



## **SCIENTIFIC PROJECTS PROPOSAL TO NINA (Network italiano Neurologia Autoimmune)**

Please describe below the project. Try to be concise in the description. NINA steering committee might ask for further specification if needed.

### **TITLE OF THE PROJECT**

Cognitive teleRehabilitation in patients with Encephalitis of AutoIMMune etiology:

CoRE-AIM study

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**FUNDING** *(Please specify if the study is already funded. If funding is needed, and the proposal is approved by the Steering Committee, NINA support can be requested to apply for specific funding)*

Autoimmune Encephalitis Alliance SEED Grant

### **SUMMARY OF THE PROJECT**

The CORE- AIM study is a pilot project to evaluate the feasibility of cognitive rehabilitation in patients affected by autoimmune encephalitis (AIE). We believe that cognitive rehabilitation could be particularly suitable for those kind of patients, considering that most of them show “functional”, rather than “structural” alterations, likely to have higher margin for improvement. Several case reports actually showed an improvement of neuropsychological performance using cognitive rehabilitation, but there are few systematic data due to the rarity of the condition. We developed and validated an efficient software for cognitive telerehabilitation (HomeCore), that could work efficiently for administer cognitive rehabilitation by remote.

One of the mechanisms exploited by cognitive rehabilitation is neuronal plasticity, the ability of the brain tissue to adapt functionally and structurally to negative and positive stimuli modifying the cerebral connectivity. A measure of brain connectivity and its changes could be detected using advanced magnetic resonance imaging techniques such as the “resting state” functional MRI (fMRI), diffuse tensor imaging MRI (DTI-MRI) and high density-EEG (hd-EEG). Likely we can evaluate the effect of cognitive rehabilitation on connectivity in patients with AIE.

### **BACKGROUND, RATIONALE AND PRELIMINARY DATA**

Autoimmune encephalitis (AIE) is a rare but treatable condition characterized by heterogeneous neuropsychiatric features, that usually improves with the administration of immunotherapy. Most studies report patient's outcome measured with general disability scales, such as the median Rankin Scale (mRS), as "good" in the majority of patients. However, many AIE patients show neuropsychiatric sequelae that can persist despite the recovery of other neurological functions, representing one of the most important contributor to morbidity. The most common long term cognitive alterations in AIE patients involve the memory and executive functions and, in some cases, these are associated with structural modifications such as atrophy in specific brain regions (mainly hippocampus and amigdala). Cognitive rehabilitation is a technique based on the administration and completion over time of different tasks, that has shown promising results in patients with several neuropsychiatric conditions including mild cognitive impairment, traumatic brain injury, Parkinson's' disease and schizophrenia. Cognitive rehabilitation would be particularly suitable for patients with AIE, especially considering that most of them show "functional", rather than "structural" alterations, likely to have a higher margin for improvement. In addition, cognitive improvement in patients with AIE is possible even several months or years after the index encephalitic event, thus supporting a role for cognitive rehabilitation even in later stages of disease. Supporting this hypothesis, several case reports showed improvement of AIE patients using cognitive rehabilitation, but systematic data collection in this field have been hampered by the rarity of the condition, the feasibility of cognitive rehabilitation in patients with AIE (that frequently show behavioral abnormalities) and the recent travel restrictions related to the SARS-CoV2 pandemics. In this scenario, the validation of a remote strategy to administer cognitive rehabilitation would facilitate its use in AIE patients. Recently, we developed and validated an efficient software for cognitive telerehabilitation (HomeCore) highly suitable for this purpose (see preliminary data). One of the mechanisms exploited by cognitive rehabilitation is neuronal plasticity, the ability of the brain tissue to adapt functionally and structurally to negative and positive stimuli modifying the cerebral connectivity. Interestingly, positive modifications in functional and structural connectivity have indeed been detected using advanced magnetic resonance imaging techniques such as the "resting state" functional MRI (fMRI) and diffuse tensor imaging MRI (DTI-MRI) in patients with Parkinson's' disease, Multiple Sclerosis and Schizophrenia that underwent cognitive rehabilitation. Modifications in connectivity are likely implicated also in AIE, as supported by the results of fMRI and DTI-MRI investigations in this group of patients, but the effect of cognitive rehabilitation on connectivity has never been evaluated in AIE. Additionally to fMRI, brain connectivity can also be measured using high density-EEG (hd-EEG), as demonstrated in patients with PD and other neurodegenerative condition, but this technique has never been used to assess the outcome in patients with AIE. In our pilot study we aim to assess the feasibility of cognitive telerehabilitation in patients with AIE, and to obtain preliminary results on its impact on cognitive outcome and brain connectivity.

## **METHODS AND SAMPLE SIZE**

A total number of 15 patients with AIE will be enrolled according to inclusion criteria. Patients at any stage of the disease and with different forms of AIE will be intentionally included, as preliminary data on specific subtypes of AIE might help to define the ideal population for a future trial. Patients will perform at the beginning of the study (T0) an evaluation including full neuropsychological battery, behavioral and depression questionnaires, usability questionnaires, hdEEG and fMRI. Afterwards, patients will receive training in the use of the HomeCore software on a touch screen laptop from a neuropsychologist and will perform a course of remote cognitive rehabilitation for 12 weeks. At the end of the course, patients will repeat within 30 days (T1) all the evaluation performed at T0.

## INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	Exclusion criteria
Age between 18 and 85 years	Complete aphasia
Autoimmune encephalitis according to Graus 2016	Neglect
Presence of cognitive alterations in at least one domain	Neurological disturbances that might interfere with the neuropsychological testing or the treatment
Available to sign the informed consent	MMSE<20

## PROJECT DURATION

This is a pilot feasibility prospective interventional study. Enrollment will last for 18 months; the total duration of the study will be 24 months.

**ETHICS AND PATIENT** *(please specify whether the project has already been approved by a local ethics committee)*

The study has been approved by the IRCCS San Matteo ethic committee (Pavia)

**SUPPORT REQUESTED BY NINA** *(please specify what type of support is requested from the network. For example, diffusion of the study to other centers to improve patients' referral for enrollment, direct enrollment in participating centres, collection of serum/CSF/DNA samples, etc.; samples, please specify inclusion criteria) (max 1000 words)*

In the present study patients will be enrolled only in Pavia. It will be required to them to come to Pavia three times, once for the screening, once to perform the required testing and receive the laptop for the cognitive rehabilitation and once at the end of the study, to give back the laptop and perform the final testing. Patients will receive a reimbursement for the travel expenses.

We ask to the network to refer potential candidates to our centre for this purpose.

**RULES FOR AUTHORSHIP** *(max 1000 words) (please specify in advance how the contribution will be considered in terms of authorship- ex: at least 5 patients enrolled to enter full authorship, etc..)*

Each center referring patients will be included in authorship (one name per centre).

**CALL FOR PARTECIPATION** *(max 1000 words) (please provide a brief text that will be published on the website and sent to all the NINA members to raise interest for your project. The full proposal will be attached to the call for participation)*

We are implementing a protocol to perform remote cognitive rehabilitation in patients with AE at any stage of the disease, even years after the acute event. Patients will be enrolled in Pavia but will have to access the Institution only two-three times in total. Travel expenses will be covered by project funding. If you are following-up patients with AE, check the project and/or contact us to discover if they are eligible!

Stiamo sviluppando un protocollo per l'esecuzione di una riabilitazione cognitiva in remoto in pazienti con encefalite autoimmune in ogni fase di malattia, anche anni dopo l'evento acuto. I pazienti saranno reclutati a Pavia ma dovranno venire in Istituto solo 2-3 volte in totale. Le spese di viaggio e soggiorno possono essere coperte dai fondi del progetto. Se segui pazienti con encefalite autoimmune, contattaci per sapere se sono eleggibili!

## CONTACTS

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