Digital solution to improve cognitive function in epilepsy: PRODDIGE project

(PROjet de Développement d'une solution DIGitale de remédiation cognitive dans l'Epilepsie : PRODDIGE)

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Acronym : PRODDIGE
Full title: Digital solution to improve cognitive function in epilepsy: PRODDIGE project

1.1 Research characteristics

- Clinical research
- Multicentric
- Transversal : patient / normal control
- Randomized trial

1.2 Product(s)/strategy observed in the research

Randomized controlled trial to evaluate the use of a digital solution on epileptic patients' cognitive complaint about lexical access disorder.

1.3 Research Rationale and Working Hypotheses

Epilepsy is one of the most common chronic neurological conditions. It leads to cognitive disorders in 20-50% of patients. In comparison to seizures, these cognitive disorders are a major additional factor in occupational, social and family disability. They are particularly frequent (50%) in temporal epilepsies and concern most of time memory and language skills. These disorders are well described, multifactorial, but no therapy (drug and/or non-drug) has yet been validated (Brissart & Maillard 2018).
Recently, cognitive rehabilitation techniques have shown benefits in some neurological pathologies, such as multiple sclerosis (Brissart et al. 2020).
In adult epilepsy, few cognitive remediation studies that have been conducted have significant methodological shortcomings that limit the scope of their results (for review Del Felice et al, 2017; Joplin et al, 2018).
Studies have shown promising results in attention and memory (Engelberts et al., 2002; Helmstaedter et al., 2008) but in language, no study has been published.
Our objective is to evaluate the effectiveness of a digital solution with language exercizes in epileptic patients.

1.4 Main Objective

Evaluate the use of digital solution in total autonomy and compare it to the use of a neuropsychologist-supervised via teleconsultations with a sample of epileptic patients.

1.5 Primary endpoint

Number of weekly connections of epileptic patients in each group.

1.6 Secondary objectives

To compare the cognitive and behavioral abilities of patients before and after the program:
- Feeling the frequency of lexical access problems
- Self-esteem,
- Score and speed of oral naming

- Verbal fluency
- Information processing speed
- Selective and sustained attention
- Short-term memory
- Working memory
- Mental flexibility capabilities
- Mood
- Anxiety

1.7 Secondary Evaluation Criteria

Scores at :
- Questionnaire language score (0 to 12 points)
- Depression scale score (Neurological Disorder Depression Inventory for Epilepsy : NDDI-E) : 6 to 24 points : 6 better outcome
- Anxiety scale score (Generalized Anxiety Disorder: GAD-7): 0 to 21 points : 0 better outcome
- Self-esteem score (Rosenberg scale): 0 to 40 points: 40 better outcome
- Number of correctly named words and response time (Batterie d'Evaluation des Troubles Lexicaux) : 0 to 50 points : 54 = better outcome
- Computerized Speed Cognitive Test (CSCT): processing speed index: number of correct items in 90 sec. 0 to 110 points : 110 = better outcome
- Immediate memory: digit span: number of digits recalled correctly in location order: 0 to 9 score : 9 = better outcome
- Working memory: backward digit span: number of digits recalled correctly in inverse order: 0 to 9 score : 9 better outcome
- Selective Attention Test: Paced Auditory Serial Audition Test 4 seconds (PASAT): 0 to 60 score : 60 = better outcome
- Verbal Initiation Test: Phonological Fluency: number of words beginning with P given in 2 minutes: 0 to 50 words : 50 = better outcome
- Category fluency test: number of words given in 2 minutes that belong to the category of Animals: 0 to 50 words : 50 = better outcome
- Boston Naming Test (BNT): number of correctly named words (0 to 50 points) and response time in seconds : 50 = better outcome
- Lexicon access tests (Denomination Orale 80): number of correctly named words (0 to 80 words) and response time in seconds : 80 = better outcome

1.8 Number of Subjects required

Main hypothesis: Investigators postulate that the group of participants supervised by a psychologist via teleconsultations will have an average weekly number of connections at least twice as high as that measured in the total autonomy group.
Secondary hypothesis: Participants who use the solution should have a lower frequency of lexicon access disorders than participants who do not use it. This study should make it possible to assess its extent and discuss its clinical relevance.
To test these hypotheses, 3 groups of participants will be constituted:
- 1 group "application supervised by a psychologist via teleconsultations" (n=30)

- 1 group "application in total autonomy" (n=30)
- 1 "control" group without using the application (n=30).
A 4th group of "healthy controls" (n=70) will also be needed to calculate the "reliable change index" (an index that evaluates the potential learning effect when a cognitive test is performed twice over a period of less than one year). The larger size of the latter group is justified by the expected higher number of people lost to follow-up on the second visit.

1.9 Description / Subject Recruitment Methods

Healthy controls will be matched to participants on age (+/-5 years) and socio-educational level (+/-2 years of study).
All subjects will be seen during a consultation.
Participants will be recruited through their neurologist or neuropsychologist during a consultation as part of their usual follow-up.
Healthy controls will be recruited through posters in the neurology department University Hospitals, and in the practices of private neurologists

1.10 Are there any specially protected persons involved in your research?

☒ **NON** ☐ **OUI**

1.11 Criteria for inclusion of subjects

Inclusion criteria of epileptic participants:
☐ Patient with epilepsy, according to Fisher et al. (2005) criteria: all type of epilepsy could be include (new-onset and drug-resistant)
☐ Treatment must have been stable for 4 months: have the same molecule
☐ Person who has received full information about the organization of the research and has not objected to his or her participation and the use of his or her data
☐ Person aged 18 and over
☐ Mandatory affiliation to a social security scheme
☐ Validated cognitive inclusion criterion: having a YES response on the cognitive complaint questionnaire :
A.Spontaneous complaint :
Does the patient spontaneously complain of language difficulties?
B.Subjective complaint :
1. Do you search for your words?
2. Do you sometimes feel like you have the word on the tip of your tongue?
3. Do you sometimes have trouble finding the names of people you know well?
4. Do you ever say one word for another?
Inclusion criteria of normal control:
- Individuals who have received full information about the organization of the research and have not objected to their participation and use of their data.
- Person aged 18 and over
- Person with no neurological and/or psychiatric history

1.12 Non-inclusion criteria

Participants :

☐ Person with another neurological condition

Participants and normal control :

☐ A person over the age of majority who is subject to a legal protection measure or who is unable to express their consent.

☐ Person deprived of liberty by a judicial or administrative decision

☐ A person who regularly uses psychoactive substances (cannabis, alcohol, etc.).

1.13 Methods of information and non-opposition of subjects

Participants and healthy controls will be informed about the research specifically and individually on the day of the inclusion visit using the information document provided.
Non-opposition of the patient and healthy control will be sought by the investigator prior to any data collection in this research.

1.14 Search process

I. PATIENT COURSE :

Inclusion visit as part of the usual follow-up:

- Participants and subjects will be informed of the study by an investigator during a consultation at their respective centers.
- A neuropsychologist will carry out the consultations
- After verification of the eligibility criteria by the investigator and presentation of the objectives of the study, an information document will then be given to the patient for an attentive reading.
- After a reflection period, if the patient agrees to participate in the research and has not objected to the use of these data in this research, then randomization will be carried out via an online module (CleanWeb). This individual randomization will be done according to a 1:1 ratio with stratification by age (+/-5 years) and socio-educational level (+/- 2 years of study) and a randomization block of 4.
- The neuropsychological assessment (V1) will be carried out by the psychologist: it consists of questionnaires and cognitive exercises lasting one and a half hours (the cognitive functions tested are listed in paragraph 1.8).
- The characteristics of each patient's epilepsy will be collected from his or her computerized medical record.

Depending on the group obtained by randomization (A/ B / C), the psychologist will present the application to the patient or not, and will inform him or her whether or not he or she will have telephone appointments.

At the end of visit 1, participants will be invited to use the digital application at their convenience for the autonomous group (B). Participants in the teleconsultation group (A) will be called once a week for 16 weeks to follow up on their connection to the application and to check that they do not present any particular difficulties in using it. A link will be provided to download the application. It will be sent to the patient on paper at the end of the visit.
The duration of use of the digital application will be 4 months.
Group C participants do not use the digital application.

- **Follow-up visit (V2) = 5 months post-inclusion (research specific)**

During this visit, participants in group A, B or C will undergo a neuropsychological assessment. The patient in group A or B will provide to the psychologist his or her number of connections to the application.

The patient in group A or B will also answer an interview on how he or she feels about using the application.

I. NORMAL CONTROL COURSE :

- **Inclusion visit (research specific)**

Normal controls are recruited through posters and on a voluntary basis in the 4 centers. They are therefore in contact (telephone or e-mail) with the neuropsychologist of the study on their own initiative. The objectives of the study are then presented during this contact. If the subject gives his agreement, an appointment is fixed in order to carry out the inclusion visit. On the day of the visit, the subject is given an information document that he or she should take the time to read. After a period of reflection, if he agrees to participate in this research and if he does not object to the use of his data within the framework of this research, the acts specific to the research may be carried out (neuropsychological assessment including only cognitive data + collection of clinical characteristics).

- **Follow up visit : 5 months post inclusion (research specific)**

During this visit, the normal control will undergo the same neuropsychological assessment as in visit V1 with the neuropsychologist.

1.15 Modality of de-identification of subjects

Check the appropriate box(es) :

☐ by a serial number assigned to the inclusion

☒ other identification mode, specify: a number for the number of the center
- the order number assigned to the inclusion - A letter for the identification Patient (C) versus Witness (T) - subject initials (first letter of the surname and first name) + a letter for randomization (A: application group + teleconsultation), (B: autonomous application group), (C: control group)
The correspondence table that links the patient's identity to his or her inclusion number will be kept in the investigator binder stored with the CRFs in the locked cabinet in box 5 of the Neurology Department.

1.16 Nature of the data collected and processed

The data are collected specifically and prospectively on a written observation notebook.

For participants, the data collected for research are:
Data present in the medical record:
- patient demographics: gender, age, years of study after graduation, manual laterality, work activity and family situation
- clinical data: characteristics of epilepsy: age of onset, number of seizures, current drug therapy, type of epilepsy.
And neuropsychological assessment data:

- Questionnaires on self-esteem, mood, anxiety and feelings about the frequency of language difficulties.
- computerized (5 in total) and paper-and-pencil (3 in total) tests to measure language, attention and executive abilities.

Digital solution data:
At the end of the second visit, the patient will download a statistical file containing the number and time of connection to the digital solution. This file will be transmitted by the patient to the investigator in a secure way (via USB on a protected file).
No private data will be collected via the digital solution.
During the second visit, the patient will be asked questions on how he or she feels about using the digital solution and the answers will be directly reported in the observation notebook.

For healthy controls, the data collected for research are:
- demographic data: sex, age, number of years of study after high school graduation, manual laterality, professional activity and family situation.
- Inclusion and follow-up neuropsychological assessment data consisting of computerized (5 in total) and paper-and-pencil (3 in total) tests to measure language, attentional and executive abilities.

1.17 Flow of personal data and procedures for ensuring their confidentiality

Data Collection

During the course of the research, the Investigator, or any person designated in writing, will record, for each person included in the research, an observation notebook in paper format specific to the research from the source data.

The Investigator is responsible for the quality, accuracy and relevance of the data collected in the Observation Notebook, the data collection form.

Data Entry

Once documented and validated by the Investigator, the pages of the Observation Notebook of the different centers are sent to the Nancy University Hospital, to be entered into the database.

An Excel file will be created by the investigator and will be strictly located on the server of the university hospital. The pseudonymized data will be collected and entered in this file by the investigator. This file will then be transmitted for statistical analysis to the UMDS in a secured way via USB key protected by a password.

Data Analysis

The statistical analyses will be carried out within the Data Management and Statistics Methodology Unit (UMDS)- DRCI.

In accordance with the third paragraph of Article 56 of the French Data Protection Act, the presentation of the results of data processing may under no circumstances allow the direct or indirect identification of the persons involved in the research.

1.18 Duration

Duration of subject participation: 5 months
Length of inclusion period : 2 years
Total research duration: 3 years

1.19 Statistical Analysis

Descriptive analysis: The parameters collected will be described in each group by percentages (categorical variables), mean +/- standard deviation, quartiles, and extreme values (continuous variables).
Main analysis: the comparison of the mean number of connections will first be carried out by a parametric (Student's t) mean comparison test or its non-parametric (Man-Withney) equivalent if the hypotheses of normality and equality of variances are not verified. In the case of significant

differences in one or more parameters between the 2 groups compared, these adjustment variables will be introduced into a linear regression model. A stepwise selection method is provided.
Secondary analysis: Before-after comparisons will be performed by tests on paired series, the Student's t-test when the variable to be compared is quantitative (or the Wilcoxon test), and Mac Nemar's Chi2 when the variable to be compared is qualitative.
The value of the "Reliable Change Index" will be obtained in the group of healthy controls by the product of the standard error of the score concerned and the standard deviation of the difference observed at 2 measurement times.
The significance threshold is set at 5%. An a posteriori power calculation is also planned.
The analyses will be performed by the UMDS, using SAS v9.4 software (SAS Institute Inc., Cary, NC, USA).

1.20 Research-related benefits

Today, no digital solution is adapted to our epileptic participants in the management of lexical access disorders.
The expected benefits are an improvement of the participants' language complaints, the regular use of a dedicated digital solution to improve their language difficulties, but also a better understanding of their disorders and an improvement of their self-esteem.

1.21 Funding

Specify the source of funding: UCB PHARMA
Participants neuropsychologist time:
- Estimated neuropsychological time (V1=2.5 hours) x 90 participants x 39€ = 8775€.
-Teleconsultation time (group A) = 16 calls from 15 min to 10.5 = 5040€
- Estimated neuropsychological time (V2=2 hours) x 90 participants x 39€ = 7020€.
-Travel to the private neuropsychologist's office: 20 participants = maximum 5 days of consultation in Strasbourg/ if we estimate inclusions per office = 1500km x 0.35 = 525€.
Healthy subjects neuropsychologist time:
- Estimated neuropsychological time (V1=2 hours) x 70 healthy subjects x 39€ = 5460€.
- Estimated neuropsychological time (V2=1 hour) x 70 healthy subjects x 39€ = 2730€.
- Travel to the private neuropsychologist's office: Healthy control = maximum 4 days of consultation in private practice/ if we estimate inclusions per office = 1200km x 0.35 = 420€.
- 20 euros per healthy subject per visit: 40€ x 70 healthy subjects: 2800€.
- Purchase 2 BETL licenses / 360€ = 720€

- Reimbursement of patient transport time: 20 *90 = 1800€
- Methodology : 1500€.
- Design of the randomization module under CleanWeb: 1000€.
- Statistical analysis, production of reports: 4000€.
- Administrative costs of setting up (1 external centre): 150 euro

Total budget estimated at 41940 €

1.22 References

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