Canada-China-Cuba Axis

A.C. Evans, D. Yao, M. Valdes-Sosa et al.

The Canada-China-Cuba Axis (CCC Axis) is a tri-national effort to build an international platform for neuroscience data-sharing. It was originally funded through 3-year grants of $100K p.a. from FRQ in Québec, $100K p.a. from the National Science Foundation of China and in-kind support from the Cuban CITMA. On March 6th, 2020, the FRQ re-affirmed its commitment to the CCC Axis initiative by supplementing its financial contribution to HBHL by a further $50K p.a. for the 4 years of April 1 2020 to March 31st, 2024 (see attached letter from Rémi Quirion, Chief Science Officer for Québec). The project has achieved most of its technical goals (see Progress Report below) and and is now positioned to expand to broader scientific engagement via the CCC Axis platform. The Chinese and Cuban governments have expressed their interest in continuing the project to this next phase but await confirmation from the Canadian side. We therefore formally request continued support from HBHL for the CCC Axis, at the level of $50K p.a., as allocated by FRQ and as documented in Table 1.

N.B. The CCC Axis Neuroimaging Neuroinformatics Platform (NNP) is based around two core HBHL NeuroHub components, the LORIS multimodal web database and the CBRAIN high-performance computing portal. As such, the CCC Axis, and its sister GBC, address a primary HBHL deliverable of improving global mental health. This outreach to underserved populations is not restricted to disadvantaged countries but is also of relevance for underserved populations in Canada, e.g. indigenous communities.

Budget Category	Year 1	Year 2	Year 3	Year 4
CCC Axis Project Manager (0.25 FTE)	15,000	15,000	15,000	15,000
CCC Axis software support (0.25 FTE)	15,000	15,000	15,000	15,000
Travel between international sites	15,000	15,000	15,000	15,000
Consumables, publication & phone costs	2,500	2,500	2,500	2,500
Conference expenses	2,500	2,500	2,500	2,500

Table 1: HBHL Fund Allocation for CCC Axis

CCC-Axis Budget Justification

CCC Axis Project Manager (0.25 FTE): We request 25% support for a project manager to oversee project logistics, data sharing, trouble-shooting, travel, conference planning.

CCC Axis software support (0.25 FTE): We request 25% support for a software. developer to maintain the project website, oversee pipeline installation, data analysis.

Travel: We request $15K p.a. to support travel of trainees between three CCC Axis sites. Based on past experience, we anticipate 10 visits p.a. @ $1,500 per visit.

Consumables: We request $2,500 p.a. to cover small equipment replacement (cabling, power supplies etc.), data transfer costs, long-distance phone charges etc.

Conference costs: We will organize one face-to-face meeting per year. Travel costs are included above but we will need to cover conference materials, banners, posters etc.

Axe trinational du vieillissement cognitif normal et pathologique

(Tri-national axis in normal and pathological cognitive aging)

Progress Report, March 25th, 2020

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Introduction

In 2017, after a meeting in Havana, Cuba the Fonds de recherche du Québec (FRQ), the Ministry of Science, Technology and Environment (CITMA) of Cuba and the National Science foundation of China (NSFC) approved a tri-country project to create a Neuroinformatics Platform that would set the stage for coordinated search for biomarkers and treatments for aging-related disorders in the three partner countries (Figs. 1,2). Jointly, the funding agencies provided ~$1M in support over three years to initiate a tripartite collaboration, dubbed the Canada-Cuba-China (CCC) Axis. The FRQ component, $100K p.a. over three years, arose from a 2017 grant entitled 'Trinational Axis in Normal and Pathological Cognitive Aging'. This project is co-directed by **Alan Evans** (McGill U.), **Dezhong Yao** (U. of Electronic Science and Technology of China, UESTC) and **Mitchell Valdes-Sosa** (Centre de Neurosciences de Cuba, CNEURO). The teams include co-investigators and 25 collaborators, including researchers from Concordia U., U. de Montréal, U. Laval in Québec, and Beijing Normal U. in China. Funding was approved in 2017 and CCC collaborative activities commenced in January, 2018. These activities provide primarily methodological and neuroinformatics support for neuroscientists of the national brain research projects as well as the integration of data/tools across the three countries, through the Neuroimaging Neuroinformatics Platform (NNP). The NNP is being used in particular to advance our understanding of the basic mechanisms of dementia and identify early biomarkers of Alzheimer's disease.

In 2019, the CCC Axis spun off a broader initiative to incorporate other countries into this network, including the US and countries in Europe and Latin America. This Global Brain Consortium (GBC) is focussed more on the application of Western brain mapping technologies in Low and Middle Income Countries (LMICs), i.e. the CCC Axis focuses on technology development whereas the GBC is more concerned with application of those technologies. The CCC platform incorporates Electroencephalography (EEG) as a primary tool to allow widespread evaluation of brain states in all economic settings, notably under-resourced areas. The GBC has held two annual workshops (in Canada and in Cuba) of ~60 attendees, most recently at the end of February, 2020.

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Objectives

Based on previous collaborative work of research teams from China, Québec and Cuba, the CCC-Axis project comprised the following work packages (WP) to cover 5 research objectives:

WP1: Harmonization of the basic NNP software and data gathering protocols

a. Adopt CBRAIN/LORIS in CCC-Axis institutions as the backbone for further development
b. Harmonization of MRI, DWI, fMRI, EEG, MEG, fNIRS, genetic, behavioral data in LORIS

WP2: Expansion of the NNP processing capabilities with validated tools

a. Integrate various processing tools into CBRAIN (REST, qEEGT, GRETNA, PANDA)
b. Integrate new data types and management capabilities in LORIS (e.g. methylation data)
c. Implement standard pipelines for data processing within LORIS with the outputs available within the LORIS querying tool (e.g. cortical thickness, FA measures etc.).

WP3: Development and incorporating into the NNP of tailored statistical toolboxes

a. Development and selection of biomarker packages
b. Diagnostic and Economic evaluation of potential stratified health actions
c. Multimodal disease progression models

WP4: Population of the shared NNP LORIS databases

a. Populate LORIS with large International Datasets (ADNI, HCP, UK Biobank, Cam-CAN)
b. Include specific datasets from validated studies from each country
c. Include pilot samples from each country to evaluate standardized protocols

WP5: Using the NNP for research and clinical studies on age-related disorders

a. Answer specific research questions about the informational capacity of inexpensive functional neuroimaging (EEG, fNRIS) versus more expensive ones (fMRI, MEG)
b. Proposal of optimal biomarker set for predicting conversion from MCI to AD

Progress

Progress is presented on the following pages, organized by Work Package. Please note that, since the CCC Axis is largely a technological initiative, the following text contains numerous technical terms.

WP1: Harmonization of the basic NNP software and data gathering protocols

Tasks

- Year 2018. Install and further develop CBRAIN/LORIS in PERFORM (Concordia U.)
- Year 2018. Deploy standardized neuroimaging protocols to sites in Cuba and China (U. Laval)
- Year 2018. Install, develop CBRAIN/LORIS in China (McGill U., UESTC, Beijing Normal U.)
- Year 2018. Install, develop CBRAIN/LORIS in Cuba (McGill U., Concordia U., CNEURO)
- Year 2018. Quality control/assurance procedure for data acquisition in Cuba, China (U. Laval)
- Year 2018. Use the Boutiques framework for applications in CBRAIN (Concordia U., McGill U.)
- Year 2018. Harmonize resting-state and cognitive fNIRS (U. Montreal, Concordia U.)
- Year 2018. Harmonize Diffusion MRI acquisition protocol (U. Sherbrooke, U. Montreal)
- Year 2019. Develop Canadian Dementia Imaging Protocol, version 2.0 (U. Laval, CNEURO)

Achievements

1) Creation of a CCC neuroinformatic platform. This allowed work between the three CCC-Axis countries using the LORIS-CBRAIN environment for data storage and processing.
2) The Cuba and China portals serve as testing facilities for new datasets and pipelines developed by CCC-Axis researchers before posting them in the main node at the MNI. They also allow optimizing of the internet connectivity between the three countries. The MNI's LORIS team visited CNEURO to install LORIS at CNEURO, Shawn Brown (MNI) visited Chengdu to install CBRAIN at UESTC and Simon Duchesne visited Cuba and Chengdu to harmonize MRI protocols.
3) The CCC-Axis currently hosts on Compute Canada, neuroimaging data for 3920 subjects from 8 countries/brain projects.
4) Canadian and Cuban imaging protocols were exchanged, to harmonize parameters.
5) The protocols for neuroimaging of patients with dementia and ataxia were harmonized with the quality parameters and standards of the CDIP.
6) The schemes and procedures for recording data in the MRI 3T Scanner at CNEURO, as well as for its quality control, were also harmonized.
8) A local LORIS server was installed and configured at CNEURO. In 2020, a Cuban researcher will visit the MNI for the development of Deep Learning methods for quality control procedures.
9) A local CBRAIN server was installed and configured at CNEURO. The FSL and Freesurfer tools were enabled and tested in this local server.
10) Development of templates and scripts for the automatic introduction of neuropsychological and demographic data within the databases in LORIS.
11) Anonymization of DICOM images of the Cuban Human Brain Mapping database, stored in LORIS.
12) Incorporation of new tools such as Docker containers and the Boutiques descriptors for the introduction of pipelines into CBRAIN.
13) New functionalities were created to allow the reading of compacted data (zip files) within the CBRAIN and automatically decompress them for the processing.

WP2: Expansion of the NNP processing capabilities with validated tools

Tasks
- Year 2018. Develop CBRAIN to support large, population datasets (Concordia U., McGill U.)
- Year 2018. Integrate Matlab platforms for EEG analysis on CBRAIN (Concordia U., McGill U.)
- Year 2018. Integrate Python processing pipelines (MEG/EEG/fMRI) into CBRAIN (U. Montreal)
- Year 2018. Install fNIRS toolboxes in CBRAIN and LORIS (U. de Montreal, Concordia U.)
- Year 2018. Deploy NIAK toolbox within CBRAIN for fMRI analysis (U. Montreal. McGill U.)
- Year 2018. Install an Electrical Brain Source Connectivity toolbox on to CBRAIN (UESTC)
- Year 2018. Install toolboxes for fMRI (GRETNA) and DTI (PANDA) (Beijing Normal U.)
- Year 2018. Install a quantitative EEG toolbox (qEEGT) on CBRAIN (CNEURO)
- Year 2019. Incorporate a BIDS-EEG format into LORIS (CNEURO, Concordia U.)
- Year 2019. Create standard pipelines for Quantitative EEG processing (CNEURO)
- Year 2019. Create standard pipelines for Quantitative MEG processing (UESTC)
- Year 2019. Create standard pipelines for structural network analysis (Beijing Normal U.)
- Year 2019. Create standard pipelines for multimodal (EEG-fMRI) fusion analysis (UESTC)
- Year 2019. Create standard pipelines for Lifestyle and social variables (Concordia U.)
- Year 2019. Create standard pipelines for Quantitative fNIRS (U. Montreal, Concordia U.)

Achievements
The Cuban Brain Mapping Project (CHBMP) database of EEG/MRI was anonymized and uploaded to LORIS in BIDS format. Furthermore, the neuroinformatic facilities created in Chengdu have allowed us to store data from 11 studies at the Chinese node in Chengdu. This information is currently being analyzed. Figs. 3,4 provides more information about these studies. At the moment, we have processed:
- 948 multimodal MRI studies from the Child Mind Institute (CMI)
- 1138 from the Parkinson's Progression Markers Initiative (PPMI)
- 840 MRIs from a longitudinal study of 245 subjects from the Prevent-AD database

All of the pipelines listed above under *Tasks* are now running on CBRAIN. The multi-modal CCC Neuroimage Neuroinformatic Platform (Figs. 5,6,7,8) allows development of fully-automated pipelines for massive processing of brain data. Salient examples include:

- work is under way to employ the BigBrain resource for neural mass modelling, taking advantage of the fine cytoarchitecture provided by this template. We plan to integrate this work within a “Virtual BigBrain” project that will make possible a binding between atlases, neural mass modelling environments and subject-specific models (both controls and patients).

- Quantitative EEG analysis at both the scalp and the sources (qEEGt) toolbox has been integrated into CBRAIN. It allows normative statistical parametric mapping of EEG source spectra (paper R1).

- A pipeline for EEG inverse solutions includes most common methods, as sLoreta, VARETA, as well as non-linear inverse methods based on sparse algorithms. It includes the new BC-VARETA, which incorporates, for the first time, simultaneous estimation of source activation and connectivity matrix.

- We have developed two processing pipelines (in Matlab): one for the computation of the electrical lead field using realistic head models and another for computing electrophysiological source localization using multiple penalized least squares methods, in collaboration with UESTC, China.

WP3: Development and incorporating into the NNP of tailored statistical toolboxes

Tasks
- Year 2018. Put REST and EEG-fMRI fusion toolboxes on CBRAIN (UESTC)
- Year 2019. Incorporate Freesurfer-based structural data into LORIS (U. Laval)
- Year 2019. Put toolboxes for diffusion MRI from FSL and MRtrix on CBRAIN (U. Sherbrooke)
- Year 2019. Integrate biomarkers toolbox for multimodal data (CNEURO, UESTC)

Achievements
- Creation of multi-national qEEGt developmental normative equations. We started this project with EEG datasets from an international collaboration with Switzerland, Mexico, Cuba and the USA, with more than 800 cases. This work is currently in preparation for publication (D9).

- The development of tools for the early detection of EEG biomarkers. This effort can combine, in the same algorithm, multimodal information from different sources. Three papers are in preparation describing this methodology. This toolbox is in preparation for integration into CBRAIN. Papers published in this topic: 10, 11, 12, 13, 16, D8).

- Containerization of a pipeline for biomarkers detection. This pipeline implements the method described in paper 10) and has been used for studies presented in papers 11), 12), 13) and 14).

- Development of a Matlab toolbox for the selection/determination of biomarkers from multimodal data. The pipeline has been integrated within CBRAIN.

WP4: Population of the shared NNP LORIS databases

Tasks

- Year 2019. Populate LORIS with International Datasets (ADNI, HCP, UK Biobank, Cam-CAN)
- Year 2019. Include specific datasets from validated studies from each country.
- Year 2019. Include pilot samples from each country to evaluate standardized protocols
- Year 2019. Simultaneous high-density EEG-fMRI resting state data into LORIS (Concordia U.)
- Year 2019. Include MRI/PET/EEG/clinical data from PERFORM (Concordia U.)
- Year 2019. Include fNIRS data from a young healthy adult group (U. Montreal)
- Year 2019. Collect pilot NIRS data in age-related disorders (CNEURO, U. de Montreal)

Achievements

- We have incorporated the ADNI, HCP databases into LORIS. We have obtained approval from the UK Biobank to host this data for local access by McGill researchers.

- We have integrated the Cuban Human Brain Mapping Project (CHBMP) database into LORIS. This dataset contains information of 282 randomly selected healthy adults. It contains high-density EEG, MRI, DTI, demography and psychological tests (draft D2). Neuropsychological tests include WAIS, Mini Mental, reaction time, handedness test, as well as weight and other physiological data. The anonymized version of the CHBMP database in LORIS is publicly available at https://cbmp-ccc.cneuro.cu/ (after registration by site administration).

- A Cuban researcher visited Dr. Gallagher's LION group for a training in collecting fNIRS data. This work will expand into production-level data collection during 2020.

WP5: Using the NNP for research and clinical studies on age-related disorders

Tasks
- Year 2020. Compare EEG/fNRIS with more expensive fMRI/MEG approaches.
- Year 2020. Propose optimal biomarker set to predict conversion from MCI to AD.

Achievements
Global Brain Consortium (GBC): The GBC initiative was born as the result of CCC-Axis activity and was created by the same researchers who are leading the CCC. It arose as a natural consequence of the CCC activity expansion, to globalize this effort and to involve a number of scientists from countries not involved in the initial CCC-Axis initiative (US, Europe, Australia). The GBC is complementary to another multi-national effort, the International Brain initiative (IBI), in that the GBC is focused specifically upon EEG applications, especially in Low- and Middle-Income Countries whereas the IBI aims to coordinate activity among the broader national brain projects around the world. GBC and CCC were represented in IBI meetings in Shanghai, China, March 2019 (Alan Evans, Dezhong Yao, Pedro Valdes Sosa and Maria Bringas) and at the IBI meeting in Daegu, Korea in September 2019 by Dr Pedro Valdes-Sosa and Maria Bringas who attended these meetings on behalf of the CCC/GBC and the Cuban and China Brain Projects. A special issue of NeuroImage, entitled “Neuroimaging for global health”, was launched in July 2019 with around 25 papers in preparation. Editors: Pedro Valdes, Christoph Michel, Tonya White, Shekkar Saxena.

AD Biomarkers: Although no definitive biomarker set has been yet been proposed for **predicting** conversion of Mild Cognitive Impairment (MCI) to Alzheimer’s disease (AD), considerable work has been completed in this direction. Specifically:

- The Prevent-AD dataset has been made public through the Canadian Open Neuroscience Platform (CONP,PI Alan Evans). This dataset is a deeply-phenotyped (imaging, genetics, clinical, behavioural data) cohort of subjects **at-risk** for developing AD through having family member(s) previously diagnosed with AD. This unique cohort offers the possibility of identifying very early biomarkers of incipient AD. A paper describing the Prevent-AD database has been submitted (paper R2) and the database is currently being analyzed in UESTC and CNEURO, making use of the CCC-Axis Neuroimage Neuroinformatics Platform (Figs. 5,6,7,8).

- Yasser Iturria-Medina, now at the MNI but an alumnus of both CNEURO and UESTC, has developed a multi-modal data analysis algorithm that identifies a personalized therapeutic fingerprint for each patient with dementia (paper 29). This paper uses control theory to match a multi-pronged therapeutic intervention to a patient’s individual metabolic and genetic profile.

- Joke Vogel, PhD student with Alan Evans at the MNI, has been investigating the role of the misfolded tau protein in the pathogenesis of AD. He has published two papers (papers 30, 31) on his work in this area, work that implicates tau protein in a pathology cascade also involving another misfolded protein, beta amyloid. For this work, he was awarded the Young Investigator Award at the 2020 Human Amyloid Imaging (HAI) conference. Dr. Evans also gave the HAI Keynote Lecture on this topic.

Other CCC-Axis Derived Results and Projects

1) The launch of the Cuban Brain Project at the Scientific Pole of Havana was broadcast at the Cuban National TV News in the presence of the Cuban President Miguel Díaz-Canel. The CCC-Axis was explained to the Cuban Government and to the general public (Figs. 1,2).

2) Longitudinal EEG studies: The co-organization and analysis of the longest EEG study in the world (>50 years), on the effect of the early malnutrition in the cognitive development in the adulthood, which was initiated in Barbados in 1977 by Dr. Janina Gallagher. These data were ingested into the CCC-Axis Platform and analyzed using CNEURO's qEEGt suite. A paper has come out from this work along with several workshop presentations. New PhD theses and papers are ongoing based on the analysis of these data. These efforts involve researchers from the three CCC-Axis nodes (Papers 7, 16, D5, D7).

3) Expansion of the CCC-Axis into the Global Brain Consortium (GBC), and at the International Brain initiative (IBI). GBC and CCC was represented in several meetings, in Shanghai March 2019 (Alan Evans, Dezhong Yao, Pedro Valdes and Maria Bringas-Vega) and the IBI meeting in Daegu Korea in September 2019 by Dr Pedro Valdes-Sosa and Maria Bringas-Vega who attended these meetings representing GBC and the Cuban and Chinese Brain Projects (draft D1).

4) Organization of the 2nd GBC meeting in Varadero, Cuba on Feb 28-29, 2020. Cuba was an ideal bridge between advanced technologies in developed countries and large populations of under-served people in Low- and Middle-Income Countries (LMIC's). Cuba has public brain health challenges that affect many LMIC's but, uniquely, has a strong scientific and technical class that can translate advanced technologies into LMIC settings. Many of these people were presenters at the meeting. The meeting had considerable input in the areas of consciousness, EEG technology, precision medicine/customized intervention and public brain health.

5) The CCC-Axis collaboration has been extended to other projects. Examples include:

a) the BIDS-EEG initiative with Cyril Pernet. A BIDS-EEG data format converter has been written following the specifications in the relevant Pernet paper.
b) EEG processing toolboxes, e.g. LOSSLESS pipeline, with J. Desjardins, U. of Toronto.
c) The Child Mind Institute (CMI): dataset of 1306 Healthy children already in the Chengdu cluster. 943 MRI processed: surfaces extracted, head model fitted, Lead Field calculated for EEG inverse solutions. Ongoing projects for EEG analysis undergoing quality control.
d) Presenilin mutation Alzheimer of Colombian family (draft D8).
e) EEG biomarker for childhood learning disorders, Dr. G. Chiarenza, Italy (papers 11,12).

6) Actions in China

a) Beijing Normal U. (BNU) has launched an EEG longitudinal study of 30,000 children to study neurodevelopmental learning disabilities. UESTC will provide EEG methodology.
b) Institute of Neurosciences ION of Shanghai (ION): The ION Director, Mu-Ming Poo, is collaborating with the CCC-Axis on creation of a mesoscale atlas of the macaque brain.
c) October 2019. Visit of Pedro Valdes and senior officers of the CITMA from Cuba to the National Science Foundation of China in Beijing, to assess their intention to extend the CCC-Axis project.
d) Visit to the Ministry of Science and Technology of China (MOST) October 2019 to promote new international cooperation

e) Creation in 2016 of the Academician Station for “Precision Brain Health” in Chengdu funded by the UESTC with 3 million RMB. The main objective is to invite academicians from other countries to collaborate in joint projects.

f) In all the above visits, the GBC was represented to invite potential Chinese partners in a Global Precision Health project.

7) Organization of meetings by CCC-Axis Leaders:

- Basic and Clinical Multimodal Imaging (BACI), Chengdu, Sep 2019 (Yao, Valdes-Sosa)
- Global Brain Consortium (GBC), Varadero, Feb. 2020 (Valdes-Sosa, Evans)
- Human Brain Mapping (HBM), Montreal, Jun. 2020 (Evans, Doyon, LOC Co-Chairs)
- International Organization of Psychophysiology (IOP), Chengdu, Sep. 2020 (now 2021)

8) Canadian EEG Network: In March, 2020, a grant was submitted to Brain Canada to establish EEGNet, a Canadian network of clinical and basic neuroscientists engaged in EEG research. The proposed network, led by Alan Evans at McGill U., comprises 31 researchers, 10 with strong methodological credentials and 21 with interests in specific clinical research applications, e.g. autism, ADHD, depression, Alzheimer’s disease, Parkinson’s disease. EEGNet will make extensive use of the CCC-Axis platforms LORIS and CBRAIN. It also has an international component that includes the CCC-Axis partners at UESTC and CNEURO. If successful, EEGNet will provide a further layer of trans-national integration in the area of electrophysiology and its applications, complementing the existing Canadian Open Neuroscience Platform, the Global Brain Consortium and the CC-Axis, all mediated by a common IT platform.

Publications

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18) Dong L, Liu X, Zhao L, Lai Y, Gong D, Liu T, Yao D (2019) *A comparative study of different EEG reference choices for event-related potentials extracted by Independent Component Analysis* **Front Neurosci 13: 1068**

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20) Gong JN, Luo C, Li XK, Jiang SS, Khundrakpam BS, Duan MJ, Chen X, Yao DZ (2019) *Evaluation of functional connectivity in subdivisions of the thalamus in schizophrenia*. **Brit J Psychiat 214: 288-96**

21) He H, Luo C, Luo YL, Duan MJ, Yi QZ, Biswal BB, Yao DZ (2019) *Reduction in gray matter of cerebellum in schizophrenia and its influence on static and dynamic connectivity* **Human Brain Mapping 40: 517-28**

22) Jiang Y, Xu L, Li X, Tang Y, Li C, Wang J, Luo C, Yao D (2019a) *ECT-induced effects on hippocampal structure and function and its differences in Schizophrenia remission and non-remission patients* **Available at SSRN 3343640**

23) Jiang Y, Xu L, Li X, Tang Y, Wang P, Li C, Yao D, Wang J, Luo C (2019b) *Common increased hippocampal volume but specific changes in functional connectivity in schizophrenia patients in remission and non-remission following electroconvulsive therapy: A preliminary study* **Neuroimage Clin 24: 102081**

24) Jiang YC, Song L, Li X, Zhang YD, Chen Y, Jiang SS, Hou CY, Yao DZ, Wang XM, Luo C (2019c) *Dysfunctional white-matter networks in medicated and unmedicated benign epilepsy with centrotemporal spikes* **Human Brain Mapping 40: 3113-24**

25) Jiang YC, Xia MQ, Li XK, Tang YY, Huan CB, Huang H, Dong DB, Jiang SS, Wang JJ, Xu J, Luo C, Yao DZ (2019d) *Insular changes induced by electroconvulsive therapy response to symptom improvements in schizophrenia* **Prog Neuro-Psychoph 89:254-62**

26) Li HC, Cao WF, Zhang XX, Sun B, Jiang SS, Li JF, Liu C, Yin WJ, Wu Y, Liu TJ, Yao DZ, Luo C (2019) *BOLD-fMRI reveals the association between renal oxygenation and functional connectivity in the aging brain* **Neuroimage 186:510-7**

27) Qin Y, Jiang S, Zhang Q, Dong L, Jia X, He H, Yao Y, Yang H, Zhang T, Luo C, Yao D (2019) *BOLD-fMRI activity informed by network variation of scalp EEG in juvenile myoclonic epilepsy* **Neuroimage Clin 22:101759**

28) Wen X, Dong L, Chen J, Xiang J, Yang J, Li H, Liu X, Luo C, Yao D (2019) *Detecting the Information of Functional Connectivity Networks in Normal Aging Using Deep Learning from a Big Data Perspective*. **Front Neurosci 13: 1435**

29) Iturria-Medina Y, Carbonell FM, Evans AC, ADNI (2018) *Multimodal imaging-based therapeutic fingerprints for optimizing personalized interventions: Application to neurodegeneration* **Neuroimage 179: 40-50**

30) Vogel JW, Mattsson N, Iturria-Medina Y, Strandberg OT, Schöll M, Dansereau C, Villeneuve S, van der Flier WM, Scheltens P, Bellec P, Evans AC, Hansson O, Ossenkoppele R, Alzheimer's Disease Neuroimaging Initiative, Swedish BioFINDER Study (2019) *Data-driven approaches for tau-PET imaging biomarkers in Alzheimer's disease* **Hum Brain Mapp 40(2): 638-51**

31) Vogel JW, Iturria-Medina Y, Strandberg OT, Smith R, Levitis L, Evans AC, Hansson O, Alzheimer's Disease Neuroimaging Initiative, Swedish BioFinder Study (2020) *Spread of pathological tau proteins through communicating neurons in human Alzheimer's disease* **Nature Comms 11(1): 1-17**

Papers in review

R1*. A quantitative EEG toolbox for the MNI Neuroinformatics ecosystem* Bosch-Bayard J, Aubert-Vazquez E, Brown ST, Kiar G, Glatard T, Scaria L, Galan-Garcia L, Bringas-Vega ML, Virues-Alba T, Rogers C, Taheri A, Das S, Madjar C, Mohaddes Z, MacIntyre L, Evans AC, Valdes-Sosa PA

R2. Tremblay-Mercier J, Madjar C, Das S, Dyke SOM, Étienne P, Lafaille-Magnan M-E, Bellec P, Collins L, Rajah NM, Bohbot V, Leoutsakos J, Iturria-Medina Y, Kat J, Hoge R, Gauthier S, Chakravarty M, Rosa-Neto P, Villeneuve S, Evans AC, Poirier J, Breitner JCS, PREVENT-AD Research Group (2020) *Creation of an Open Science dataset from PREVENT-AD, a longitudinal cohort study of pre-symptomatic Alzheimer's disease* **(bioRxiv 976670**)

Papers in preparation

D1. A position paper about the Global Brain Consortium. A paper is in preparation for Nature or Lancet. The paper is co-authored by the Global Mental Health department at the World Health Organization (WHO). It will describe an original WHO 2016 meeting in Geneva (co-organized by WHO, Pedro Valdes-Sosa and Alan Evans) as the scene-setting for the eventual CCC and GBC objectives.

D2. The Cuban Human Brain Mapping Project (CHBMP) database. This initiative is prepared to be submitted to Nature Scientific Data journal with a link to LORIS and CBRAIN. CCC-researchers at CNEURO and the MNI are co-authors.

D3. Nature Neuroscience perspective for the COBIDAS MEEG in preparation. “Best practices in data analysis and sharing in neuroimaging using MEEG. Cyril Pernet, Marta Garrido, Alexandre Gramfort, Natasha Maurits, Christoph M. Michel, Elizabeth Pang, Riitta Salmelin, Jan Mathijs Schoffelen, Pedro A. Valdes-Sosa & Aina Puce”

D4. A special issue of NEUROIMAGE “Neuroimaging for global health”. This was an agreement of the WHO meeting in 2016 and later form the GBC. The special issue was launched in July 2019 with around 25 papers in preparation. Editors: Pedro Valdes, Christoph Michel, Tonya White, Shekkar Saxena.

D5. Nature paper about Barbados, Malnutrition and Mediation.

D6. Nature Methods about the BC-Vareta.

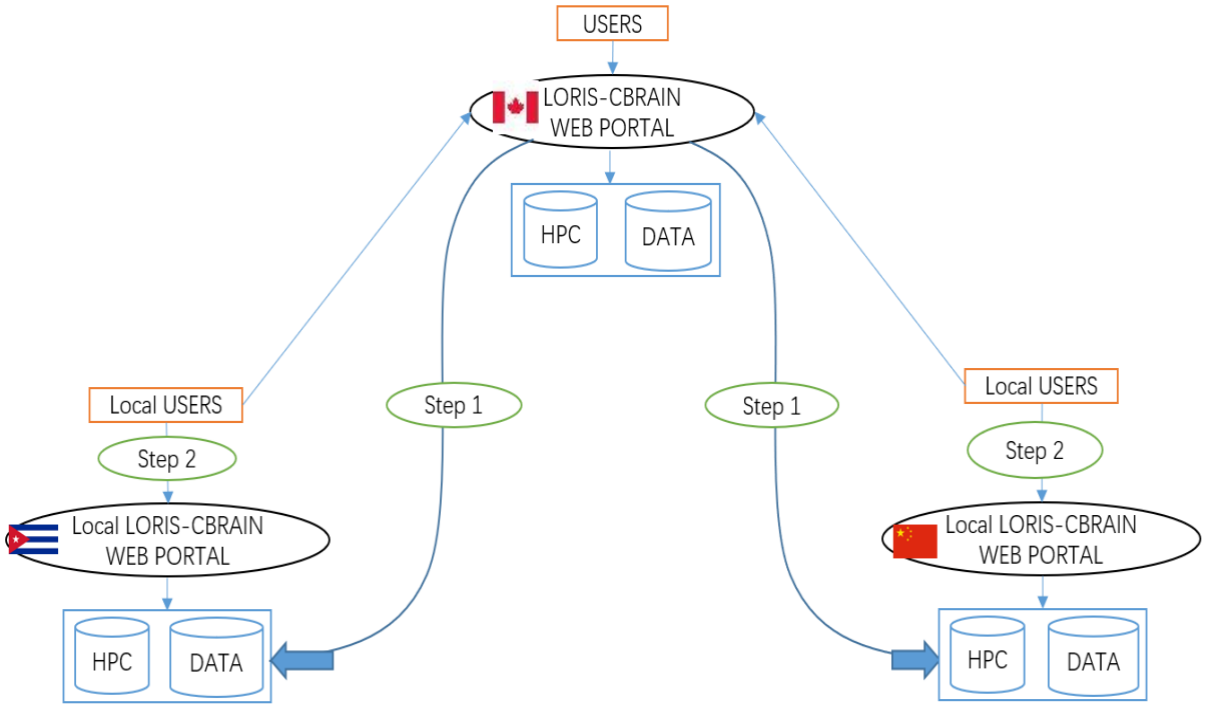
D7. NEUROIMAGE. Barbados longitudinal study EEG in two times.

D8. NEUROIMAGE. High accuracy classifiers using EEG source analysis in the special population of PSEN1 E280A (E280A) mutation in Antioquia Colombia.

D9. BCVareta EEG multinational norms

Figures: CCC-Axis in Cuba, China and Canada using CBRAIN and LORIS

Fig 1: Launch of Cuban Brain Project at CNEURO. Note CBRAIN image on wall screen.



- Currently: International USERS can use CBRAIN web portal to access HPC/Data resources in Canada. Local Cuba/China users can also use this way.
- Step 1: Connect CBRAIN web portal to HPC/Data resources in Cuba/China.
- Step 2: Create local CBRAIN web portals in Cuba/China connected to local HPC/Data resources, to be used only by local users.

Fig. 2: CCC-Axis Neuroimage Neuroinformatic Platform (NNP) for three nodes.

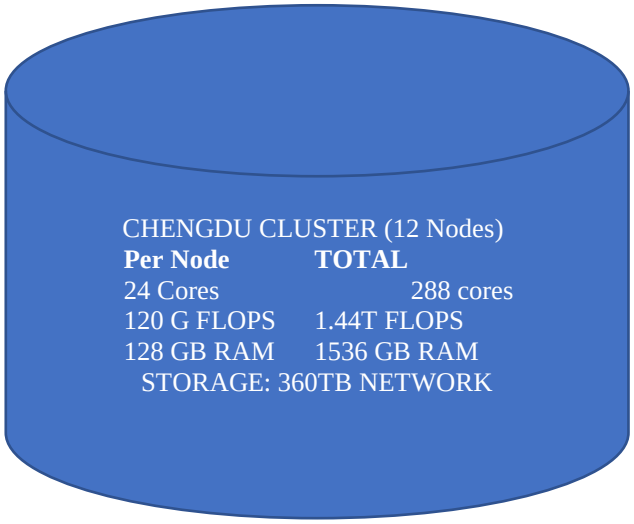


Fig. 3: Neuroinformatic facilities installed in the CCC lab at UESTC in China

	Group	MRI	fMRI	EEG	MEG	DWI	ECoG	ASL	PET/SPECT	Behavior
BARBADOS	Malnutrition, Healthy			108						108
CAMCAN	Healthy	655	650		647	627				708
CHBMP	Healthy	202		86		201				86
CHINA	Healthy			113						113
Colombia	Alzheimer			45						45
CMI-HBN	Healthy Children	1306	1306	1306		1306				1306
HCP S-1200	Healthy	1113	889		95	889				1206
OMEGA	Healthy, patients ADHD, chronic pain	184			184					184
Parkinson-CIREN	Parkinson	24	24	25						25
PPMI	Parkinson, Healthy	1198	338			1291			72	2279
Prevent AD	Healthy over 55 years old	232	232			229		232		

Fig. 4: LORIS-mediated databases processed at CCC-Axis site in UESTC, Chengdu.

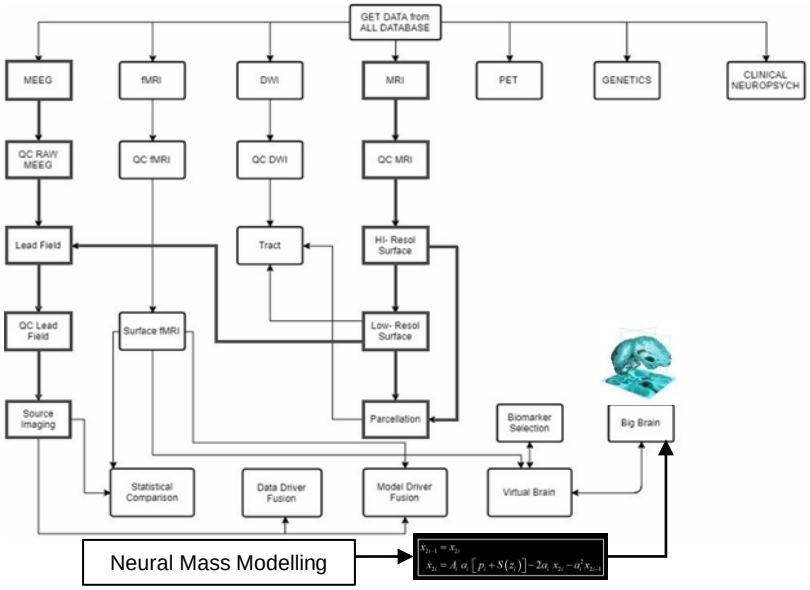


Fig. 5: CCC Neuroinformatic pipelines in Cuba (CNEURO), China (UESTC) and Canada (MNI).

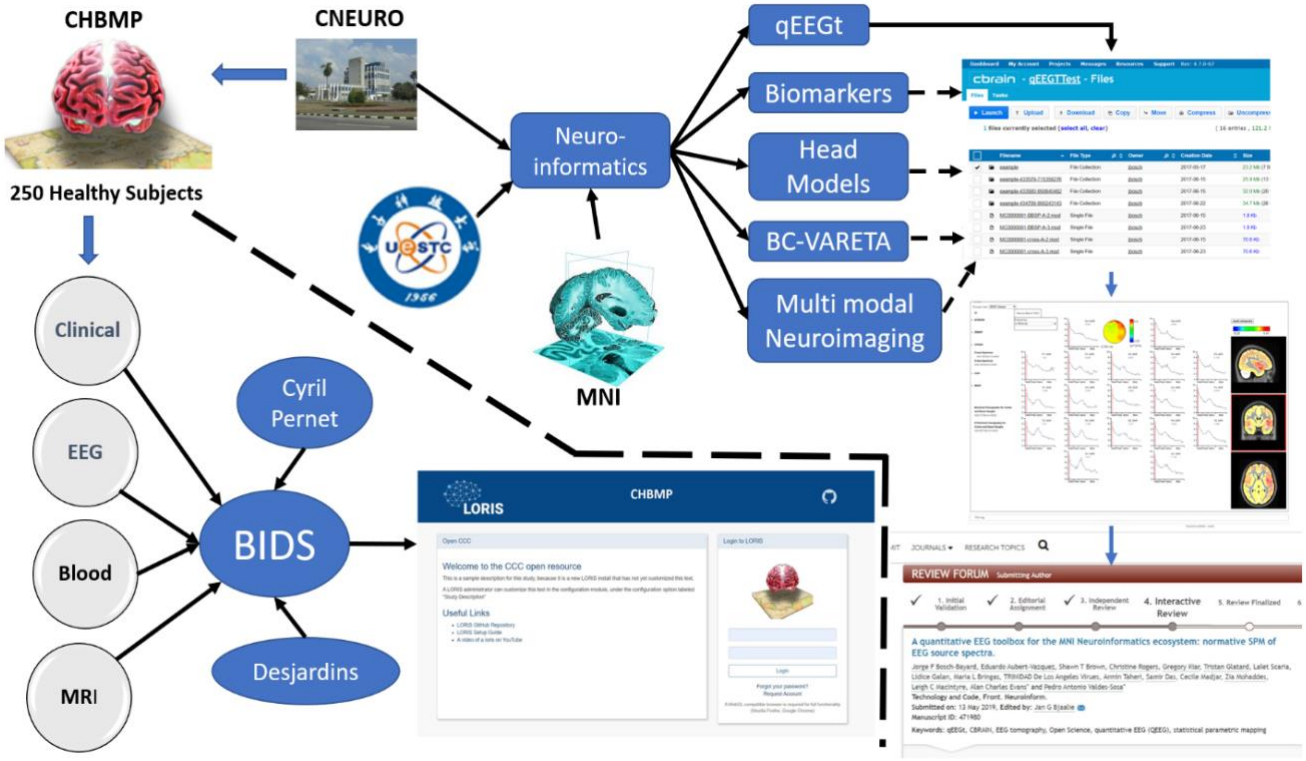


Fig. 6: Overview of the CCC-Axis Neuroimage Neuroinformatic Platform organization.

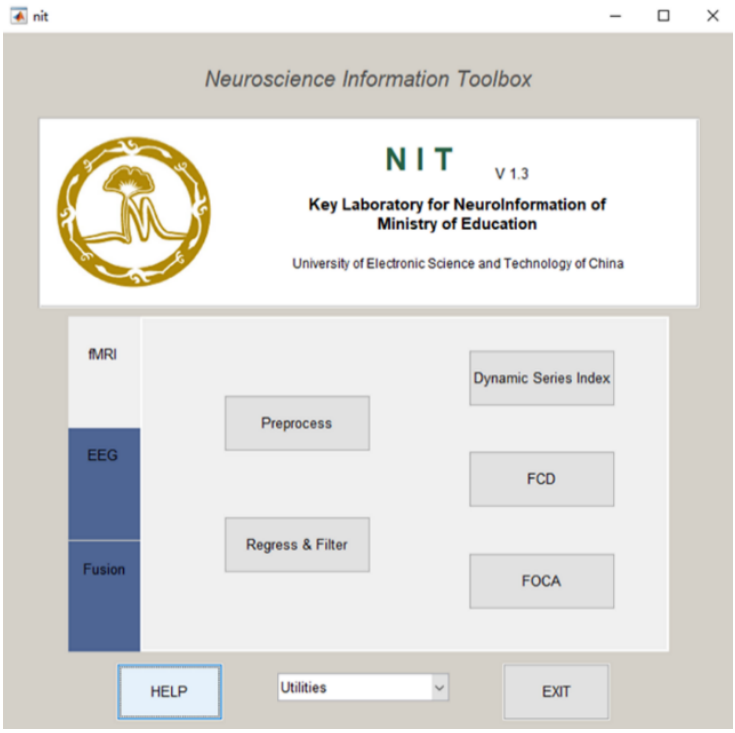
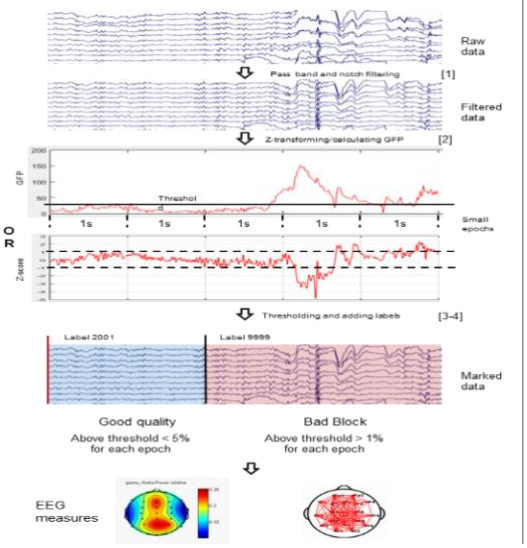


Fig. 7: Neuroscience Information Toolbox (NIT): Open Source toolbox for EEG-fMRI multimodal fusion analysis (http://www.neuro.uestc.edu.cn/name/shopwap/do/index/content/101)



Tools	Description
WB_EEG_REST	EEG REST re-referencing
WB_EEG_CalcPower	Calculating EEG power indices
WB_EEG_Mark	Automatically Marking bad block/good quality EEG data
WB_EEG_CalcNetwork	Calculating EEG network at scalp level
WB_EEG_CalcERP	Creating averaged ERPs at scalp level
WB_EEG_runICA	Runing ICA decomposition on EEG data
WB_EEG_CalcNetMeasures	Calculating network measures based on graph theory
∘ ∘ ∘	∘ ∘ ∘

Fig. 8: Example CCC-Axis EEG software analysis pipelines developed at UESTC.

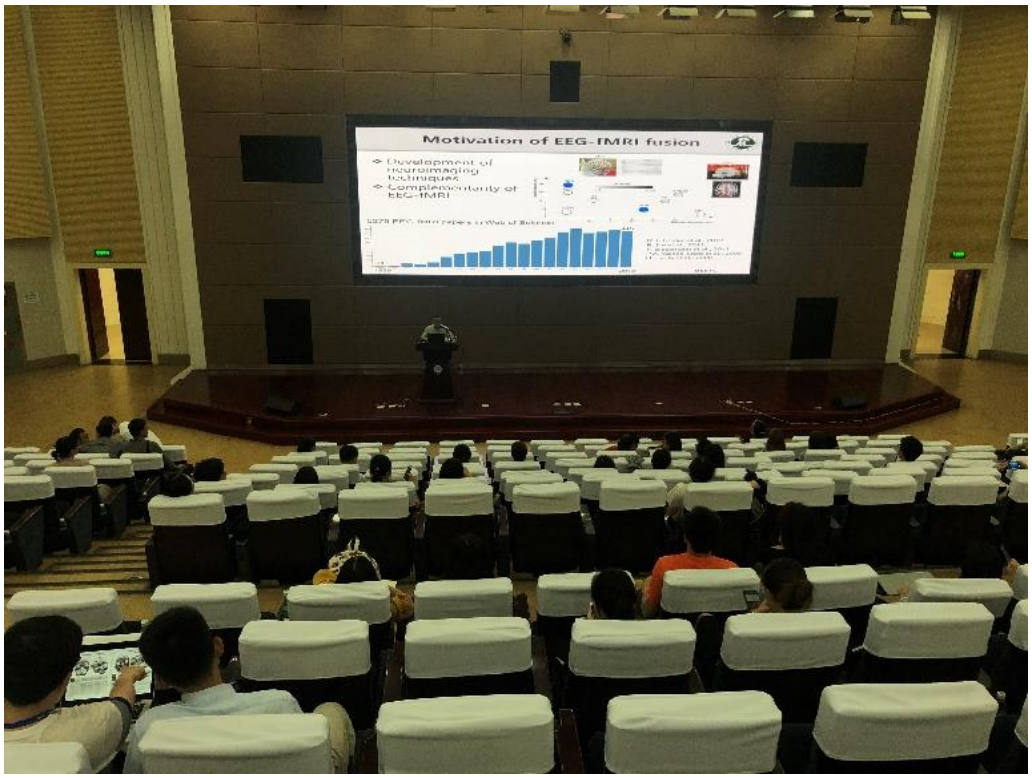


Fig. 9: Introduction of EEG-fMRI tools and cloud computing platform supported by CCC-Axis, at 4th Int. Conference on Basic and Clinical Multimodal Imaging, UESTC (10-14 Sep, 2019).

Fig. 10: CCC-Axis workstation environment at UESTC for **(L)** EEG processing using LossLess analysis suite (implemented in Canada and Cuba via CBRAIN) **(R)** BigBrain analysis.

Québec

Bureau du scientifique en chef

PAR COURRIER ÉLECTRONIQUE

Le 6 mars 2020

Dr Alan Evans
Directeur scientifique
Cerveau en santé, gage d'une vie en santé
Université McGill - MNI
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Courriel : alan@bic.mni.mcgill.ca

Objet : Complément de subvention pour l'initiative *Cerveau en santé, gage d'une vie en santé* (Health Brains for Healthy Lives – HBHL)

Dr Evans,

Nous avons pris connaissance de votre demande pour le renouvellement du financement pour le projet intitulé *Axe trinational (Canada-Cuba-Chine) sur le vieillissement cognitif normal et pathologique*. Ce projet collaboratif est des plus pertinents, en raison notamment de la complémentarité des équipes de recherche impliquées. La Chine produit beaucoup de données (venant de millions de patientes et de patients) et contribue grandement au progrès dans le domaine des statistiques avancées (développement d'outils nécessaires pour examiner de larges banques de données). Le Neuro (Canada) est expert en plateformes bioinformatiques (les plateformes CBRAIN et LORIS notamment) qui permettent d'instaurer des méthodes d'archivages standardisées et de partage de données pour fonctionner en mode *Open Science*. Ainsi, les chercheures et les chercheurs peuvent mutualiser et comparer des données de provenances diverses. Cuba, en revanche, n'a pas beaucoup de ressources pour la collecte de données, mais excelle dans la recherche translationnelle, pour faire, par exemple, des ponts entre des découvertes en recherche fondamentale et des questionnements propres à la santé publique.

Le financement du projet jusqu'à maintenant s'est fait par l'entremise d'un appel à projets ciblés pour la recherche en imagerie cérébrale et neuroinformatique, un appel issu d'une entente de partenariat entre le Québec et Cuba. Notez que l'octroi attribué au projet *Axe trinational sur le vieillissement cognitif* a aussi été intégré au soutien financier des Fonds de recherche du Québec (FRQ) au programme Apogée *Cerveau en santé, gage d'une vie en santé* (tel que stipulé dans lettre d'octroi de 2017). Puisque le financement de ce projet vient à échéance, les FRQ proposent de majorer le financement de *Cerveau en Santé* de 450 000 $ à 500 000 $ pour

maintenir son engagement à mettre à la disposition de *Cerveau en santé* 500 000 $ par année sur une période de 7 ans (toujours tel que stipulé dans lettre d'octroi de 2017). Ainsi, vous serez en mesure de continuer à financer l'axe trinational si vous jugez que ce projet demeure un investissement stratégique.

L'aide supplémentaire des FRQ, d'un montant total de 50 000 $ pour une durée de quatre (4) années, s'ajoute donc à l'octroi de 450 000 $ par an déjà versé à *Cerveau en Santé* jusqu'en 2024. Ce soutien s'insère dans les priorités définies dans le cadre des Grands défis de société (Développement durable incluant les impacts des changements climatiques et du numérique) et se répartit comme suit :

Répartition de la subvention

Période d'octroi	**Montant**	**Rapports de suivi et financiers attendus le**
1er avril 2020 au 31 mars 2021	50 000 $	30 juin 2021
1er avril 2021 au 31 mars 2022	50 000 $	30 juin 2022
1er avril 2022 au 31 mars 2023	50 000 $	30 juin 2023
1er avril 2023 au 31 mars 2024	50 000 $	30 juin 2024

Conformément aux objectifs de la Stratégie québécoise de la recherche et de l'innovation 2017-2022, la contribution des FRQ au programme *Cerveau en Santé* s'accompagne de certaines attentes en termes de retombées. Cette enveloppe financière doit ainsi contribuer à assurer une capacité de recherche de classe mondiale, appuyer le développement des meilleurs talents et soutenir l'intégration des chercheures et des chercheurs du Québec à des réseaux nationaux et internationaux (voir la lettre d'octroi 2017 pour plus de détails).

Remarques

- Ce financement est offert par les FRQ. Le FRQ-Santé est désigné comme le fond gestionnaire.
- L'octroi de cette subvention est assujetti au*x Règles générales communes* des FRQ.
- Les octrois consentis par les FRQ sont conditionnels à l'allocation des crédits par l'Assemblée nationale du Québec et aux décisions des conseils d'administration des FRQ. Ils peuvent donc être modifiés en tout temps, sans préavis.
- En vue de la reddition de comptes, la personne titulaire de l'octroi doit fournir annuellement un rapport de progrès. De plus, un rapport financier détaillé doit être soumis chaque année. Un seul rapport d'activité et financier sont attendus pour la totalité du 500 000 $ versé par année.

- La personne titulaire de l'octroi est tenue de mentionner l'aide financière reçue et le nom des partenaires dans toute publication et tout document officiel réalisés grâce à cette subvention de recherche.
- La personne titulaire de l'octroi est tenue de respecter la *Politique sur la conduite responsable en recherche* des FRQ.

Les FRQ espèrent que ce soutien financier donnera encore plus d'élan à l'initiative *Cerveau en santé, gage en santé* pour se démarquer par la qualité de ses recherches en neurosciences et par ses contributions importantes, voire disruptives, en science ouverte.

Nous vous prions d'agréer, Dr Evans, nos sincères salutations.

Le scientifique en chef du Québec,

Rémi Quirion, O.C., C.Q., Ph.D., m.s.c.r.

La directrice aux défis de société et maillages intersectoriels (DSMI),

Denise Pérusse, Ph.D.

c.c. : Madame Martha Crago, vice-principale à la recherche et l'innovation, Université McGill
Madame Karine Assal, directrice de l'administration, FRQ
Monsieur David Côté, directeur du service des finances, FRQ
Madame Marie-Pierre Cossette, responsable de projets intersectoriels, DSMI, FRQ

Québec
Bureau du scientifique en chef

BY E-MAIL March 6, 2020

Dr. Alan Evans
Scientific Director
Healthy Brain Healthy Lives
McGill University - MNI
3801 University Street
Montreal (Quebec) H3A 2B4
Email: alan@bic.mni.mcgill.ca

Subject: Complementary grant, Healthy Brains, Healthy Lives (HBHL) initiative

Dr. Evans,

We have taken note of your request for the renewal of funding for the project entitled *Trinational Axis (Canada-Cuba-China) on normal and pathological cognitive aging*. This collaborative project is most relevant, in particular because of the complementarity of the research teams involved. China produces a lot of data (from millions of patients) and contributes greatly to progress in the field of advanced statistics (development of tools necessary to examine large databases). The Neuro (Canada) is an expert in bioinformatics platforms (CBRAIN and LORIS platforms in particular) which allow the implementation of standardized archiving and data sharing methods to operate in Open Science mode. Researchers can therefore pool and compare data from various sources. Cuba, on the other hand, does not have many resources for data collection, but excels in translational research, to make, for example, bridges between discoveries in basic research and questions specific to public health.

Funding for the project to date has been through a targeted call for projects for research in brain imaging and neuroinformatics, a call resulting from a partnership agreement between Quebec and Cuba. Note that the grant allocated to the *Trinational Axis project on cognitive aging* has also been integrated into the financial support of the Fonds de recherche du Québec (FRQ) in the HBHL (as stipulated in the letter 2017). Since the funding for this project is coming to an end, the FRQ propose to increase the funding for Cerveau en Santé from $ 450,000 to $ 500,000 to maintain its commitment to make available to HBHL $ 500,000 per year over a period of 7 years (always as stipulated in the 2017 grant letter). Thus, you will be able to continue to finance the trinational axis if you consider that this project remains a strategic investment.

The additional assistance from the FRQ, totaling $ 50,000 for a period of four (4) years, is therefore in addition to the grant of $ 450,000 per year already paid to Cerveau en Santé until 2024 This support is part of the priorities defined in the context of the Great societal challenges (Sustainable development including the impacts of climate change and digital) and is distributed as follows:

Distribution of the grant

Grant period	Amount	Monitoring and financial reports expected
April 1, 2020 - March 31, 2021	$ 50,000	June 30, 2021
April 1, 2021 - March 31, 2022	$ 50,000	June 30, 2022
April 1, 2022 - March 31, 2023	$ 50,000	June 30, 2023
April 1, 2023 - March 31, 2024	$ 50,000	June 30, 2024

In accordance with the objectives of the 2017-2022 Quebec Strategy for Research and Innovation, the contribution of the FRQ to the Brain in Health program is accompanied by certain expectations in terms of spinoffs. This financial envelope must therefore contribute to ensuring world-class research capacity, support the development of the best talent and support the integration of Quebec researchers into national and international networks (see 2017 letter of approval for more details).

Remarks

This funding is offered by FRQ. The FRQ-Santé is designated as the managing fund.

The award of this grant is subject to the Common General Rules of the FRQ.

The grants granted by the FRQ are conditional on the allocation of credits by the National Assembly of Quebec and on the decisions of the boards of directors of the FRQ. They can therefore be changed at any time, without notice.

For reporting purposes, the grant holder must provide an annual progress report. In addition, a detailed financial report must be submitted annually. A single activity and financial report is expected for the entire $ 500,000 paid per year.

The grant holder is required to mention the financial assistance received and the names of the partners in any publication and any official document produced thanks to this research grant.

The grant holder is required to comply with the FRQ Policy on Responsible Conduct in Research.

The FRQ hope that this financial support will give even more impetus to the HBHL initiative, to stand out by the quality of its research in neuroscience and by its significant, even disruptive, contributions in open science.

Please accept, Dr. Evans, our sincere greetings.

Rémi Quirion, O.C., C.Q., Ph.D., m.s.c.r. Denise Pérusse, Ph.D.

cc: Ms. Martha Crago, Vice-Principal, Research and Innovation, McGill University
Ms. Karine Assal, Director of Administration, FRQ
Mr. David Côté, Director of Finance, FRQ
Mrs. Marie-Pierre Cossette, intersectoral project manager, DSMI, FRQ