INDIVIDUAL FELLOWSHIPS

Project n°: PIOF-GA-2009-254780

Project Acronym: TSPUMMNRPS

Project Full Name: Temporal spiking precision underlying memory measured by neuronal recordings and photo-stimulation

Marie Curie Actions

IOF-Final Report

Period covered: from 09-01-2010 to 08-31-2013

Period number: Final report

Start date of project: 09-01-2010

Project beneficiary name: Dr Antal Berényi, MD, PhD

Project beneficiary organisation name: University of Szeged, Szeged, Hungary

Date of preparation: 10-15-2013

Date of submission (SESAM): _____

Duration: 36 months

Version: 1.0

STARTPAGE

PEOPLE

MARIE CURIE ACTIONS

International Outgoing Fellowships (IOF)

Call: FP7-PEOPLE-2009-IOF

"Temporal spiking precision underlying memory measured by neuronal recordings and photo-stimulation"

Final report

Project Acronym: "TSPUMMNRPS"

1. PUBLISHABLE SUMMARY

The overall hypothesis underlying the present research program was that the variability of neuronal activity in higher cortical structures, independent of the physical features of sensory inputs, is due to brain-derived ("cognitive") processes. Accordingly, activity patterns (*spike trains) in neuronal populations (functional cell assemblies) should show coordinated activity beyond that predicted by the time-course of external sensory input*. The results of these experiments provide an important step towards understanding how coordinated neuronal activity results in overt and cognitive behavior. According to the "cell assembly" hypothesis, information in the brain is represented by groups of synchronously firing neurons, whose membership reflects an interaction between sensory input and internally generated patterns. The requisite temporal precision of spiking to maintain the assemblies by synchronous firing is unknown. The hypothesis tested in the current work is that precise spike timing in neural networks is required for information processing in the brain. Quantitatively, the question is what temporal precision of multineuronal spiking is required to support reliable behavior. Here, we interfere with naturally-occurring spiking by injecting noise into the brains of behaving rats or mice, and measure the precision of multi-unit spike timing at which behavior deteriorates.

During the outgoing phase of my international outgoing fellowship, my training included hands-on tutorials on the handling of freely moving rodents (including legal and ethical, as well as practical aspects), on performing large scale in vivo recordings, handling silicon electrodes. Moreover I gained insight to the state of the art problems of systems neuroscience. My scientific maturation was also promoted by weekly lectures and seminars given by well acknowledged, highly reputed lecturers of various fields of neuroscience, who visited the host and neighboring institutes. The most significant results of my work during the reporting period are:

A major oscillatory activity that synchronizes the firing pattern of the hippocampal neurons is the theta rhythm that originates mainly from the medial septum of the thalamus. This theta rhythm is a conductor which orchestrates the individual timing of each neurons firing pattern, forming unique, highly reliable constellations of these single unit firing patterns. The significance of these complex patterns in information coding is well known, e.g. in the case of the coding of the animals spatial position. To investigate the requisite of such internal temporal precision of the assemblies in order to successfully code information, we decided to interfere with the theta rhythm generator cells in the medial septum (MS), and investigate the effect of such perturbation on the hippocampal assembly synchrony, and on the behavioral performance. To selectively perturb the activity of the GABAergic or cholinergic MS neurons, we used an optogenetical approach as suggested in the project proposal; however a number of difficulties arose. In collaboration with the Zeng group (Allen Institute, Seattle, WA) we developed a new transgenic mouse line for optogenetical experiments. The results of this project are published in a high impact journal (Nature Neuroscience), and the strains are accessible for the neuroscience community through The Jackson Laboratory.

To overcome the spatial and weight constrains mentioned above I developed a new recording system. The main principle of the device is to transmit the signal of 32 recording channels through a single data transmission wire by multiplexing them directly on the head of the animal. Using this new approach the number of simultaneously recorded channels could be increased to 96 in the case of freely moving mice, and 512 in the case of freely moving rats, which finally gives a broader picture of the

behavior of larger cell assemblies. In a set of experiments I combined the new recording system with a custom designed silicon electrode, which was designed and prototyped in parallel with the multiplexing amplifier system. The first results gained in a freely moving rats using this new multiplexer amplifier system is published in a high impact journal (Science), and it's significance and the general working principle is demonstrated through 512 channel freely moving rat two accepted, and two under-review papers in leading scientific journals (Neuron, Journal of Neuroscience, Nature).

I also investigated whether electrical stimuli delivered from the outer surface of the skull can by sufficiently high in magnitude to change the state of neuronal oscillatory networks, and thus to change temporal synchrony. These experiments led finally to a unique closed loop system where the developed circuitry can detect the evolution of epileptic seizures in real time, and deliver electrical pulses transcranially with a fine temporal precision in order to stop the initiation of the seizures. We proved that the method can successfully decrease the duration of epileptic episodes with more than 60%. I published these striking results and the methodology in one of the most prestigious scientific journals (Science). To continue these experiments I successfully applied for an EU FP7 ERC Starting grant, which will support the continuation of my work as an independent research group in the next five years.

During the one year of the return phase I established an experimental setup in Szeged allowing large-scale neuronal recordings, in combination with photo-stimulation in chronically implanted behaving rodents and cats. By experimenting with our initially chosen animal model it turned out that its suboptimal for the investigation of visual information processing in freely moving animals due to various technical reasons. The main bottleneck was the extremely long training period before achieving an acceptable yield in the chosen task performance. Moreover the necessary head fixation was an unwanted constrain that was suspected to influence the neuronal responses comparing to natural behavior. Considering these circumstances we decided to change the animal model to a freely moving non-restrained rat model. We chose the Long-Evans strain, which has higher visual acuity comparing to other strains and an innate ability to perform various spatial navigation tasks. Since it is almost impossible to train a freely moving rat to fixate its sight onto a pre-defined place, we trained them to run back and forth on a linear maze, where the optical stimuli were projected on the translucent walls and floor through a specially designed set of mirrors. With this arrangement the stationary, but trial-by-trial variable visual stimuli was perceived as a visual motion, with a velocity defined by the free motion of the animal. We found that this experimental approach is the best available to resemble natural conditions, while the experimenter has still complete control on the parameters of the stimulus. The analysis of the recorded dataset is currently in progress, we are focusing on the translation of the rendered visual information by synaptically connected neurons. The interim results are going to be presented as two posters on the Society for Neuroscience Meeting, San Diego, CA, USA, in 2013 November.

I believe, that my progress toward the objectives is in full agreement with my project proposal, and I was able to exploit almost all opportunities to gain the host institutes knowledge. I feel being on a more advanced level of scientific maturity then before this period, which makes me ready to start my reintegration and independent carrier at my home institution. To continue my experiments, and to provide adequate funding for my new independent research group, I successfully applied for the EU FP7 ERC Starting grant. The contract preparation has already been started, and expectedly the project will start in 2013 November. This financial support helps me to continue my work along the same principles and standards in the next five years.

Section A (public) – DISSEMINATION MEASURES

This section should describe the dissemination measures, including any scientific publications relating to foreground and specify any applications for patents etc in accordance with article II.11. Its content will be made available in the public domain thus demonstrating the added-value and positive impact of the project on the European Community.

- **Dissemination activities**

The results of the project are already disseminated in the popular press, and have been presented on open lectures, public outreach programs, etc.

The scientific results themselves were published as 6 peer reviewed papers, with a cumulative impact factor of approx.70.

The Science publication of the epileptic seizure suppressing effect of the transcranial electrical stimulation was advertised in the News section of the Nature, and many thematic online sites, e.g. EpilepsyU.com. The results of the experiments were cited more than 100 times in the recent two years. The success of this research was presented by the Hungarian media many times in a language understandable by non-experts as well.

I also participated in a number of conferences where I presented my work as a poster. These included the annual Society for Neuroscience conference, the meeting of the Hungarian neuroscience society every year.

I was an invited lecturer to the HIVE and ICON conferences, to the RIKEN institute in Japan, and many times within Hungary by different research centers, universities and radio stations.

The research I performed during the outgoing phase of my project was selected and advertised by the ERC as a ‘Success Story’.

The Marie Curie Actions has been recently advertised in the city of my returning host institute on a Europe Direct event, where I was invited to talk about the exploitable career building possibilities of the ERC funded scholarships for the general audience.

- **Publications (peer reviewed)**

LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES								
NO.	**Title**	**Authors**	**Title of the periodical or the series**	**Number, date or frequency**	**Publisher**	**Place of publication**	**Year of publication**	**Relevant pages**
1	Closed-loop control of epilepsy by transcranial electrical stimulation	Berényi A, Belluscio M, Mao D, Buzsáki G	*Science*	*337*	*American Association for the Advancement of Science*	*USA*	*2012*	*735-737.*
2	A toolbox of Cre-dependent optogenetic transgenic mice for light-induced activation and silencing	Madisen L, Mao T, Koch H, Zhuo Jm, Berényi A, Fujisawa S, Hsu Yw, Garcia Aj 3rd, Gu X, Zanella S, Kidney J, Gu H, Mao Y, Hooks Bm, Boyden Es, Buzsáki G, Ramirez Jm, Jones Ar, Svoboda K, Han X, Turner Ee, Zeng H.	Nature Neuroscience	15	Nature Publishing Group	USA	2012	793-802
3	Traveling theta waves along the entire septotemporal axis of the hippocampus	Patel J, Fujisawa S, Berényi A, Royer S, Buzsáki G	Neuron	75	Cell Press	USA	2012	410-417
4	Local generation and propagation of ripples along the septo-temporal axis of the hippocampus	Patel J, Schomburg E, Berényi A, Fujisawa S, Buzsáki G	Journal of Neuroscience	In press	Society for Neuroscience	USA	2013	In press
5	Large-scale recording of neurons by movable silicon probes in behaving rodents	Vandecasteele M, M S, Royer S, Belluscio M, Berényi A, Diba K, Fujisawa S, Grosmark A, Mao D, Mizuseki K, Patel J, Stark E, Sullivan D, Watson B, Buzsáki G	Journal of Visualized Experiments	61	JoVE	USA	2012	e3568
6	Co-oscillation and synchronization between the posterior thalamus and the caudate nucleus during visual stimulation	Gombkötő P, Berényi A, Nagypál T, Benedek G, Braunitzer G, Nagy A	Neuroscience	242	Elsevier	USA	2013	21-27

Section B (confidential) - EXPLOITABLE FOREGROUND AND PLANS FOR EXPLOITATION

This section should specify the exploitable foreground and provide the plans for exploitation. It will be kept confidential and will be treated as such by the REA.

***The applications for patents, trademarks, registered designs**, etc. shall be listed according to the template provided hereafter.*

The list should, specify at least one unique identifier e.g. European Patent application reference. If applicable, contributions to standards should be specified.

TABLE B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.			
Type of IP Rights: Patents, Trademarks, Registered designs, Utility models, etc.	Application reference(s) (e.g. EP123456)	Subject or title of application	Applicant(s) (as on the application)
N/A	**N/A**	**N/A**	**N/A**

Please complete the table hereafter:

TABLE B2: **OVERVIEW TABLE WITH EXPLOITABLE FOREGROUND**					
Exploitable Foreground (description)	**Exploitable product(s) or measure(s)**	**Sector(s) of application**	**Timetable, commercial use**	**Patents or other IPR exploitation (licences)**	**Owner & Other *Beneficiary*(s) involved**
N/A	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*

In addition to the table, please provide a text to explain the exploitable foreground

Since the project was mainly focusing on basic research, there is no patent application, trademark, etc involved. The exploitable foreground is not possible to predict, the acquired knowledge in hand with the experiments of the following five years of the ERC starting grant MAY serve in the future as a basis of some new therapeutical approach in the human medicine. However the production a 'consumable' device must be preceded by very strict clinical trials (including safety tests), which is out of the focus of these research projects.

1. SCIENTIST IN CHARGE QUESTIONNAIRE

RESEARCH TRAINING (IEF-IOF)/TRANSFER OF KNOWLEDGE (IIF) ASSESSMENT:

What is the size of the hosting research group?	17 person

How many researchers have you supervised, within the past 10 years? Of which funded by:	
EC/Marie Curie actions	0
EC Other Funding	0
If yes please specify contract number, programme and directorate general in charge	N/A
University fellowships	5
National public bodies	0
Industry	0
Other, please specify:	0

How many researchers have you supervised within this project?	4
Corresponding to how many person months?	44

Number of publications resulting directly from the research project:	
Recruited researcher(s) and yourself	6
Recruited researcher(s) alone	0
Recruited researcher(s) with authors other than yourself	0

Participation of the fellow researcher at conferences (number):	
Passive	0
Active	14
How do you rate the overall success of the research training (IEF, IOF)/ transfer of knowledge (IIF)?	Very successful

General assessment:
I consider the project very successful, since the two main purposes of the Marie Curie IOF programs (namely to import knowhow from a 3rd country to the returning host institutes, and to train researchers on the beginning of their career and preventing the brain-drain) were completely met.

RESEARCHERS ASSESSMENT:

Rate the overall level of the fellow researcher integration in the research team and the host organisation with regards to:	
participation in meetings/seminars	Very active
discussions of results and project-related topics	Very active
co-operation with other team members	Daily, successful cooperation
co-operation with other researchers of the host institution	Occasional, on-demand cooperation

Rate the overall performance of the fellow researcher with regard to:	
originality of fellow approach towards research (initiative/independent thinking)	Well prepared, original research ideas, independent, scientifically mature thinking
capacity to develop new skills and to benefit from training	Very satisfactory
productivity (research results/publications/international conference attendance)	Produced a high number of very high standard publications himself as well, as in collaboration with other team members
communication skills	Speaks English fluently, can successfully present his ideas, transmit his knowledge, open minded.
group leader skills (collaboration with other groups/project management)	A leader personality, ready to become an independent researcher and to establish his own research group.
training and/or teaching skills	The researcher was training PhD students during his project, as well as teaching medical physiology for Hungarian and English speaking medical students during the returning phase. A well prepared teacher with a good attitude, good teaching skills, and broad knowledge.
Please comment: N/A	

RESEARCH TRAINING OUTCOMES (IEF-IOF)/TRANSFER OF KNOWLEDGE (IIF):

Has this project provided additional links with other research groups or institutions?	yes
If yes, indicate the number of contacts in each case	
Universities	5
Research Centres	5
Industry/private companies	3
If Other, please specify: N/A	

Rate the importance of the following outcomes of the research training/transfer of knowledge:	
results of the research	8/10
number of publications	8/10
development of research	10/10
establishment of international collaborations	9/10
transfer of knowledge/technology	10/10
training of researcher	8/10
further academic qualifications (PhD, habilitation etc.) for fellows	8/10
Please comment: N/A	

YOUR OPINION ABOUT THE MARIE CURIE ACTIONS:

Do you have any other comments or suggestions of how to improve the concerned Marie Curie actions? N/A

Did you have previous knowledge of the Marie Curie actions?	Yes, from other Marie Curie fellow scientists

If yes, what sort of image do you think that the Marie Curie actions have among the scientific community in your research area?	High prestige, top level program.

Attachments:	

Date: Szeged, October 15, 2013 **Signature Scientist in Charge:** _____ **Attila Nagy, MS, PhD**	**Date: Szeged, October 15, 2013** **Signature Researcher:** _____ **Antal Berényi, MD, PhD**

ENDPAGE

PEOPLE

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