids		
Taille		
PC		
IMC		
TA		

#### INTERROGATOIRE

Mode de garde	Parents	<input type="checkbox"/>	Grands-parents	<input type="checkbox"/>
	Autre :			<input type="checkbox"/>
Situation familiale	Couple	<input type="checkbox"/>	Parent isolé	<input type="checkbox"/>
	Autre :			<input type="checkbox"/>
Fratrie	Non	<input type="checkbox"/>	Oui	<input type="checkbox"/>
	Si oui, rang : /			
Bilinguisme familial	Non <input type="checkbox"/> Oui <input type="checkbox"/>			

Scolarisation	Plein temps	<input type="checkbox"/>	Temps partiel	<input type="checkbox"/>
	Classe ou établissement si scolarisation spécifique :			
Prise en charge spécifique à l'école (soutien, RASED ...)	Non	<input type="checkbox"/>	Oui	<input type="checkbox"/>
AVS	Non	<input type="checkbox"/>	Oui	<input type="checkbox"/>

Appétit	Normal	<input type="checkbox"/>	Médiocre	<input type="checkbox"/>
	Sélectif	<input type="checkbox"/>	Important	<input type="checkbox"/>
Texture	Gros morceaux		Autre :	
Grignotage	Non	<input type="checkbox"/>	Oui	<input type="checkbox"/>

 **Merci de bien vouloir nous rappeler systématiquement les n° de téléphone :**

- mère :

- père :

- domicile :

Sommeil		Oui	Non
Endormissement - sans problème - difficile / avec présence d'un parent		<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>
Réveils nocturnes		<input type="checkbox"/>	<input type="checkbox"/>

Propreté	Acquise	Non acquise
diurne	<input type="checkbox"/>	<input type="checkbox"/>
nocturne	<input type="checkbox"/>	<input type="checkbox"/>

Pathologies observées depuis le dernier examen		
Nombre d'hospitalisations	/ /	Motifs :
Pathologies chroniques	Non <input type="checkbox"/>	Si oui, préciser type de pathologie et traitement éventuel :
	Oui <input type="checkbox"/>	

Suivi	Prise en charge <u>en cours</u>	Libéral	CAMSP	CMP CMPP
Pédiatre	<input type="checkbox"/>			
Neuropédiatre Médecin rééducateur	<input type="checkbox"/>	Kinésithérapie	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	Psychomotricité	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	Psychologue	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	Orthophoniste	<input type="checkbox"/>	<input type="checkbox"/>
Autre :	<input type="checkbox"/>	Autre :	<input type="checkbox"/>	<input type="checkbox"/>

## Appendix 2: Factors associated with BLR

	BLR < 85 n = 25	BLR 85-100 n = 91	BLR > 100 n = 27	p
<b>Maternal characteristics</b>				
Maternal age (years), mean +/- sd	29,9 +/- 5,8	30,3 +/- 5,2	30,3 +/- 4,3	0,862
High maternal education level <sup>a</sup> , n (%)	8 (42,1%)	37 (49,3%)	5 (26,3%)	0,192
Multiple pregnancy, n (%)	4 (16%)	36 (39,6%)	9 (33,3%)	0,084
Chorioamnionitis, n (%)	2 (8%)	9 (9,9%)	0	0,258
<b>New-born characteristics</b>				
Gestational age (weeks), mean +/- sd	28,8 +/- 2,4	29,1 +/- 2,1	29,8 +/- 2	0,196
Boy, n (%)	14 (56%)	50 (54,9%)	19 (70,4%)	0,352
Apgar test (5 min), mean +/- sd	8,9 +/- 1,8	8,5 +/- 2,2	8,3 +/- 1,9	0,381
Antenatal corticosteroids, n (%)	23 (92%)	71 (78,9%)	25 (92,6%)	0,112
Small for gestational age <sup>b</sup> , n (%)	2 (8%)	10 (10,9%)	3 (11,1%)	> 0,99
Bronchopulmonary dysplasia, n (%)	11 (45,8%)	39 (44,8%)	8 (29,6%)	0,345
Postnatal corticosteroids, n (%)	0	6 (6,7%)	1 (3,7%)	0,634
IVH 3-4 or periventricular leukomalacia, n (%)	0	5 (5,7%)	0	0,532
Necrotising enterocolitis <sup>c</sup> , n (%)	1 (4%)	2 (2,2%)	1 (3,7%)	0,624
Early onset sepsis <sup>d</sup> , n (%)	4 (16%)	6 (6,7%)	0	0,073
Breastfeeding, n (%)	15 (60%)	62 (71,3%)	19 (73,1%)	0,509
Duration of parenteral (days), mean +/- sd	18,6 +/- 9,5	20,3 +/- 14,6	18,9 +/- 22,1	0,26
Length of hospital stay (days), mean +/- sd	63,3 +/- 27,7	64,6 +/- 28,9	72,1 +/- 90,6	0,668
<b>Normal EEG</b>	13 (52%)	45 (49,5%)	21 (77,8%)	0,032

Abbreviation: sd = standard deviation, IVH = intraventricular haemorrhage

Mann Whitney or Student test for continuous variables.

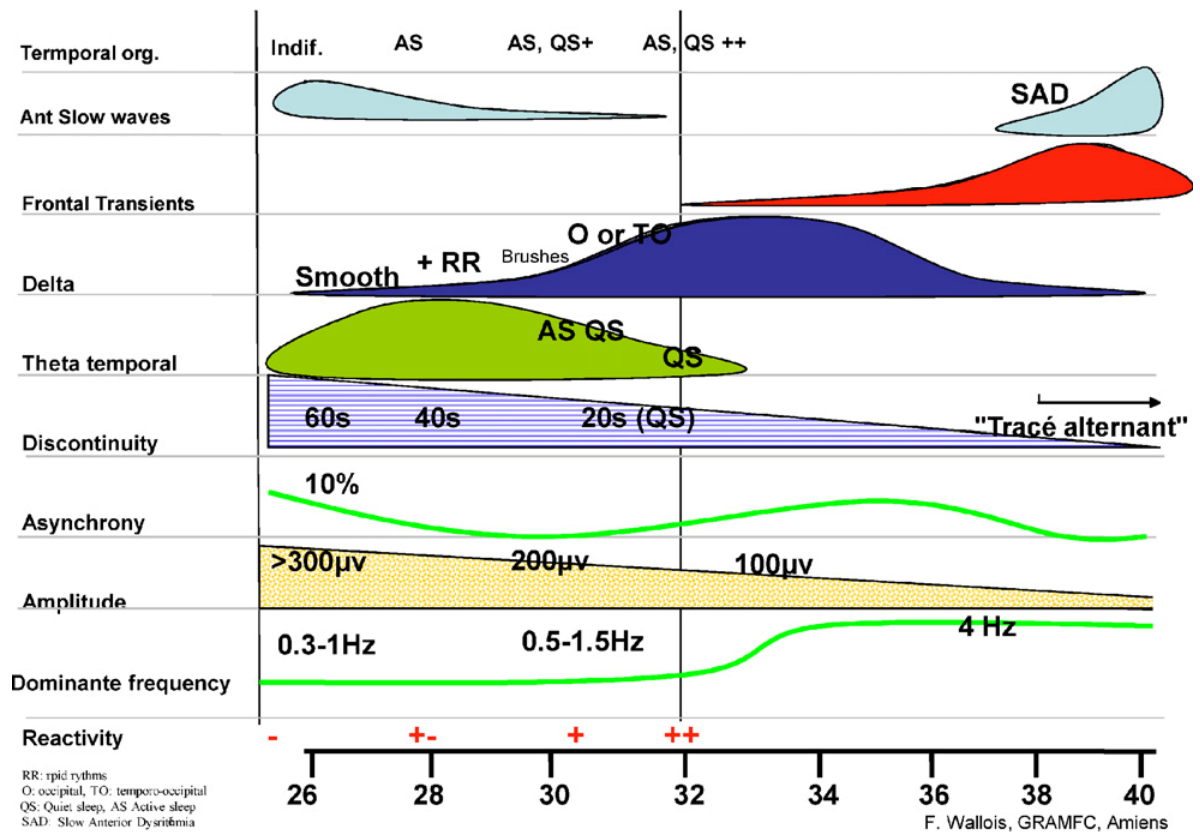
Fisher or  $\chi^2$  test for categorical variables.

<sup>a</sup> High maternal education level: university studies. <sup>b</sup> Small for gestational age: birthweight < 3e percentile. <sup>c</sup>

Necrotising enterocolitis:  $\geq$  Bell's stage 2. <sup>d</sup> Early onset sepsis: isolation of bacteria or fungi from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring  $\leq$  72 hours of life.

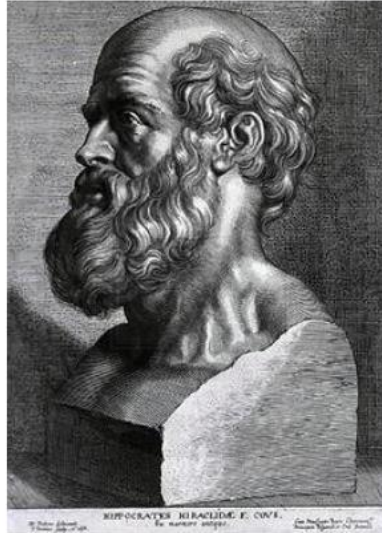


### Appendix 3: Maturation of specific features in EEG of premature neonates.



**Figure 1** Synopsis of maturation of specific features in EEG of premature neonates.

## Serment d'Hippocrate



### **SERMENT D'HIPPOCRATE**

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*

# PREMASCOL-EEG: CORRELATION BETWEEN NEONATAL EEG AND SCHOOLING AT AGE 5 IN PRETERM CHILDREN BORN BEFORE 33 WEEKS

Céline BRUNEAU BIBOULET *[Données à caractère personnel]*

Thèse soutenue à la faculté de Grenoble le 22/09/2021

Jury :

Monsieur le Professeur Thierry DEBILLON (Président)  
Madame le Docteur Alexa GARROS (Directrice de Thèse)  
Madame le Docteur Cécile SABOURDY  
Monsieur le Docteur Guillaume MORTAMET

## **Abstract**

**Context:** Preterm infants represent a large population (11% of birth every year worldwide), they are at high risk of neurodevelopmental sequelae and learning disabilities. A recent study has shown a correlation between neonatal EEG and neurodevelopmental outcome at 2 years old evaluated by Brunet-Lézine test.

**Objective:** To study the correlation between neonatal EEG grading and schooling at 5 years old, in very preterm infants born before 33 weeks of GA.

**Methods:** The study was monocentric and retrospective, it included children born before 33 weeks of GA between 01.01.2010 and 01.01.2014 in Grenoble Alpes University Hospital and followed in the local network "Naitre et Devenir". Neonatal EEGs were performed at 28 and 32 weeks of GA and could be controlled at full term or if there were abnormalities. Depending on the result of each EEG (normal, moderately abnormal, or severely abnormal) children were classified in three categories: normal, transiently moderately abnormal and very abnormal. Schooling was assessed at age 5 and classified in two groups: normal (unassisted age-appropriate schooling) and not normal.

**Results:** 420 EEGs were performed in 208 infants. EEG following was normal in 55%, transiently moderately abnormal in 23% and very abnormal in 22%. At the age of 5, 71% had a normal schooling. In univariate analysis schooling at age 5 was associated with neonatal EEG grading ( $p = 0,02$ ). The relationship was no longer significant after adjustment on confounding factors (gestational age, maternal education level, bronchopulmonary dysplasia, and sex).

**Conclusion:** Neonatal EEG surveillance could add information to help predicting neurodevelopmental outcome at age 5 in preterm newborns when associated with other predictors.

**Key words:** EEG, preterm, neurodevelopmental, schooling.

## **Résumé**

**Contexte :** Les prématurés représentent une grande population (11% des naissances chaque année à travers le monde), ils ont un risque accru de trouble du neurodéveloppement et de difficultés scolaires. Une étude récente montre une corrélation entre les anomalies de l'EEG néonatal et le score neuro développemental de Brunet-Lézine à 2 ans.

**Objectif :** Etudier la corrélation entre la surveillance EEG en période néonatale et la scolarité à 5 ans chez les prématurés nés avant 33 SA.

**Méthodes :** Cette étude monocentrique et rétrospective a inclus les enfants prématurés nés avant 33 SA entre le 01.01.2010 et le 01.01.2014 hospitalisés au CHU de Grenoble Alpes et suivis dans le réseau « Naitre et Devenir ». Les EEG néonataux ont été réalisés à 28 et 32 SA et ils pouvaient être contrôlés à terme ou s'ils étaient anormaux. En fonction des résultats de chaque EEG (normal, modérément anormal ou sévèrement anormal) les enfants ont été classés en 3 catégories (0: normal, 1: anormal modéré et transitoire, 2: très anormal). La scolarité a été évaluée à 5 ans et classée en 2 catégories : normale (classe appropriée à l'âge sans aide) et anormale.

**Résultats :** 420 EEG ont été réalisés chez 208 enfants. La surveillance EEG était normale dans 55% des cas, anormale de façon modérée ou transitoire chez 23% et très anormale chez 22%. A l'âge de 5 ans, 71% des enfants avaient une scolarité normale. En analyse univariée, la scolarité à 5 ans était associée avec la surveillance EEG néonatale ( $p=0,02$ ). La relation n'était plus significative après ajustement sur les facteurs de confusion (âge gestationnel, dysplasie bronchopulmonaire, niveau d'éducation maternel et sexe).

**Conclusion :** La surveillance EEG néonatale peut apporter des informations pour aider à prédire le neurodéveloppement à 5 ans chez les enfants prématurés quand elle est associée aux autres facteurs prédictifs.

**Mots clés :** EEG, prématurité, neuro développement, scolarité