

# INNOVATION HUMAN BRAIN PROJECT

Newsletter

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**START-UPS  
SOLUTION  
WORKSHOPS**



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**FIRST HBP  
INNOVATION AWARD**

**FOR VIKTOR JIRSA AND THE VEP TEAM**



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# FIRST HBP INNOVATION AWARD FOR VIKTOR JIRSA AND THE VEP TEAM

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*One more step towards a highly personalised medicine in epilepsy with the VEP. The scientific leader shares with us some of the experiences gained in the exciting and challenging journey of this fantastic technology.*

Innovation does not just require new technologies and products, but also new applications, solutions. New product, process, and distribution technologies provide powerful levers for creating competitive value. With the proposal to promote innovation the Innovation Team and DIR created the "Innovation Awards" to recognize the on-going efforts made in innovation activities by HBP researchers and teams.

After the evolution of brilliant candidates, the DIR made the decision to grant the first Innovation Award to Viktor Jirsa and the Virtual Epileptic Patient (VEP) team. Here we would like to present the interview with Viktor Jirsa.

*What is the problem addressed and the advantages of the solution provided? Please explain the contribution of the technology to the potential of EBRAINS.*

Epilepsy is a disorder that affects 1% of the world population. 30-40% of epilepsy patients are drug resistant and candidate for resective surgery. In these cases, it is of great importance to know well the epileptogenic zone, which is the target of surgery. Our technology, the Virtual Epileptic Patient (VEP), provides the clinician with a computational tool for better decision making. VEP combines information from highly heterogeneous sources in a patient-specific brain model. For instance, the patient's own MRI

data are used to reconstruct his/her brain connectivity and link it to computational models running on EBRAINS. Machine Learning techniques allow to further personalize the brain model to the patient's own brain imaging data.

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*“VEP combines information from highly heterogeneous sources in a patient-specific brain model”*

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The advantage of VEP is that it provides a balanced judgement of the contribution of the various factors influencing seizures, including regional epileptogenicity, the patient's brain connectivity, but also electrode placements. Furthermore, it can simulate brain activity, test clinical interventions, and reveal brain activity, which is not accessible otherwise. For instance, sometimes a clinician would like to have an extra electrode in the patient's brain, which could not be implanted originally, and VEP can simulate the electrode and generate the missing data.

*How was the innovation conceived and by whom? We would like to know the role played by HBP in this conception.*

I am the scientific leader of The Virtual Brain (TVB), a full-brain simulation platform, which was first released in 2012 as part of the efforts of the Brain Network Recovery Group (2005-2015), coordinated

by Randy McIntosh and with participation of Petra Ritter. When I joined HBP in 2014, there was a crossing of three streams of development, that is my efforts in TVB, mean field theory building in HBP (\*SP4), and the availability of stereotactic EEG epilepsy patient data in HBP (\*SP3) and my home institution at Aix-Marseille University. When I tried to integrate these efforts, it became evident that they will be useful for the patient only, if we manage to render predictions patient-specific. With my colleagues from neurobiology, Christophe Bernard, and clinics, Fabrice Bartolomei and Maxime Guye, we then designed the steps for a workflow that leads from

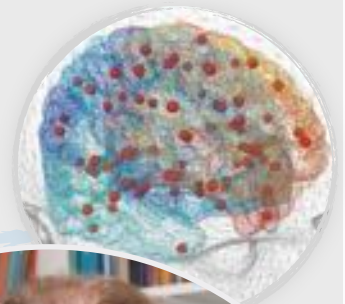


Image: Viktor Jirsa  
Institut de Neurosciences des Systèmes  
Aix- Marseille University  
Reference: “Virtual Brain Modeling for  
Epilepsy: The Next Generation”

the patient's data to the individual brain model and back to the patient and clinical decision making. TVB engineers Marmaduke Woodman and Huifang Wang did all the initial engineering. Every single step, such as epileptic mean field modeling (Epileptor), TVB seizure modeling, personalization of brain model through inference, was a task in HBP work packages during \*\*SGA1, SGA2, SGA3, ultimately leading to what we know today as VEP workflow. All the colleagues above (except CB) are today members of HBP and have grown into a strong and engaged team working in the HBP ecosystem.

*What are in your opinion the most impactful applications of the technology? How is the technology positioned in relation to other trends and solutions in the area?*

Now, the immediate application of VEP is its diagnostic use in epilepsy, aiding in better identifying the epileptogenic zone of a patient. We use Monte Carlo Markov Chain (MCMC) techniques for the estimation of model parameters, which are powerful as they provide many diagnostics for reliability and confidence testing, but they are also notoriously difficult to use. Other technical solutions are easier to use (such as

frequentist approaches) but provide no information on “how right or wrong they are” and do not allow to integrate prior knowledge (such as anomalies visible in the MRI). In our judgement, we think that the advantages of MCMC out-perform its difficulties. But the most impactful application in the long term will be the use of the generative mode-

ling capacity of VEP, in which the patient-specific brain model is used to simulate brain activity under new conditions, other than the ones used to build it. This allows, for instance, to explore novel clinical interventions such as brain stimulation, which can be optimized to the patient's brain. I consider this the most original and distinguishing feature of VEP compared to other trends and technologies, which rather emphasize the data analysis than the data generation. It is also very much in the spirit of HBP.

*“This allows, for instance, to explore novel clinical interventions such as brain stimulation, which can be optimized to the patient's brain.”*

## ■ INNOVATION MANAGEMENT

*What is the market potential of the technology? What type of users could be interested in utilizing it? Are there many users of the tool registered today?*

The market potential of VEP is quite significant in a mid and longer-term perspective.

The entry point, the first functionality developed and meant to reach the market, is a pre-operative planning tool for the surgery of drug-resistant



*The VEP team: (Outer circle clock-wise starting from the top) Jayant Jha, Spase Petkoski, Maxime Guye, Borana Dollomaja, Meysam Hashemi, Huifang Wang, Anuska Stoka, Lisa Otten, Marmaduke Woodman, Fabrice Bartolomei. (Inner circle clock-wise starting from the top right) Jean-Didier LeMarechal, Samuel Medina, Julia Scholly, Jan-Paul Triebkorn.*

epileptic patients. The patients' population eligible for surgery represents 10% of the global population of epileptic patients.

This first application of the technology is currently tested in a clinical Trial (EPINOV) including 13 of the most prominent reference centres of epilepsy surgery in France. The clinicians involved in EPINOV are today the main users of VEP. It essentially means that (i) the targeted future users are already using it in a prospective clinical trial environment, and (ii) we can reasonably believe that we are close to a commercial market release of the VEP soon.

As we progress and develop less invasive options (like the minimally invasive VEP), and develop or co-develop new functionalities (diagnostic, prognostic, therapeutic options with the neurostimulation, ...), the corresponding market potential will evolve and become more important. To be specific, there are now approximately 16.5 million drug-resistant epilepsy patients globally, and 1.2 of which in the United States, one of the markets we have obviously targeted for the future commercial release.

The next step, after the progressive penetration of the epilepsy market, will be to consider other types of neurologic and neurodegenerative diseases that TVB

will help address. We will then switch to a much larger market potential and will be in a position to offer new alternatives to the neurologists, in an area where the clinical needs are largely unmet.

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*“Scientists and researchers, through partnerships that could be promoted, organized, or coordinated by EBRAINS, but also industry or clinical research consortia”*

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Beyond the clinical applications of the tool, other types of users will find a great interest in using TVB. I think here of scientists and researchers, through partnerships that could be promoted, organized, or coordinated by EBRAINS, but also industry or clinical research consortia, which could likely benefit from a tool like the VEP first, and its generalizations to other diseases later, for instance to optimize the findings and outcome of patients included in clinical trials in their domains. Although these are projections and aspirations for the future, they are becoming more concrete now.

*How is the technology currently used or tested by researchers and other industrial or medical users? May you briefly describe your experience with the clinical trials?*

A first version of the VEP technology is currently tested by medical users within the clinical trial EPINOV. The trial study is conducted in 13

hospital centers in France and has started in June 2019. The study will last four years and aims at guiding therapeutic strategies to improve surgical prognosis. It will include about 400 prospective patients (adults and children over 12) who have been diagnosed with drug-resistant epilepsy and identified as potential candidates for resective epilepsy surgery. The EPINOV Trial is the largest randomized multi-site trial ever conducted in epilepsy surgery and has been funded by the French scientific excellence program “Investissements d’Avenir” (Investment in the Future) entitled « Recherche Hospitalo-Universitaire en santé » (RHU) operated by the National Research Agency (ANR). The conditions in the past two years were challenging due to the sanitary situation, with intermittent closures of surgery centers, but as of today we have included more than 180 patients, of which 120 were randomized and virtualized. EPINOV is thus on track despite the difficult conditions.



*What market-oriented steps you will take during the next two years? and after the finalisation of HBP? (Licensing, patenting selling, cross licensing, services, facilities, consultancy, personnel exchange, start-ups, joint ventures, etc.)*

The decision to exploit the research and development around VEP and TVB has been made some time ago and the creation of a dedicated start-up, VB-Tech (VB-Tech for Virtual Brain Technologies), is now imminent. Its future CEO, Jean Marc Ferrier, drafted an ambitious and aggressive business plan and organized an international initial shareholders' group ready to support the project. You will probably hear more about this in the coming weeks. The start-up will coordinate and implement the technology transfer strategy, including the industrialization of the technology in a Quality Assurance environment, obtaining the CE mark for Europe and the 510(k) clearance for the US market as first priorities, and construction of the relevant commercial strategy to reach the market. As far as the possible options to reach the market are considered, several are on the table at this point: direct exploitation, licensing and distribution agreements, and co-developments with partners presenting synergetic technologies with the VEP/TVB.

*Have you explored any venture capital (or similar) investing*

*options to get funding?*

Yes, of course we did. The first pre-seed and non-dilutive funding plan is in place, the SEED round is already planned as early as in 2022. The SEED round is the first capital opening to investors, in other words the first dilutive funding operation.

Early contacts have been made with several VCs, some in France, others in Europe, anticipating the future significant financial rounds (series A, B, ...) that will take place in the midterm. We will pay special attention to the choice of VCs that will accompany VB-Tech, as the quality of the relationship and the trust between investors on one side, and the management and science-engineering team on the other side, will be a critical success factor for the start-up. Essentially, we will be looking for investors clearly motivated and passionate about the project, and able to support us on the long term.

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***“We will be looking for investors clearly motivated and passionate about the project, and able to support us on the long term.”***

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*Could you summarise what have been, in general, the most important difficulties and barriers found (technical, economic, ethical issues, etc.)?*

The technical development

of the core technology has obviously been a great challenge. Here, dealing with the intra- and inter-patient variability in clinical real-world scenarios poses immense technical challenges and the VEP engineering team has been fantastic in this respect. In HBP today, two of its showcases are directly dedicated to this problem of variability. If you read texts of Daniel Kahneman, it is precisely such low-validity environments where algorithmic approaches should be used and can have the most impact.

Among the other difficulties encountered, one of the main challenges has been to build a highly multidisciplinary team including clinicians, neurologists and radiologists, data scientists, engineers, etc... who are critical in a project like ours to allow for an optimal transition from a purely scientific project to a translational activity, with the chance to have this technology benefit the patients one day.

If we further consider that the project has matured for a long time, involving different stake-holders and partners at various stages of the project and multiple funding sources, it is inevitable that interests have evolved heterogeneously, sometimes generating political tensions, conflicts of interests and divergent claims of ownership, and even pressure as the project evolves and

approaches the market. The management of this “project heritage”, and the necessity to address and clarify all the pre-existing situations have definitely caused difficulties that I believe have been overcome by now.

## ■ CONCLUSIONS

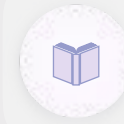
*What recommendations would you give to young scientists and researchers in terms of innovation and entrepreneurship?*

If your aspirations as a scientist and researchers are geared towards clinical translation, I strongly recommend considering the equivalent of a science strategy of market pull, rather than techno push. Essentially, it means that you identify and analyse the challenges in the clinical real-world environment, and then derive the appropriate technology from your science to solve the actual problem. I often hear the comment that I got lucky with my clinical colleagues, but luck may not have played the major role. My clinical colleagues are outstanding (see my next point), but most importantly, they are engaged because VEP addresses one of their most important needs in clinical routine.

Next, bring on board the right partners, in relation with your final objective. As an example, if you plan to develop a new therapeutic innovative solution, you need a clinician in your team, who

*“Identify and analyse the challenges in the clinical real-world environment, and then derive the appropriate technology from your science to solve the actual problem”*

VIKTOR JIRSA-  
RESEARCH LEADER WP1-  
HBP - HUMAN MULTISCALE  
BRAIN CONNECTOME



Read more about the [Virtual Epileptic Patient](#)

is an undisputable expert in the field. This needs to happen early to give the right orientation in your technical development. Not only this clinical partner will help you develop the right positioning for your technology, but he/she will be your first partner to evaluate clinically the technology you developed together.

Importantly, reach first a certain level of maturity and proof of concept before considering a transfer to the market, to be in a better position to attract early investors, and to negotiate their entry in the project in optimal conditions. As an example, in our project, the SATT SE (the Aix-Marseille University Technical Transfer Office (TTO)), has supported us efficiently in the (costly and time-consuming) maturation effort, which allows us today to consider the market transfer in very good conditions, with several strong assets (patents), with a prototype already developed, with the possibility to show an initial proof of concept, and with a technology already in the clinical phase of validation. Finally, if you consider bringing your innovative technology to the market, bring the relevant management resources on board early, as the entrepreneurial process is a more

and more complex one. The main two characteristics of the management resources you should be looking for are: experience, and personal fit between you and him/her. The HBP Innovation Team at UPM (Universidad Politécnica de Madrid) led by Gonzalo León and participation of Guillermo Velasco played an important role in supporting the development of these plans. Earlier this year they provided a state-of-the-art

*“This input was critical guidance for us in constructing the foundations of the start-up and its business model”*

professional market review focusing on the VEP, including supplementary documents covering the top 5 collaboration opportunities and a list of potential VEP lead customers. This input was critical guidance for us in constructing the foundations of the start-up and its business model. It also demonstrates the high degree of dedication of HBP to accompany translation.

16.5

million drug-resistant epilepsy patients globally



■ The UPM Innovation Team supports market analysis and exploitation plans for the VEP\* and other HBP technologies:

- Spiking network modelling and Training
- HBP applications and tools for hospitals
- Brain Simulation & NEST
  - Brain Atlases
- The Medical Informatics Platform (MIP)

\*Duran, T., Velasco, G., León, G., Strange, B. (2020). VEP Market Review. Human Brain Project.



LEARN MORE



1%

of the world's population is diagnosed with epilepsy

\*SP: *supbproject* (units in which the project was formerly organised)

\*\*SGA1, SGA2, SGA3: *phases of the HBP project (Specific Grant Agreements)*