CoBeN

Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioural Neurology

H2020-MSCA-RISE-2016-734718

2nd PROGRESS REPORT

(1. 3. 2018 – 28. 2. 2020)

Description from Participant Portal:

The second Progress report will present and summarize ***two years of the research project (1. 3. 2018 – 29. 2. 2020)****, including* ***reports on clinical and MRI data acquisition and analysis and on MRI data acquisition*** *for tasks completed within the period.*

1. General Progress of the action

1.1 Please indicate the progress of the action during the period covered by this report:

- (•) The action has fully achieved its objectives for the period.
- ( ) The action has achieved most of its objectives for the period with relatively minor deviations.
- ( ) The action has achieved some of its objectives but corrective action is required.
- ( ) The action has failed to achieve critical objectives and/or is severely delayed.

1.2 Please describe the general scientific progress of the action during the period covered by this report (including by giving qualitative indicators and by describing deliverables and milestones achieved):

General progress of the project

The work done in the first year of the project (1. 3. 2017 – 28. 2. 2018) was summarized in the first progress report approved by EC on June 19, 2018. During the following 2-years period (1. 3. 2018 – 28. 2. 2020), we have secured successful dissemination by finishing the majority of the publication activities as well as public and scientific workshops. This was ensured by a sufficient pace of data collection and, above all, by effective communication between all sites. We were able to analyze all the key parts of WPs, such as the language and kinematic assessment, and MRI. Regarding the NIBS WP, we completed the exploratory study and subsequently continued to collect data for the repeated NIBS, followed by the submission of the key manuscript. Finally, thanks to the successful risk management plan we were able to either avoid or minimize potential internal threats that would hinder the fulfillment of the study objectives.

The progress within the individual work-packages is described below:

WP1: Universal and language-specific neural network architectures for reading and spelling (MU)

For the WP1, the data collection of healthy subjects has been completed. The main focus has been put on the complete recruitment of the stroke (~69% recruited in UofA + USZ), PPA (92% recruited in UofA) and Alzheimer 's patients (54% recruited in MU); and to recruit extra subjects to substitute the ones that have been excluded due to missing or corrupted data.

Deliverables and milestones achieved within WP1:

- **D1.2: Specific protocols for language assessment** (UoA, Approved by EC)
- **MS2: Language assessment and analyses completed** (UoA)
- **MS3: MRI data collection and analyses completed** (UoA)

WP2: Motor networks for speech production (MU)

All healthy subjects have been recruited for this work package as well, and thus, we are scheduling the remaining subjects for the groups of: stroke patients (69% recruited), Alzheimer's patients (54% recruited),

PPA patients (92% recruited) and Parkinson's patients. Regarding the group of Parkinson's patients, all the data have been completed for the rTMS part at MU and 70%, 100% and 55%, of data have been collected for language network study part done at MU, USZ, and UoA, respectively. Finally, extra subjects are needed for this work package to substitute the excluded ones due to missing or corrupted data.

Deliverables and milestones achieved within WP2:

- **D2.2: Standardized protocol for language and acoustic assessment and analysis** (MU, Approved by EC)
- **D2.3: Specific behavioural and task-induced fMRI protocols for language and acoustic assessment** (MU, Approved by EC)
- **D2.4: Novel parametrization software for acoustic analysis** (MU, Approved by EC)
- **MS6: Linguistic and acoustic data acquired and assessment analysis completed** (MU)
- **MS7: MRI data analyses completed** (MU)

WP3: Motor networks for handwriting (MU)

For the WP3, the data of all healthy subjects have been collected. We have been focusing on recruitment the remaining neurological patients for kinematic and MRI analysis: stroke patients (69 % recruited in UoA + USZ), Alzheimer's patients (54 % recruited in MU), PPA patients (92% recruited in UoA), and Parkinson's patients (75 % recruited in UoA + USZ + MU). In the exploratory study of rTMS effect on handwriting, 50 % of patients with Parkinson's disease have been recruited.

Deliverables and milestones achieved within WP3:

- **D3.2: Kinematic abnormalities produced by damage to the cortical vs. subcortical components of the handwriting motor control network** (MU, Approved by EC)
- **M11: Kinematic assessment analysis completed** (MU)
- **M12: MRI data analyses are completed** (MU)

WP4: Top-down attentional regulation of visual processing and working memory (USZ)

As for the final scientific work package, the data collection progress is in accordance with the WP1-WP3 with still ongoing recruitment of Parkinson's patients at Partners MU and UoA; and completed recruitment of healthy controls by all sites.

Deliverables and milestones achieved within WP4:

- **D4.2: Standardized protocol for cognitive assessment and composite domain z-score calculation** (MU, Approved by EC)

WP5: Project management (MU)

See *Section 4 Additional Information*. Deliverables and milestones achieved within WP5:

- **D5.2: Mid-term Meeting of the CoBeN consortium** (MU, Approved by EC)

Brief reports of the seconded staff describing their secondments' activities and transfer of knowledge

Within this reporting period, we organized 9 secondments at the University of Arizona in total duration of almost 42 person-months.

Specifically, the coordinating institution **Masaryk University** seconded **7 ESR** (PhD students) - **Luboš**

Brabenec (6 months), **Monika Pupíková** (5,5 months), **Zoltán Galáž** (5 months), **Alžběta Minsterová** (almost 3 months), **Dominik Pižem** (almost 4 months), **Kristína Mitterová** (4 months), and **Adrian Pieš** (3 months). The Hungarian partner USZ (University of Szeged) seconded one ER (researcher fellow) **Krisztián Kocsis** (for 10 months altogether, 6 months in 2018) and one PhD student, **Bence Bozsik** for 6 person-months. The following short reports of the seconded persons describe the conducted research activities and acquired experience:

Secondment of Luboš Brabenec (MU –> UoA, 1. 1. 2018 – 1. 7. 2018)

Luboš Brabenec was partially setting up the neuropsychology battery and norms. He also performed cognitive examination of healthy controls and patients with Parkinson's disease. Luboš was involved in data encryption and he was defacing MRI data. He also prepared a system for data storage and sharing. During his stay, he learnt and performed resting state functional connectivity analysis of language networks in Conn toolbox. Luboš was also involved in preparation of special resting state questionnaire that will be used in future studies. He also helped with creation of promotion materials for participant enrolment.

Secondment of Monika Pupíková (MU –> UoA, 28. 1. 2018 – 10. 7. 2018)

Secondee Monika Pupíková was involved in data collection for WP1 and WP3. She was responsible for correct MRI acquisition and behavioral measures outside the scanner in patients and healthy control subjects. She also performed psychological examination of participants during her stay. She was responsible together with Luboš Brabenec for preparation of data storage and sharing. She helped with resting state functional connectivity analysis of language networks in Conn toolbox.

During her stay, she learnt about different ways of MRI and fMRI data acquisition, preprocessing and analysis. She also gained deeper knowledge of neurobiology of language and its pathology across different patient groups (mainly PPA patients and patients after stroke).

Secondment of Zoltán Galáž (MU –> UoA, 2. 7. 2018 – 23. 11. 2018)

During the exchange period, the secondee worked mainly on the acoustic analysis of the recordings of the participants participating in the CoBeN. It included acoustic and visual inspection, pre-processing, feature extraction and consequent statistical analysis.

Regarding the acoustic analysis, the secondee also worked on the data preparation (e.g. segmentation, labeling, etc.), and parametrization of the corpus of data acquired in all of the associated institutions. The data parametrization comprised extraction of the acoustic features quantifying voice/speech impairment in the area of phonation, articulation, prosody, and lexical stress. Moreover, new acoustic features for the apraxia of speech quantification were developed and tested.

Secondment of Alžběta Minsterová (MU –> UoA, 11. 1. 2019 – 4. 4. 2019)

Alžběta focused on analysis of imaging data especially from patient's groups of stroke and primary progressive aphasia (PPA) patients. These patients' data require special care during the normalization, because of the presence of the lesion. There has been transfer of knowledge from Dianne Patterson (US), who is an expert in this field.

Alžběta performed tract-based spatial statistics analysis comparing the stroke and PPA groups from both Szeged and Tucson, and then comparing a single patient subject to group of healthy controls from Brno. Moreover, she started to work with BCBtoolkit (TRACTOTRON), what is a novelty in both Brno and Tucson. This tool calculates the probability and percentual damage of different white matter tracts caused by the stroke/PPA lesion. It is possible to extend the calculations also to gray matter regions of interest. These metrics can be correlated with results from language and neuropsychology testing. The functionality of the tool was tested and proved on older datasets. Both TBSS and TRACTOTRON approaches will be used

for the analyses in COBEN, when all data are acquired. Alžběta was also present during the MRI scanning sessions.

Secondment of Dominik Pižem (MU –> UoA, 8. 1. 2019 – 1. 5. 2019)
Dominik was present during the MRI scanning sessions and, as an experienced medical student participated predominantly in visual inspection of brain scans as well as lesion mapping. Dominik spent a significant amount of time in the Banner hospital, where he, under the supervision of dr. Rapcsak helped with the assessment of participants and patients with stroke, which was also a valuable experience for the beginning of his career.

Secondment of Kristína Mitterová (MU –> UoA, 1. 10. 2019 – 1. 2. 2020)
Secondee Kristína Mitterová was involved in data collection for WP1 and WP3. She was helping MRI data acquisition and performed neuropsychological assessment of patients and healthy control subjects. Due to data collection part of the project, being finalized in 2020 she was also responsible for data control, reporting, management and distribution to all the study sites.

During her stay, she deepened her knowledge in assessment, neurobiology, and therapy of language pathologies in degenerative disorders and stroke.

Secondment of Adrián Pieš (MU –> UoA, 20. 9. 2019 – 18. 12. 2019)
During the exchange period, Adrián Pieš helped with the MRI scanning process and, similarly, as Dominik, participated predominantly in visual inspection of brain scans as well as lesion mapping. He gained significant knowledge during his internship at the Banner hospital, where he, under the supervision of Dr. Rapcsak helped with the assessment of participants and patients with stroke and other neurological conditions, which not only helped the project but was also a valuable experience for the beginning of his career.

Secondment of Krisztián Kocsis (USZ –> UoA, , 2. 5. 2018 – 31. 8. 2018) and Bence Bozsik (USZ –> UoA, 18. 6. 2019 – 11. 12. 2019)
The second stay of Kriszstián Kocsis at UoA followed up to his work done in 2017. Both secondees worked mainly on the scientific tasks specified within the WP4 and the main output of their work is summarized in the Deliverable 22, which will be submitted to the Participant Portal in March 2020.

2. Corrective Measures

2.1 Please explain any delays accumulated in the secondments / activities / deliverables foreseen in the Grant Agreement and the measures taken to oversee them.

Some Deliverables were submitted to the Participant Portal with a short delay due to various ad hoc reasons (technical, personal changes etc.) as explained to the Project officer in advance. Some other potential problems, which could have caused delays in the project implementation and preparation of project Deliverables are described in the table of risks below, as these were anticipated already at the stage of project preparation. However, thanks to the very efficient and successful collaboration between all sites of the consortium, we minimized potential internal threats that would hinder the fulfillment of the study objectives.
So far, also all secondments at the University of Arizona have been implemented according to the original timeline. We have already prepared a clear plan of secondments until the end of the project CoBeN, including a final visit of Prof. Irena Rektorová (project coordinator) at the University of Arizona, where she plans to discuss further scientific cooperation and possible follow-up RISE project with Dr. Steve Rapcsak.

However, actual critical situation with COVID-19 epidemic spread worldwide, will affect negatively the mobility activities of fellows and other CoBeN project staff as well as their participation in the meetings and outreach events organized in the framework of CoBeN projects. This new fact is being communicated with the Project officer, added to the table of risk and implemented in the Secondments Chart (see below).

2.2 Please indicate any potential risks identified and suggested approaches to mitigate them.

The table below shows the risks as identified in the project proposal and their current mitigation, where applicable.

Risk No	Description of Risk	WP No.	Proposed mitigation measures
R1	Patients recruitment with be slower than planned	WP1-4	There is a possibility to prolong patient recruitment for specific tasks, e.g. tasks that involve fMRI and rTMS studies since these are supposed to start later than behavioural studies
Risk monitoring and mitigation with the monitored period (M13-36)			Not relevant anymore (see WPs description including exact % of recruited patients).
R2	Some patient groups will be more difficult to enrol	WP1-4	At MU the PI is head of the Dementia Centre and deputy head of the Movement Disorders centre at the Dept. of Neurology in University hospital. In each centre approx. 500 patients with AD and 500 PD are followed. We also have established collaboration with practical neurologists in Brno. The UofA has active clinical and externally funded research programs in stroke, AD, PD, and PPA plus established collaboration with community neurologists for the referral of appropriate patients. At USZ The Department of Neurology provides care for more than 450.000 patients in southern Hungary on 96 inpatients bed and on a general as well as specialized outpatients clinics. The 25 beds of the Stroke Unit include a 15 bed subintensive unit. Nonvascular neurological diseases are treated on the 31 bed General Neurology Unit. A Neurorehabilitation unit works right next to the other two wards.
Risk monitoring and mitigation with the monitored period (M13-362)			We did not face to problems with enrolment of any groups of patience.
R3	Protocols/ examinations may be too long for patients	WP1-4	The examination can be divided into 2 sessions if necessary and if patients prefer this. We are able to cope with possible delays (see R1)
Risk monitoring and mitigation with the monitored period (M13-36)			No problem occurred with the length of the protocols and examinations.
R4	There may be technical problems at our core facilities MRI/TMS labs	WP1-4	These problems would be fixed quickly and would not harm the time schedule of the WPs. In MU we have 2 3T MRI machines (Siemens Prisma) just for research and a team of experienced technicians, MRI experts in the CF and service contract ensuring fixing of any problem within one week; and we have a well-equipped NIBS lab with 5 PhD students working in it. UofA has a 3T Siemens Skyra dedicated research MRI scanner with appropriate technical and image analysis support staff. At USZ the new 3T GE scanner is under installation in addition to the 1.5 T GE scanner. The Department of Neurology has a dedicated research time on both machines. The IT infrastructure at the Neuroimaging Research Group is available for the data analysis: several desktop computers and a high processing speed 24 core grid engine.
Risk monitoring and mitigation with the monitored period (M13-36)			High level of core facilities (including their equipment, technical knowledge and qualified work force) at all project partner sites ensured a smooth process of measurements without any technical problems or time delays.

R5	Some seconded people might not be able to travel	WP1-4	We have enough interested and flexible young PhD students/ postdocs to substitute those who are not able to go.
Risk monitoring and mitigation with the monitored period (M13-36)			So far, we have not any problems with students' secondments as all participants have been selected carefully with a stress on their scientific experience and travel ability. **However, a new and unexpected risk has occurred in the form of travel prohibition related to the extremely dangerous COVID-19 spread worldwide, which obviously affects secondments of fellows planned in the last period of the CoBeN project.**

Due to the COVID-19 outbreak, the principal distribution of secondments to UofA and therefore the successful implementation of the original Secondment chart is deemed not feasible. This concern results from the measures that have been applied by national governments, namely, suspended issuing of visa to the US, closing of borders for non-essential travel, etc**.** The presence of the two remaining MU seconders (5 person-months altogether) at UofA is crucial mainly for completion of the data collection which cannot be made up for locally due to social distancing.

At the moment it is difficult to predict development of the situation with the COVID-19. The outbreak is still ongoing and we do not know how long it will last. To secure successful termination of the project, we propose two variants of implementation of the remaining secondments (5 person-months). The proper variant will be chosen and requested in a form of amendement once the outbreak is terminated and we will have a better view of the situation.

The variants are the following:

1) Secondment of MU at UofA (SEC ID 33) Jaroslav Točík (3 person-months) originally scheduled from January to March 2020 will be postponed to autumn (October to December 2020) and secondment (SEC ID 12) Marek Bartoň (2 person-months) originally scheduled from September to October 2020 will be postponed to next year (April and May 2021). It is desirable that Jaroslav Točík as a psychologist will carry out a secondment earlier then Marek Bartoň. Jaroslav Točík will be in charge of recruiting psychological data and Marek Bartoň will be helping with MRI data acquisition as well as finalizing dissemination.
2) If the situation does not improve, both secondments will be postponed to the next year. Jaroslav Točík from January to March 2021 and Marek Bartoň from April to May 2021. The main reason for this postponing would be that the coronavirus situation is not yet contained which particularly interferes with the contact nature of testing as that would be unsafe for our elderly subjects.

The secondment of USZ at UofA was scheduled from the 19th May 2020 (the seconder had his visa and flight ticket already), but it was impossible to travel during that period, therefore, we propose postponing the secondment to autumn of 2020. This secondment does not necessitate an extension of the project, but we consider it important to mention this fact in the report. The cancellation of reservations is currently being dealt with.

The secondment (SEC ID 24) remains unchanged. Implementation of SEC ID 44 depends on the situation with COVID-19, as it is not necessary for the successful implementation of the project.

According to an announcement of President Robert C. Robbins, the University of Arizona plans to resume in-person classes in the fall semester, which begins on Aug. 24
https://uanews.arizona.edu/story/president-robbins-uarizona-plans-resume-inperson-classes-fall

Since the secondments and deliverables are yet to be achieved (they depend on results of secondments) and cannot be implemented within the original duration of the project (1.3.2017-28.2.2021), we would like to request 4 months of extension (1.3.2017-30.6.2021) – the number of months we lost due to the COVID-19 situation as we could not carry on the scheduled data collection.

The Secondments charts below show planned secondments for the last year of the project before the COVID-19 situation (Fig.1) and the newly proposed plan with the possibility of project extension (Fig. 2 and Fig.3)

CoBeN - SECONDMENTS CHART														
		2020											2021	
		35	36	37	38	39	40	41	42	43	44	45	46	47	48
SEC ID	**FROM**	**TO: UofA**													
11	MU														
12	MU														
21	MU														
22	MU														
23	MU														
24	MU														
31	MU														
32	MU														
33	MU														
34	MU														
41	MU														
42	MU														
43	MU														
		TO: UofA													
14	USZ														
26	USZ														
36	USZ														
45	USZ														
		TO: MU/USZ													
13	UoA														
25	UoA														
35	UoA														
44	UoA														

WP1	WP2	WP3	WP4	

Figure 1 The original Secondments chart of the project proposal – last year of the project realization

	CoBeN - SECONDMENTS CHART																							
		2020												2021										
		35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58
SEC ID	**FROM**	**TO: UofA**																							
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44	UoA																								
WP1	WP2	WP3		WP4																					

Figure 2 The proposed Secondments chart reflecting the COVID-19 situation – Variant 1

	CoBeN - SECONDMENTS CHART																							
		2020												2021										
		35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58
SEC ID	**FROM**	**TO: UofA**																							
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WP1	WP2	WP3	WP4																						

Figure 3 The proposed Secondments chart reflecting the COVID-19 situation – Variant 2

3. Ethical Issues

Please indicate how the ethical issues have been addressed during the period covered by this report and mention all the approvals/authorisations already provided to the REA (if applicable).

The ethical issues have been addressed within the **WP6: Ethics**. All the required approvals were collected and sent to REA according to the article 34.2 of the GA until M12. We have not encountered any ethics issues during the research activities. Specifically, all research subjects have understood the information in the informed consents and signed the documents, and we have had no subjects drop-out due to ethics-related issues.

4. Additional information

Please indicate any additional information, which you may consider useful to assess the project implementation during the period covered by this report, including management issues.

Project Management:

The consortium has been conducting regular Telco conferences and Skype calls to monitor the research progress, plan the next steps in project realization and consulting any potential research and administrative issues. **The Mid-Term meeting of CoBeN** took place on 4th June 2018 at the premises of CEITEC, Masaryk University in Brno, Czech Republic. The REA Project Officer **Dr. Thierry Jacquin**, together with an external expert **Prof. Riitta Salmeni** (Department of Neuroscience and Biomedical Engineering, Aalto University, Finland) were attended the meeting and presented with the current state of the project implementation by the whole team of project consortium. The progress of CoBeN implementation was evaluated positively, as the pace of secondments implementation and the results had been generally in line with the schedule.

Dissemination:

Researchers participating in the project CoBeN present regularly their experience and lessons learned at the internal seminars of the Masaryk University in order to motivate other scientific colleagues for the MSCA RISE proposal preparation. They also participated in the **National Information Days on MSCA** organized by Czech National Contact Point for MSCA at the Technological Centre of Academy of Sciences in Prague on 21st March 2018. CoBeN secondee **Patrik Šimko** presented his research experience from the University of Arizona, where he spent 6 months in 2017 working on project outputs (see his secondment description in Progress Report 1).

Prof. Steven Rapcsak from University of Arizona introduced CoBeN project and related scientific topics to the experts from St. Anne's University Hospital Brno and Faculty of Medicine, Masaryk University during his invited lecture on *"The Neural Basis of Language: Converging Evidence from Neurodegenerative Disorders and Stroke"* held on 23rd March 2019.

CoBeN team participated in two **Researchers' Nights** organized by the Masaryk University and its faculties and institutes on 5th October 2018 and 27th September 2019. The team presented basic neuropsychological methods the visitors could try out. They also introduced the main aims of the CoBeN project and explain how transcranial magnetic stimulation operates, its potential benefits for human cognitive functioning, and its key role in neuropsychological experimental research. The machine was on site, but obviously was not used practically for ethical reasons. The stand was very popular and helped us to promote neuropsychological research, CoBeN's specific topics, and our international collaborations.

The main outreach activity of the CoBeN team has been initialized and framed up by the coordinator of the project, prof. Irena Rektorová, who specified four main topics that could be easily communicated to the general audience. The Series of lectures is entitled **"Labyrinth of the Brain: Research the Most Complex Structures on Earth"** and so far, three of them have successfully been held at the **Brno Observatory and Planetarium**. More than 200 people were introduced into the subjects of:

10th October 2019: **Brain, sight and the picture of reality**

Annotation: At first glance, it may seem that vision is a very simple and straightforward process. However, the opposite is true! Let us look at how human vision differs from that of animals. We will also visit the world of visual illusions, focusing on hallucinations and other visual disturbances.

21st November 2019: **Brain and the mystery of language**

Annotation: Is the language a unique human ability? What speech problems can people have after a stroke? Why young children can learn a foreign language so easily? Where in the brain could we find the center of speech? How does our language affect our perception of the outside world? Not only these questions, but also many others, we will be looking for an answer together in our lecture.

20th February 2020: **Brain and lost neurons: Alzheimer's and Parkinson's diseases**

Annotation: Neurodegenerative diseases, such as Alzheimer's or Parkinson's, are great scarecrows of mankind, mainly because of the aging population in developed countries. How do these diseases develop? What could we do to prevent these diseases? How can we help people with neurodegenerative diseases and what does contemporary science say? Together, we will look at how the brain loses neurons.

One more lecture is planned for autumn 2020 (topic: **Brain and stimulation: a new form of biohacking?**)

See the press release here (in Czech only): https://www.ceitec.eu/visit-the-mysterious-world-of-the-brain-accompanied-by-scientists-from-the-ceitec-research-center/t10132. The events have been announced and promoted also via social networks (Facebook, Twitter, Instagram):

https://twitter.com/CEITEC_Brno/status/1182332510094741504
https://www.instagram.com/p/B3cbR4encyu/?utm_source=ig_web_copy_link
https://www.ceitec.cz/1-prednaska-mozek-zrak-a-obraz-reality/a3725
https://www.facebook.com/CEITEC/posts/3081397555209695
https://twitter.com/CEITEC_Brno/status/1197606294095577088
https://www.instagram.com/p/B5I9S37nsNu/?utm_source=ig_web_copy_link
https://www.ceitec.cz/2-prednaska-mozek-a-tajemstvi-jazyka/a3727
https://www.facebook.com/CEITEC/posts/3187526227930160