



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

H2020-MSCA-RISE-2016-734718



PROGRESS REPORT

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

At the MU, during the first year of the project, we have started collecting data from healthy controls. We started with short pilot study (10 HC subjects), which led to the optimization of the protocols, especially MR protocol and behavioural tasks. Then we continued with data acquisition in healthy controls (up to date 17 HC subjects) and PD patients for WP 2, WP3 and WP4 (6 PD patients). We have also data from 2 AD patients for WP1. At the UoA they are in the process of completing behavioural and neuroimaging data collection on 2 patients with PPA, 2 patients with PD, 1 patient with stroke, as well as 3 HC. USZ had encountered some delay in the data acquisition, but this have been mitigated (see 2. *Corrective measures*).

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

WP1,2

Data from 15 HC subjects (i.e. pilot data analysis) was acquired and the pilot data analysis has been completed. Reading and writing tasks induced activations in relevant language areas and processing non-words led to enhanced activation of the dorsal attentional network compared to processing real words. This is in line with our hypotheses.

Deliverables and milestones achieved within WP1: **D1.1 Pilot MRI and language assessment data, M1: Enrolment of subject groups is completed**

Deliverables and milestones achieved within WP2: **D2.1 Pilot fMRI data for language and acoustic assessment, M5: Enrolment of participants groups completed**

WP3

The fMRI activations during Sentences reading task were quality control checked for 15 HC and acoustic data was sent to Brno University of Technology to be processed.

Milestone achieved within WP3: **M10: Enrolment of subject groups completed**

WP4

Both behavioural and fMRI data from 11 HC was processed. Pilot behavioural results of Faces/Scenes task show mean accuracy of 87% for Faces and 82% for scenes, specificity of 96% for both Faces and Scenes and sensitivity of 78% for Faces and 68% for Scenes. Concerning Faces/Scenes Recognition Test there was accuracy of 60% for faces with attention and 53% for faces without attention, 58% for scenes with attention and 41% for scenes without attention. Whole brain fMRI activations were checked for both Faces and Scenes. In addition, enhancement/suppression of activations in fusiform face area and parahippocampal place area was calculated.

Resting state fMRI pilot data from 15 HC were analysed using independent component analysis (ICA). The resulting networks included ventral visual network (VN), dorsal attentional network (DAN), insular network (IN), right frontoparietal network (rFPN), default mode network (DMN), frontal network (FN) and cerebellar network (CN).

Milestone achieved within WP4: **M14: Enrolment of subjects Completed,; M15: Cognitive assessment completed, USZ, M10, WP4**

Brief reports of the seconded staff describing their secondments' activities and transfer of knowledge in 2017:

The first year of the project provided European partners with their first experience with the host institution of the University of Arizona. Within 2017, we started four secondments and by the end of 2017 completed three of them in total duration of 16 person-month (2017).

Specifically, the coordinating institution, the MU (Masaryk University), seconded two PhD students – Marek Bartoň and Patrik Šimko (for 9 months altogether, 8 months in 2017) and one technician – Patrícia Klobušáková (3 months). The Hungarian partner, the USZ (University of Szeged) seconded one PhD student – Krisztián Kocsis for 5 person-month (approx. 4 in 2017). The following short reports of the seconded persons describe the conducted research activities and acquired experience.

Secondment of Marek Bartoň (MU -> UoA; 1.3.2017 – 31.7.2017)

Marek Bartoň was setting up the imaging protocol (in Tucson) for the WP1 - reading and writing tasks using words and non-words. Plausibility of the technical solutions and stimulus sets was tested during a few pilot scanning sessions.

The next activity concerned technical equipment for handwriting data acquisition and speech recording outside the MRI environment. This equipment was installed, tested and pilot recordings were sent to Brno for quality assessment. On the basis of the quality check outcome, the settings of the handwriting tablet and speech recording setup were finalized.

Data analysis of fMRI data was done. This dataset consisted of healthy young Czech subjects - measured in the Czech republic prior to research stays in US. It concerns handwriting and reading (words and non-words) tasks. The transfer of knowledge focused on neurobiology of language with respect to interpreting such functional neuroimaging data (transfer of knowledge from US - Dr. Rapsak to CR - M. Barton).

We continued with finalization of a manuscript concerning visuo-motor integration during handwriting of single letters.

Secondment of Patrícia Klobušáková (1.7.2017 – 30.9.2017)

Patrícia Klobušáková helped Marek Barton with setting up E-prime task for the WP1 (reading/writing). She also worked on setting up the imaging protocol in Tucson, and testing and adjusting technical equipment for speech recording and handwriting acquisition (WP3). Then she set up E-prime tasks for WP4 (visual processing). All tasks were tested and pilot data were checked and analysed.

She worked on fMRI exploratory data analyses concerning language regions connectivity in PD patients in comparison to healthy controls and also analysed pilot CoBeN data from Czech Republic in order to ensure sufficient quality, the right settings and the accuracy of WP4 and WP2 tasks.

There has been transfer of knowledge (Dianne Patterson - US → Patricia Klobusiakova - CR) concerning a specific type of DTI data analysis - bidirectional probabilistic tractography, with an extensive feedback on improving this method and data pre-processing.

Secondment of Patrik Šimko (1.10.2017 – 31.1.2018)

Patrik Šimko was setting up the neuropsychology protocol at the UoA (gathering the battery tests and norms) for all work packages and creating the manual for behavioural testing.

Another activity related to behavioural testing in which he was involved was the synchronization of the language batteries across the centres (specifically the generation of the words and non-words task).

He was also involved in creating the behavioural data database for the VBM analysis from PPA patients and HC. Similarly, he helped with creation of the behavioural data database for the VLSM from post/stroke patients and HC.

During his stay he learnt semi-automatic lesion segmentation in ITK-snap and manual segmentation using MRI-cron/FSL. Related to segmentation he manually segmented around 50 scans of post-stroke patients for the VLSM (WP1).

He also did 3 cognitive assessments with 2 PD patients and one non-fluent PPA patient.

Secondment of Krisztián Kocsis (21.8.2017 – 21.2.2018):

During the exchange time period the secondee worked on the following items (augmented that more of them are still under progress, unfinished: those will be ready during the second exchange period):

- 1: A database of 100 stroke patient's MRI scans were selected and created (research/clinical scans)
- 2: From various semi-automated lesion segmentation softwares, the ITK-snap software was first tested and done.
- 2b: The BIANCA (Brain Intensity AbNormality Classification Algorithm) built in FSL software was tested and particularly done.
- 2c: The research scans (with same parameters and high resolution) were manually segmented thus a database was created to use in any further analysis (comparing the efficacy of different methods e.g.)
- 3: Single subject VBM analysis were done on the new enrolled PPA patient's T1 images to identify atrophy (semantic and nonfluent variant).
- 4: Whole-brain VBM analyses were done to compare the PPA and healthy controls (age, gender matched) to identify the aphasia subtype -specific atrophy.
- 5: Freesurfer-cortical thickness analyses was began, aiming to compare with the VBM approach
- 6: Voxel-based lesion symptom mapping analyses was began with the stroke lesion data

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.

The secondments have been implemented according to the plan. So far, no delay have been occurred. The secondment plan is kept up t date and we have already a clear and agreed plan of secondments till 1.Q. of 2019.

There have been delays in submission of ethics deliverables. This concerned mainly the European partners who did not have enough experience and processes established in this field fitting in terms of formal addressing of the requirements. However, the track has been beaten and the ethics aspects of the project have been running smoothly.

The ethics regulations of the US partner required a yearly update of ethics approval, which had been arranged for an the update of the UoA's approval was obtained in due term (January 2018).

Some of the other delays are described in the table of risks below, as these were anticipated already at the stage of project preparation.

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

The table below show the risks as identified in the project proposal and their current mitigation, where applicable (coloured and in *Italics*).

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
<i>Risk monitoring and mitigation with the monitored period (M1-12)</i>			<p><i>UoA: Delays in neuroimaging data acquisition were experienced at the UofA due to moving the MRI facility to a different location. We expect the research scanner to be available and operating at full capacity by the end of March, 2018.</i></p> <p><i>MU: approximately 60 PD patients should be enrolled during the study and we foresee that given the relatively high number, this may be risky. Therefore, we contacted the President of the patient society Brno Group Parkinson to help with patient enrolment. Prof. Rektorova (PI) gave a lecture for this patient group and had a radio talk on the project in order to increase knowledge about the project itself and about the disease.</i></p> <p><i>USZ: USZ team had to wait for the Digitizing Tablet to be purchased for writing movement acquisition and analysis. This will be solved in March when 2 students from MU will come to install and help to start data acquisition on the Tablet that was purchased at the MU. New visits will be scheduled for those who already participated in any of the WPs in order to acquire the missing data from the handwriting.</i></p>

R2	Some patient groups will be more difficult to enroll	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 includes 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 (M1-12)			<i>See above – mitigation related specifically to the MU (R1)</i>
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 (M1-12)			<i>We collect the data form one subject in three approximately 2 hours long sessions divided into 2-3 days. Patients find it optimal and they do not show signs of fatigue. We will follow this procedure to ensure high quality of the acquired data and to minimise potential drop-out of patients.</i>
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 (M1-12)			<i>No problems with the MRI facility have occurred up to this date.</i>
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 (M1-12)			<i>We have not encountered any case of a person either to refuse or not to be seconded.</i>

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. We have collected all the required approvals and sent REA the statement confirming this according to the article 34.2 of the GA. 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. The ethics approvals of the University of Arizona have been updated in due time for 2018 (D6.2).

The following list of obtained approvals includes of the WP6's deliverables:

D6.1 – Monitoring of the on-going competence of the vulnerable adults

D6.2 - Ethics approvals

D6.3 – Data protection – compliance with EU legislation

D6.4 – Copies of confirmation by competent Institutional Data Protection Officers

D6.5 – Appointment of an independent Ethics Advisor

D6.6. – Authorization of Material

Ethics declaration on compliance with article 34.2 of the GA.

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.

The consortium has been conducting regular (quarterly) T-conferences to monitor the research progress, as well as to plan the next steps and consulting any potential research and administrative issues. To this date, we have had three Skype calls that were planned at the kick-off meeting held on 25.4.2018 for the whole calendar year. This communication format proves to work sufficiently for our small consortium.

Apart from that, CEITEC researchers have made several short research visits at the University of Szeged facilitating the activities related to data harmonisation of the data acquisition.

We included new pregraduate students from the Faculty of Medicine and from the Psychological Faculty at MU. Students are very enthusiastic and helpful in acquiring the data and helping with HC and patient enrolment.

Dissemination:

- an interview with prof. Rektorova was issued in the printed and on-line magazine of the MU, available at this link: <https://www.online.muni.cz/en/science/9836-aiming-for-early-detection-of-alzheimer-s-and-parkinson-s>
- an interview with prof. Rektorova on the Czech Radio (only in Czech): <https://brno.rozhlas.cz/apetyt-6676527?player=on>
- prof. Rektorova was nominated for the Women of Czechia 2017 award.
- All media presence presented at the project website: <http://coben.ceitec.cz/media/>