EUROPEAN SYNCHROTRON RADIATION FACILITY

INSTALLATION EUROPEENNE DE RAYONNEMENT SYNCHROTRON

Experiment Report Form

The double page inside this form is to be filled in by all users or groups of users who have had access to beam time for measurements at the ESRF.

Once completed, the report should be submitted electronically to the User Office via the User Portal:
https://wwws.esrf.fr/misapps/SMISWebClient/protected/welcome.do

Deadlines for submission of Experimental Reports

Experimental reports must be submitted within the period of 3 months after the end of the experiment.

Experiment Report supporting a new proposal ("relevant report")

If you are submitting a proposal for a new project, or to continue a project for which you have previously been allocated beam time, you must submit a report on each of your previous measurement(s):

- even on those carried out close to the proposal submission deadline (it can be a *"preliminary report"),*
- even for experiments whose scientific area is different form the scientific area of the new proposal,
- carried out on CRG beamlines.

You must then register the report(s) as "relevant report(s)" in the new application form for beam time.

Deadlines for submitting a report supporting a new proposal

- 1st March Proposal Round - **5th March**
- 10th September Proposal Round - **13th September**

The Review Committees reserve the right to reject new proposals from groups who have not reported on the use of beam time allocated previously.

Reports on experiments relating to long term projects

Proposers awarded beam time for a long term project are required to submit an interim report at the end of each year, irrespective of the number of shifts of beam time they have used.

Published papers

All users must give proper credit to ESRF staff members and proper mention to ESRF facilities which were essential for the results described in any ensuing publication. Further, they are obliged to send to the Joint ESRF/ ILL library the complete reference and the abstract of all papers appearing in print, and resulting from the use of the ESRF.

Should you wish to make more general comments on the experiment, please note them on the User Evaluation Form, and send both the Report and the Evaluation Form to the User Office.

Instructions for preparing your Report

- fill in a separate form for each project or series of measurements.
- type your report in English.
- include the experiment number to which the report refers.
- make sure that the text, tables and figures fit into the space available.

- if your work is published or is in press, you may prefer to paste in the abstract, and add full reference details. If the abstract is in a language other than English, please include an English translation.

ESRF	**Experiment title:** Localization of fibrillar polymorphs in human brain tissue	**Experiment number**: LS3086
Beamline: ID13, ID21	**Date of experiment**: from: 10/11/2022 to: 13/11/2022	**Date of report**: 09/03/2023
Shifts: 12	**Local contact(s)**: Manfred Burghammer (ID13), Marine Cotte (ID21)	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

Jiliang Liu*
Lee Makowski*

Report:

Preliminary results

We have conducted scanning µXRD at ID13 and scanning µXRF at ID21. The preliminary results are extreme informative. As shown in Figure 1, we have performed µXRD and µXRF on a section of Dentate Gyrus of a subject diagnosed with Pick's disease. These data provided significant information on the distribution of fibrillar polymorphs among different plaques and tangles. The fibrils within Amyloid plaques and NFT is composed of β-sheets structures having a periodicity of 4.7 Å along longitudinal direction. µXRD exhibited patterns correlated to this featured structure, which allowed us determine the distribution of plaques and tangles. Furthermore, µXRD exhibited distinct patterns (Figure 1a) correlated to the novel structures, having periodicity of 5.2 Å, for the plaques and NFTs. Figure 1b showed the significant difference between the distribution of the map of 4.7 Å and the map of 5.2 Å. µXRF provided high resolution map of different element distribution, especially light element like Phosphate and Calcium, which has been thought great impacting the formation of plaques and tangles. The µXRF results were well correlated to µXRD results.(Figure 1c) The preliminary results indicate that the abnormal accumulation of Calcium and phosphate could give rise to a novel structure other than β-sheet structure for Amyloid plaques and neurofibrils tangles.

Improvement on samples preparation and experiment setup

Due to limited beamtime and initial issues with tissue flatness, we have not yet been able to measure tissue sections from all relevant brain regions for subjects with a full range of disease stages. However, we have developed a protocol for mounting tissue samples flat on Si_3N_4 membranes that has greatly enhanced data quality. Thus, to complete our characterization of the pathological pathway of Tau pathology, we propose to measure six brain regions from three patients at different stages of disease by µXRD at ID13 and µXRF at ID21. We will track - as a function of disease stage - the distribution of polymorphs and abnormal elemental

distribution within the six brain regions most severely impacted by disease. These observations should reveal clues as to the molecular mechanism of disease progression.

Scientific expectation

The preliminery results are very interesting and encouraging. Combation of µXRD and µXRF could resolve the molecular structural variation directly from tissues. With the improvement of sample preparation and sufficient beam, we should be able to measure the tissue samples from different regions of pathological pathway of neurodisease. Thus, we propose to apply for the additional beamtime, that will provide the missing structural infromation between synthesized plaques firbils and real fibrils deposited within tissues.

We highly appreicate the support from the local contact from ID13 and ID21. Their supporting and suggestions are essential for the successful experiment.

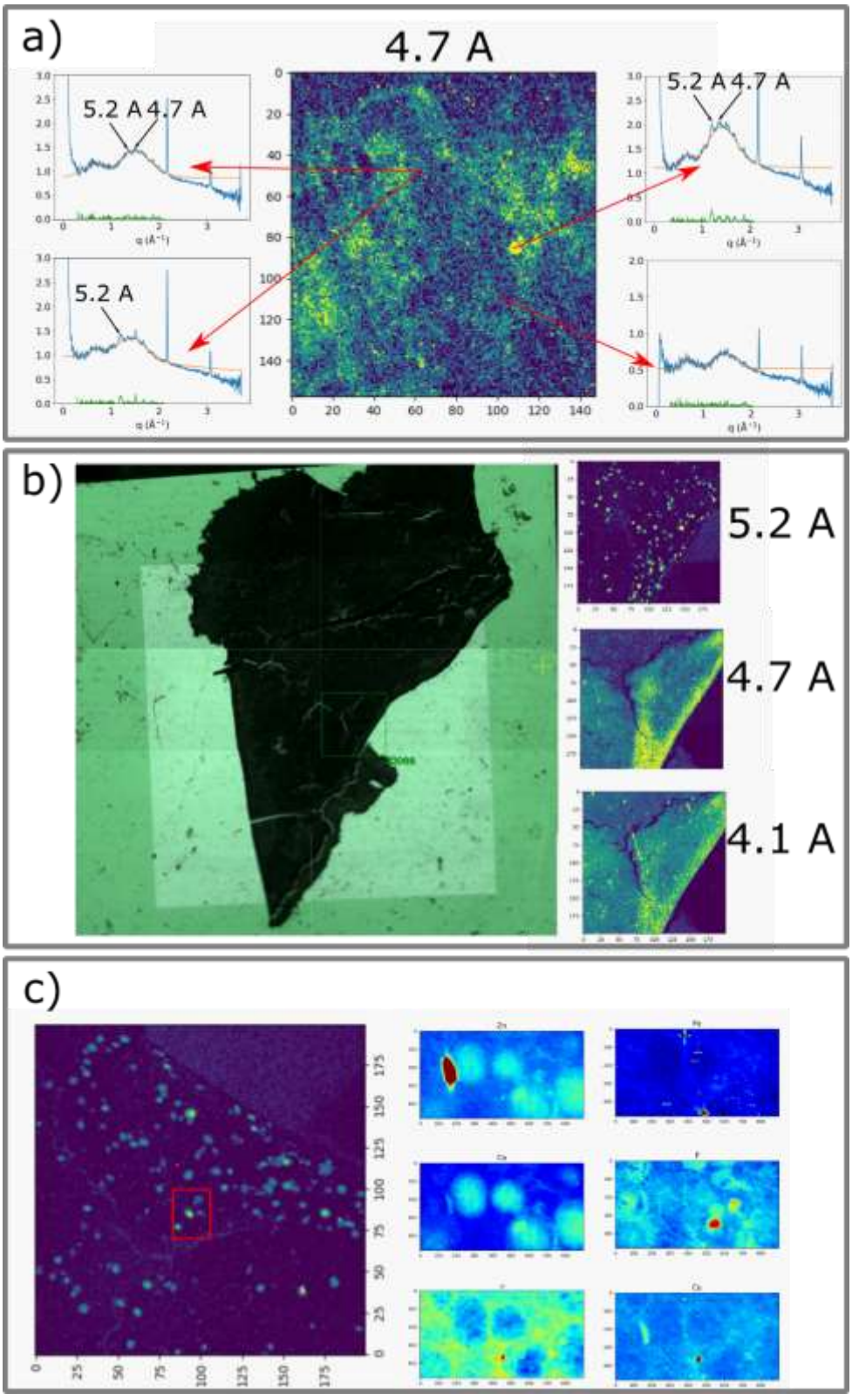

Figure 1. Combining scanning XRD and scanning XRF are could reveal unprecedent information within tissue samples. From a. we could find that XRD pattern from different region of tissues shows different patterns. (top-left, 1D intensity profiles shown weak 4.7 Å and 5.2 Å structural pattern; bottom-left shown 1D intensity containing signficant 5.2 Åpattern; center is the integral intensity map of 4.7 Å pattern; top-right is 1D intensity profile containing both 4.7 Å and 5.2 Å structural pattern; bottom-right is 1D intensity profile from tissue region with plaques and tangles.) b. the distribution of the XRD patterns shows clearly morphological distribution. (Left is the opitical microscope image shows the tissue and roi for µXRD; top-right is the map of 5.2 Å pattern, center-right is the map of 4.7 Å pattern; bottom-right is the map of 4.12 Å pattern.) c. correlating XRF and XRD, the element distributions, such Zn, Ca and P, are well correlated to the morphological features in the map of 5.2 Å patterns (90 rotated red box in the map of 5.2 Å patterns).