SYNAPTIC MODIFICATION IN SUBJECTIVE COGNITIVE DECLINE

Project presentation - 21 /10/2020

GIGA CRC - Aging & Memory
Prof. E. Salmon

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PLAN

1. Scientific context
2. Questions, hypothesis, and experimental design
3. Data acquisition & subjects
4. Data processing & inference
5. Expected results and interpretation
6. Project management
7. Project administration

PLAN

1. Scientific context
    1. Alzheimer’s pathology
    2. Subjective cognitive decline
    3. “SCD plus”
    4. SV2A
    5. [18F]UCB - H
2. Questions, hypothesis, and experimental design
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1. Scientific context : Alzheimer pathology

- **Pathological hallmarks :** beta-amyloid + hyperphosphorylated tau protein + synapses loss
- Complex relationship and progressive pre-clinical temporal evolution
- Study of the earliest stages of the pathology
- Synaptic brain dysfunction : early marker ?
- Synaptic decrease in the inferior temporal cortex in MCI

1. Scientific context : Subjective cognitive decline (SCD)

- **Individual's self-perception of the worsening of one's cognitive capacities despite normal objective performance level in standard cognitive testing**
- Memory-specific complaints
- Heterogeneous population by definition comprising non-AD pathology
- Identification of sub-population with increased risk of MCI - AD conversion

1. Scientific context : SCD ”plus”

- Age > 60y at onset
- Onset >5y
- Associated worries
- Informant’s assessment
- “Biomarkers” : APOE4, CSF, PET, MRI, …
- **(Para-)hippocampal regions :** GM atrophy, hypometabolism, beta-amyloid / tau deposits

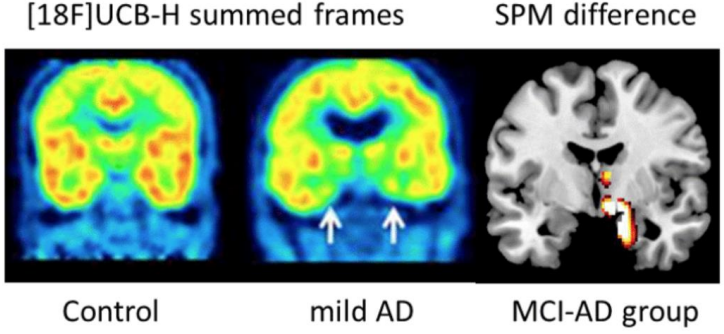
1. Scientific context : Synaptic vesicle protein 2A

- Glycoprotein in the membranes of synaptic vesicles
- Ubiquitous. Biomarker of synaptic density
- Physiological role is unclear
- Therapeutic target of antiepileptic drug (levetiracetam)
- **Reduced in hippocampus** in dementia (post-mortem)

1. Scientific context : [18F]UCB-H

- Specific biding to SV2A sites in rodents
- Acceptable dosimetry for human studies
- Consistent human brain distribution

- **Moderate AD :** decreased in MTL, precuneus and lateral associative cortices
- **MCI – AD :** decreased in medial and inferior temporal cortex



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2. **Questions, hypothesis, and experimental design**
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2.1. : Primary objectives

- **To quantify SCD** (measured with Ecog) and awareness about SCD (with questionnaires to participants and relatives) and their relationships with **biomarkers for preclinical AD**

- To study **MR imaging biomarkers** of cognitive fitness related to preclinical AD stages **(synaptic loss and amyloid brain deposition).**

- To explore the **relationship between** short-term (18 months) **cognitive evolution** and AD-MCI conversion **and neuroimaging markers**

2.2. : Hypotheses

- **Hypothesis 1a :** SCD severity and worries (as dependant variable) will be better explained by loss of hippocampal synaptic density (SV2A-PET) than brain amyloid deposit (FLUT-PET).
  - **Hypothesis 1b :** SCD severity and worries will also be related to anxiety, age, sex, education and ApoE as covariates

- **Hypothesis 2 :** Hippocampal synaptic density (SV2A-PET) will be related to transentorhinal cortex atrophy (MRI), cortical amyloid deposit (FLUT-PET) and to data from MPM of the basal forebrain

- **Hypothesis 3 :** Awareness for SCD (and anosognosia) will be related to loss of hippocampal synaptic density (SV2A-PET), with possible higher default mode network connectivity (fMRI).

- **Hypothesis 4 :** 18-month longitudinal evolution of memory performance, SCD severity and awareness of memory functioning will be best related to decrease in hippocampal and posterior cingulate synaptic density.

2.3. : Experimental design (1/2)

- **18 month longitudinal observational multimodal study**
- Cohort of “normal” individual aged 50 – 70
- Evaluation of risk factors of AD :
  - Neuropsychological evaluation
  - Affective status
  - Amyloid – PET (Flutemetamol)
  - SV2A-PET (UCB-H)
  - Quantitative structure MRI
  - ApoE polymorphism
- **T1 =** Month 1 (Visit 1 + Visit 2)
- **T2 =** Month 18 (Visit 1 + Visit 2)

2.3. : Experimental design (2/2)

- **Visit 1 (2h30) :**
  - General and medical evaluation (1h)
  - Amyloid-PET (45min)
  - MRI (45min)
- **Visit 2 (3h) :**
  - Neuropsychological testing (1h15)
  - SV2A – PET (1h50)
  - Saliva for ApoE (5min)

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3. Data acquisition & subjects

- N SCD = 60 + N Control group = 20

- **Inclusion criteria =** General SCD definition ; Age 50 - 90
  - Subjective experience of cognitive difficulties (memory +/- other domains)
  - Neuropsychological measures within normal range
  - Complaints > 6 month

- **Exclusion criteria**
  - Major psychiatric disorder
  - Comorbidities affecting cognition (cancer, stroke, …)
  - Chronic alcohol consumption
  - Medications affecting cognitive (including long-acting bzd)
  - Objective deficit in any neuropsychological or functional evaluation (CDR, Lawton, MMSE, …)
  - Exclusion criteria for MRI

3. Data acquisition : Clinical evaluation

- **Wednesday or Thursday**
- **Team :** 1 MD + 1 neuropsychologist
- **Medical questionnaire and examination**

Participant	Informant
Beck depression inventory STAI Modified Hachinski ischaemic scale ECog (every day cognition) Clinical dementia rating	CDR Lawton ECog Neuropsychiatric Interview

3. Data acquisition : Amyloid -PET

- **Wednesday or Thursday**
- **Team :** 1 MD + 1 Nurse
- Flutemetamol = Vizamyl®. Synthesized on site by Nucleis S.A. and the radiopharmacist will confirm vial adequation for human use.
- Single dose in an antecubital vein (target dose app. 185 MBq)
- In the GIGA CRC medical unit under the supervision of the principal investigator (ES), who will monitor adverse events.
- Classical acquisition method on an ECAT EXACT+ HR scanner (Siemens, Erlangen, Germany)
- Image acquisitions will start 85 minutes after injection, and 4 frames of 5 minutes will be obtained.
- Images will be reconstructed using filtered back-projection algorithm including corrections for measured attenuation, dead time, random events, and scatter using standard software (Siemens ECAT - HR+ V7.1, Siemens/CTI, Knoxville, TN, USA)

3. Data acquisition : MRI

- **Wednesday or Thursday**
- **Team :** 1 qualified + 1 “witness”
- 3T MRI at the CRC
- Multiparameter mapping (MPM) with longitudinal relaxation rate (R1), effective transverse relaxation rate (R2*), percent saturation because of magnetization transfer (MT), effective proton density (PD)
- Classical resting state functional MRI (360 volumes)
- Hippocampal sequence

3. Data acquisition : Neuropsychological testing

- **Tuesday**
- **Team :** 1 Neuropsychologist

- Modified PACC5 (computed sum z-scores):
  - Free and Total Recall in the Free and Cued Selective Reminding Test (FCSRT)
  - Delayed Recall in the Logical Memory Test (+ 7d)
  - Delayed Recall in CVLT (+ 7d)
  - Digit Symbol Substitution Test
  - Verbal Fluency Test for animal category
  - Mattis Dementia Rating Scale
- Memory for entities
- Stroop
- TMT

3. Data acquisition : SV2A-PET (1/2)

- **Tuesday PM**
- **Team :** 1 MD + 1 Nurse
- In the GIGA CRC medical unit under the supervision of the principal investigator (ES), who will monitor adverse events.
- UCB-H®. Synthesized on site by Nucleis S.A. and the radiopharmacist will confirm vial adequation for human use.
- 20 seconds bolus into an accessible vein
- Mean injection will be 150 MBq. The effective total body dose is about 1.70E-02 mSv/MB
- 100 mins brain PET image acquisition plus 10 mins transmission
- Activity in the carotid artery as input function

3. Data acquisition : SV2A-PET (2/2)

- **For 10 participations :** Arterial blood input function
- Arterial cannula inserted (and removed) by a registered anesthetist
- Arterial blood samples collected (1ml/sample ; max 15ml) during acquisition
- Determination of whole blood activity, plasma free fraction and level of [18F]UCB-H metabolites

3. Data acquisition : Saliva sample

- **Tuesday PM**
- **Team :** 1 investigator
- Saliva collection for ApoE testing

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4. Data processing

- PET average image will be created using all frames
- Averaged PET images will be manually reoriented and automatically co-registered to the structural magnetisation transfer map in individual space
- Co-registered PET image will be spatially normalized
- **FLUT-PET :** SUVR will be calculated using the whole cerebellum as reference region
- **SV2A-PET :** Regional brain activity will be obtained with a Logan method
- SPM12 will be used for multiple regression analyses

4. Data processing

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-019-04461-x

ORIGINAL ARTICLE

Check for updates

In vivo imaging of synaptic loss in Alzheimer's disease with [18F] UCB-H positron emission tomography

Christine Bastin[1] · Mohamed Ali Bahri[1] · François Meyer[1] · Marine Manard[1] · Emma Delhaye[1] · Alain Plenevaux[1] · Guillaume Becker[1] · Alain Seret[1] · Christine Mella[1] · Fabrice Giacomelli[1] · Christian Degueldre[1] · Evelyne Balteau[1] · André Luxen[1] · Eric Salmon[1]

Received: 23 April 2019 / Accepted: 24 July 2019

4. Data processing

- Multiple regression analyses
  - **Continuous variable :** Clinial variables, PET data and anxiety
  - **Covariate :** Age, sex, education, ApoE status

- **Correlation with synaptic density (SV2A PET) :**
  - Severity of SCD
  - Awareness of cognitive decline
  - Neuropsychological assessments

- **Influence of MRI measures** on these correlations

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5. Expected results and interpretation

- Negative correlation between the severity of subjective memory complaints and synaptic activity
- Positive correlation between memory test results (within the range of normality) and synaptic activity in the MTL.
- Possible influence of MRI measures on the previous relationship, looking for mediation of remote connectivity in the default mode network
- Prediction of cognitive (short-term) evolution based of imaging biomarkers

5. Expected results and interpretation

- We expect to bring further characterization and understanding of SCD subjects and to better predict pejorative cognitive evolution.

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6. Project management

In the team who is in charge of

- Subject recruitment and planning : FM
- data acquisition : FM, ES, SL, EL, CH, AL, MB/AP, CB
- raw data storage (→ mass-storage?) and organisation (→ BIDS?)
- scripting and batching for analysis : FM, MB, CP, CB
- results checking and reproducibility **:** SL, CB
- discussion and interpretation : FM, ES, CB
- manuscript writing : FM, ES
- making data open and data sharing **:** to be discussed

FM : François Meyer ; ES : Eric Salmon ; SL : Sophie Laloux ; EL : Erik Lambot ; CH : Catherine Hagelstein ; AL : Alexia Lesoinne ;
MB : Mohammed Bahri ; CP : Christope Phillips; CB: Cristine Bastin; AP: Alain Plenevaux

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7. Project administration : Ethical committee

Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège (707)

LIÈGE université

CHU de Liège

Sart Tilman, le 25/08/2020

Monsieur le **Prof. P. MAQUET**
Monsieur le **Prof. E. SALMON**
Service de **NEUROLOGIE**
CHU B35

Concerne: Votre demande d'avis au Comité d'Ethique
Nr EudraCT ou Nr belge : 2018-002343-29 ; Notre réf: 2020/168

Cher Collègue,

J'ai le plaisir de vous informer que le Comité d'Ethique a donné une réponse favorable à votre demande d'avis intitulée :

"Synaptic modifications in subjective cognitive decline. A study using [18F] UCB-H, a synaptic vesicle 2A radiotracer. "
Protocole : **CRCSV2A18**

Vous trouverez, sous ce pli, le formulaire de réponse reprenant, en français et en anglais, les différents éléments examinés et approuvés et la composition du Comité d'Ethique.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments les meilleurs,

Prof. V. SEUTIN
Président du Comité d'Ethique

7. Project administration : Insurance

ETHIAS ASSURANCE
Rue des Croisiers, 24
4000 Liège
www.ethias.be
Tel : 04/220.31.11
Fax : 04/249.65.30

ethias ASSURANCE

2020-168 – Prof. E. SALMON

ATTESTATION D'ASSURANCE

Ethias SA, rue des Croisiers n° 24 à Liège, certifie que par la police n° **45.118.230** souscrite par le Centre Hospitalier Universitaire de Liège, Domaine universitaire, B.35 à 4000 LIEGE, elle garantit, dans les limites des conditions générales et spéciales du contrat, conformément aux dispositions de la loi du 7 mai 2004 relative aux expérimentations sur la personne humaine telle que modifiée par la loi du 27 décembre 2005 et tous arrêtés royaux d'exécution qui seraient adoptés en application des dispositions précitées, la responsabilité civile qui pourrait incomber au **Prof. E. SALMON** en sa qualité de promoteur, du chef de dommages causés aux participants et/ou à leurs ayants droit dans le cadre de l'étude clinique suivante :

« Synaptic modifications in subjective cognitive decline. A study using [18F] UCB-H, a synaptic vesicle 2A radiotracer. »

Nombre de participants : 100

Etude monocentrique

Durée de l'expérimentation : 4 ans à partir du 1er août 2020

Classe : III

Montants de Garantie :

La garantie est acquise à raison de **2.500.000 €** par sinistre, tous dommages corporels, matériels et immatériels consécutifs confondus. Ce montant constitue également la limite de la garantie pour l'ensemble des dommages déclarés dans le cadre de l'essai précité.

Par ailleurs, la garantie est limitée à **500.000 €** par victime.

Fait en double à Liège
Le 09 juillet 2020

Pour le Comité de direction,

Florian Pirard
Head of Property & Liability
Underwriting Public & Corporate

7. Project administration : Funding source

- GMP production of radioligand from GE Healthcare and Nucleis S.A.
- F.R. - F.N.R.S
- Fondation Léon Fredericq : Crédit Forfaitaire, Prix de l’Espoir

LIÈGE université
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Thank you for your attention!