

# **ESF Exploratory Workshop on The Subiculum in Normal and Pathological Brain Function Oxford, September 21st-23rd 2005.**

## **Executive summary:**

1. Is the subiculum the end of the trisynaptic pathway or the heart of the hippocampal formation? Maybe this title, from Mark Stewart (Brooklyn, NY), gives the most explicit reason to meet and discuss the specificities of the neurobiology of this relatively neglected area of the temporal lobe. The meeting was generously supported by the European Science Foundation and was held in Oxford on the 21-23rd September 2005.

Twenty scientists currently working in eight European countries and the USA participated. Each of them brought a distinct expertise from their different approaches to the anatomy, physiology, psychology and pathologies of the subiculum. The meeting concluded that the subiculum, if not perhaps the heart of the hippocampus, needs at least to be moved closer to the centre of studies on the hippocampal formation.

2. The meeting commenced with a helpful explanation of the diverse funding mechanisms of the ESF from Andrzej Trzebski (Warsaw, Poland). This was followed by a keynote presentation from Fernando Lopes da Silva (Amsterdam, Holland) a senior expert in the field who managed to summarise succinctly the development of past studies on the subiculum and to set the stage for future directions. Presentations over the next two days were organised into thematic sessions with abundant time for group discussions. The themes considered were:

**Circuit architecture:** We began with an anatomical vision of the structure of the subiculum and its implications for function.

**Functional organization of subicular circuits:** This set the stage for data on the microcircuitry of the subiculum and the physiology and plasticity of subicular cells and synapses.

**The subiculum: behaviour and the normal brain:** We considered how the subiculum contributes to cognitive behaviours including spatial memory in a larger context.

**The subiculum and the pathological brain:** The meeting ended with presentations on a specific role of the subiculum in pathologies including Alzheimers disease, schizophrenia and human epilepsies.

3. The meeting ended with a general discussion on the state of the field. We asked how the momentum and identity for subicular research that was built over the course of formal and informal discussions during the meeting could be sustained. Decisions were taken to publish a meeting report in the journal "Hippocampus", to maintain a website developed during the organisation of the meeting and to explore funding mechanisms, possibly from the ESF, to permit a second meeting and to facilitate exchanges between the laboratories of participants.

## Scientific content of the meeting:

### *Context.*

The hippocampus is one of the most-studied regions of the brain and is known to be involved in some memory processes as well as certain epilepsy syndromes. The subiculum has long been considered as a simple input and output region interposed between the hippocampus and the temporal cortex. However recent evidence suggests the subiculum may have vital and specific roles in the cognitive functions and pathological deficits of this region. Our meeting gathered together a group of experts with distinct competences united by an interest in the subiculum. Our goal was to confront anatomical and physiological data on the subiculum, to contrast neuronal processing at the cellular and synaptic level with long-range interactions involving other brain regions and to compare pathological activities with those involved in cognitive functions. Fernando Lopes da Silva (Swammerdam Institute for Life Sciences University of Amsterdam) began the meeting with an overview of previous work on the subiculum, situating research on the subiculum in a wider context of hippocampal studies and pointing to unresolved questions that should be considered.

### *Microstructure and microcircuits of the subiculum.*

The first thematic session of the meeting focussed on the anatomical micro-structure of the subiculum, providing an excellent framework for later sessions on cellular properties and interactions. Nissl staining shows that somata of subicular pyramidal cells are arranged in a loose cloud in contrast to the strict layering of the dentate, CA3 and CA1 regions. Menno Witter (Department of Anatomy, Vrije University, Amsterdam) described the anatomical basis of a pyramidal cell organisation in loosely defined rows and columns. The cloud-like disposition of pyramidal cell somata was further illuminated in beautiful rapid Golgi data from Mark Stewart (Department Physiology, State University of New York at Brooklyn) who examined also the physiological consequences of diverse dendritic alignments.

Electrically, subicular pyramidal cells are diverse. Some of them fire in bursts, rather like CA3 pyramidal cells, and others discharge repetitively as do CA1 pyramidal cells. Liset Menendez de la Prida (Department Neurobiología-Investigación, Hospital Ramón y Cajal, Madrid) examined this diversity and provided new insights into interneurone and pyramidal cell firing in subicular population activities. Nelson Spruston (Dept Neurobiology, Northwestern University, Chicago) emphasised the role of R-type Ca channels in pyramidal cell burst firing.

### *The subiculum and its nearest neighbours: CA1 and the Entorhinal cortex.*

Physically the subiculum is located between the Entorhinal cortex and the CA1 regions and receives synaptic inputs from both regions. Fernando Lopes da Silva and Fabien Kloosterman (Swammerdam Institute for Life Sciences University of Amsterdam) stressed how this

position puts the subiculum at the heart of three nested recurrent synaptic loops involving the entorhinal cortex, or the entorhinal cortex and the CA1 region or the entorhinal cortex, dentate, CA3 and CA1 regions. The subiculum might, participate in reverberating activities on three different time scales, and they presented physiological evidence for such reverberation in the loop involving the entorhinal cortex, CA1 and the subiculum that was supported by data from John Gigg (Faculty of Life Sciences, University of Manchester) on inputs from CA1 in vivo.

#### *Distant connections to and from the subiculum*

The subiculum makes and receives specific long-range connections. Thomas van Groen (Dept. Neuroscience and Neurology, University of Kuopio) focussed on the morphology of connections with different thalamic nuclei as well as the septum and the mammillary bodies. Sarah French and Susan Totterdell (Dept Pharmacology, Oxford University) showed exquisite electron microscopic data on subicular projections to the nucleus accumbens which may function as an interface between limbic and motor systems and on inputs to the subiculum from the basolateral amygdala. Yves Gioanni (INSERM U114, College de France, Paris) followed a physiological approach to reveal a strong projection from the subiculum to both interneurons and pyramidal cells of the prefrontal cortex. This direct pathway, which may be involved in memory consolidation exhibits reversible LTP. Therese Jay (INSERM U117, Hôpital Sainte-Anne, Paris) described how plasticity at subicular prefrontal synapses is down-regulated by dopamine and stress and is restored by anti-depressants acting on mono-aminergic systems.

#### *The subiculum: synaptic and cellular plasticity.*

The long-range connectivity of the subiculum and its looped connections with local structures suggest it may play a critical role in memory functions mediated by the temporal cortex. Data presented at the meeting suggests both synaptic and cellular plasticity of the subiculum are intriguingly different from their counterparts in the CA3 and CA1 regions. Joachim Behr (Forschungszentrum der Charité, Humboldt University Berlin) showed that synapses made by CA1 afferents to burst firing subicular cells express a large pre-synaptically initiated LTP while potentiation at connections with repetitively firing cells is smaller and initiated post-synaptically. Nelson Spruston ((Dept Neurobiology, North-western University, Chicago) focussed on plasticity in cellular discharges, showing that theta pattern stimulation enhances subicular cell burst firing via a mechanism depending on Ca entry via mGluR and L-type Ca channels.

#### *The subiculum: cognitive processes and memory.*

Following these excellent presentations on short and long-range anatomical connections and on the specific physiology of cellular and synaptic function in the subiculum, we devoted a session to its behavioural and especially cognitive functions. The subiculum clearly has a

distinct role in the cognitive mapping functions of the temporal cortex. It includes both cells that respond to head direction as well as place cells that fire at specific sites in an environment. Shane O'Mara (Lloyd Institute, Trinity College Institute of Neuroscience, Dublin) suggested that burst firing subicular cells contribute little to place mapping and that place fields of subicular cells are generally larger than those of CA1 pyramidal cells. Data from Pat Sharp (Dept Psychology, Bowling Green State University, OH) and Colin Lever (Spatial Memory Group, Dept Anatomy, University College London) confirmed the idea of a larger subicular place field and also suggested that the subiculum retains a stable, possibly universal spatial map while place fields of CA1 cells are modifiable as an environment changes.

### *The pathological subiculum.*

Our final session focussed on growing evidence that the subiculum has a role distinct from that of the hippocampus in certain pathologies. Several speakers described their work on the involvement of the subiculum in different psychiatric and neurological diseases. Thomas Van Groen (Dept. Neuroscience and Neurology, University of Kuopio) showed that the plaques and tangles of Alzheimers disease appear in the subiculum early in the progression of this degenerative disease. Richard Greene (MRC Centre for Synaptic Plasticity, Department of Anatomy, Bristol University) demonstrated changes in behaviour and in synaptic function and plasticity in socially isolated animals, arguing that the subiculum may contribute specifically to the emergence of schizophrenic syndromes.

The subiculum may have a particular role in epilepsies of the temporal lobe. Gunter Sperk (Department of Pharmacology, Medizinischen Universität Innsbruck) showed a detailed view of changes in receptor expression in subicular neurones of tissue from epileptic patients. Richard Miles (INSERM U739, CHU Pitié Salpêtrière, Paris) suggested that the subiculum, partially denervated by the loss of CA1 pyramidal cells in the sclerosis often associated with temporal lobe epilepsies, might generate a spontaneous interictal-like activity due to changes in Cl-homeostasis in a minority of pyramidal cells. Javier de Felipe (Instituto Cajal, Madrid) presented data from human epileptic tissue showing reciprocal expression of the Cl- transporter molecules, NKKC1 and KCC2, as well as reductions in the complexity of inhibitory synaptic microcircuits in the subiculum.

## Assessment, future directions & outcome of the meeting:

As we left Oxford, there was a general agreement that the meeting had been a great success. Many of the attendees, even those working with similar approaches, had not previously met. We found that twenty-or-so researchers was a nice sized group which favoured discussions with all of the participants. A group identity did seem to emerge - perhaps because people working on the subiculum could escape together from the shadows of the hippocampus.

The cross-disciplinary nature of the meeting highlighted several questions which will provide material for future work.

- \* Does the diversity of subicular cells, the specificity of local inhibitory and excitatory synaptic connectivity and absence of layering give clues to function?
- \* Do functional modules exist in the subiculum? How does the subicular formation treat simultaneous inputs from CA1 and the entorhinal cortex?
- \* Can we detect activity reverberating in three feedback loops predicted from anatomy?
- \* How do differences in long range connectivity between the subiculum and the CA1 region of the entorhinal cortex illuminate their specific functions?
- \* Can subicular pyramidal cells switch between burst firing and repetitive firing phenotypes?
- \* How do elementary properties of cells and circuits contribute to the construction of place fields with distinct properties in the the subiculum, the CA1 region and the entorhinal cortex?
- \* What further studies on the human subiculum or in animal models are needed to identify specific roles in psychiatric and neurological diseases?

During a final discussion session, we arrived at several decisions on how we could contribute to the future organisation of the field.

1. A meeting report will be written by the organisers, submitted to all the participants and after appropriate scientific review we hope will be published by the journal Hippocampus.
2. The website that we created for the meeting (<http://hobbes.fmc.uam.es/liset/esfprog.htm>) will be maintained, in part by posting parts of the presentations of speakers at the meeting.
3. There was strong support for the organisation of another meeting on the subiculum. A delay of two or three years was felt to be appropriate. Several sites and funding mechanisms were suggested. We agreed to maintain contact via e-mail and the website to start organising the meeting in good time. A meeting in the US might help us widen the group of participants.
4. Most importantly, the impetus from the meeting led us to consider how we might arrange scientific collaborations and exchanges of young researchers between laboratories with an interest in studies on the subiculum. Dr. Trzebski was at this stage especially helpful in directing us towards specific instruments of the European Science Foundation that might help us reach these goals.

## Final programme:

### Wednesday 21 September 2005

- 15.00 – 17.30 Welcome and Registration
- 17.30 – 17.45 Opening Address: **Richard Miles**
- 17.45 – 18.00 **Andrzej Trzebski** (Standing Committee for the European Medical Research Councils)  
Presentation of the European Science Foundation (ESF)
- 18.00 – 18.45 Keynote Lecture: **Fernando Lopes da Silva**

### Thursday 22 September 2005

#### Session 1: Circuit architecture

- 09.00 – 09.30 **Menno Witter** Subicular architecture and cortical connectivity
- 09.30 – 10.00 **Thomas Van Groen** Subcortical connections of the subiculum
- 10.00 - 10.30 **Sarah French** Interactions between hippocampus and amygdala: sites in ventral striatum and ventral subiculum
- 10.30 – 11.00 **Fabian Kloosterman** Organization of (para)hippocampal-subicular networks. The pivotal role of the subiculum

#### Session 2: Functional organization of subicular circuits

- 11.30 – 12.00 **Joachim Behr** Synaptic plasticity at CA1-subiculum synapses
- 12.00 – 12.30 **Theresa Jay** Up and down regulation of subiculo-frontal synaptic plasticity
- 12.30 – 13.00 **Mark Stewart** Subiculum: end of the trisynaptic pathway or "heart" of the hippocampal formation?
- 14.00 – 14.30 **John Gigg** Laminar responses in subiculum to CA1 stimulation in vivo
- 14.30 – 15.00 **Yves Gioanni** Influence of the subiculum on the activity of prefrontal pyramidal cells and interneurons in the rat
- 15.00 – 15.30 **Liset Menendez de la Prida** Functional features of the rat subicular microcircuits

### **Session 3: The subiculum: behaviour and the normal brain**

16.00 - 16.30	<b>Shane O'Mara</b> The subiculum and the normal brain
16.30 – 17.00	<b>Nelson Spruston</b> Activity-dependence and long-term plasticity of action potential bursting in subiculum
17.00 – 17.30	<b>Patricia E. Sharp</b> The subiculum as a cognitive map
17.30 – 18.00	<b>Colin Lever</b> The subiculum and place cells
18.00 – 18.45	General Discussion

### **Friday 23 September 2005**

### **Session 4: The subiculum and the pathological brain**

09.00 – 09.30	<b>Richard Green</b> The electroneuropathology of prion disease in the subiculum
09.30 – 10.00	<b>Richard Miles</b> CI signalling mechanisms and the epileptiform activity of human subiculum
10.00 - 10.30	<b>Guenter Sperk</b> The subiculum in human temporal lobe epilepsy: Histochemical studies
10.30 – 11.00	<b>Javier DeFelipe</b> The subiculum in the sclerotic hippocampus of epileptic patients
11.00 – 11.30	<b>Thomas Van Groen</b> The subiculum in Alzheimer's disease
12.00 – 12.45	General Discussion
12.45 – 13.00	Summary and Thanks

## Final list of participants:

Joachim BEHR

Neurowissenschaftliches Forschungszentrum der Charité

Humboldt Universität Berlin

Schumannstr. 20/21

10117 Berlin

Germany

Tel: +4930-450-539031

Email: joachim.behr@charite.de

Javier DEFELIPE

Instituto Cajal - CSIC

Ave. Dr. Arce, 37

28002 Madrid

Spain

Tel: +3491 585 4735

Email: defelipe@cajal.csic.es

Sarah FRENCH

Dept Pharmacology

Oxford University

Mansfield Road

Oxford OXI 3QT

United Kingdom

Tel: +44 1865 271892

Email: sarah.french@pharmacology.oxford.ac.uk

John GIGG

(Co-Convenor)

Faculty of Life Sciences

Moffat Building Vision Centre

University of Manchester, PO Box 88

Manchester M60 1QD

United Kingdom

Tel: +44 161 200 3876

Email: [j.gigg@man.ac.uk](mailto:j.gigg@man.ac.uk)

Yves GIOANNI

INSERM U114

College de France

11 place Marcelin Berthelot

75231 Paris Cedex 05

France

Tel: +33 1 44 27 12 23

Email: yves.gioanni@college-de-france.fr

J. Richard GREENE

MRC Centre for Synaptic Plasticity

Department of Anatomy

Bristol University, University Walk

Bristol BS8 1TD

United Kingdom

Tel: +44 117 928 8621

Email: J.R.T.Greene@bristol.ac.uk



Theresa JAY  
Hôpital Sainte-Anne  
INSERM U117  
2ter Rue d'Alesia  
75014 Paris  
France

Tel: +33 1 40 78 86 31  
Email: jay@broca.inserm.fr

Fabian KLOOSTERMAN  
Center of NeuroSciences  
Faculty of Science  
Swammerdam Institute for Life Sciences  
University of Amsterdam  
Kruislaan 320  
1098 SM Amsterdam  
Netherlands

Tel: +31 20 525 76 37  
Email: fkloos@mit.edu

Colin LEVER  
Spatial Memory Group  
Dept Anatomy  
University College London  
Gower St  
London WC1E 6BT  
United Kingdom

Tel: +44 20 7679 3388  
Email: ucgacle@ucl.ac.uk

Fernando H. LOPES DA SILVA  
Center of NeuroSciences  
Faculty of Science  
Swammerdam Institute for Life Sciences  
University of Amsterdam  
Kruislaan 320  
1098 SM Amsterdam  
Netherlands

Tel: +31 20 525 76 37  
Email: silva@bio.uva.nl

Liset MENENDEZ DE LA PRIDA  
Hospital Ramón y Cajal  
Fundación para la Investigación Biomédica  
Departamento Neurobiología-Investigación  
Planta 1D  
Ctra Colmenar Km 9  
28034 Madrid  
Spain

(Co-Convenor)  
Tel: +34 913 368 168  
Email: liset.m.prida@hrc.es

Richard MILES  
INSERM U739  
CHU Pitié Salpêtrière  
105 boulevard de l'Hôpital  
75013 Paris  
France

(Convenor)

Tel: +33 140 778 166  
Email: rmiles@chups.jussieu.fr

Shane Michael O'MARA  
Department of Psychology  
Lloyd Institute  
Trinity College Institute of Neuroscience  
Dublin 2  
Ireland

Tel: +353 1 608 1175  
Email: smomara@tcd.ie

Patricia E. SHARP  
Dept Psychology  
Bowling Green State University  
Bowling Green OH 43403  
United States

Tel: +1 419-372-8059  
Email: psharp@bgnet.bgsu.edu

Günther SPERK  
Neuropharmacology Group  
Department of Pharmacology  
Medizinischen Universität Innsbruck  
Peter Mayr Str 1a  
6020 Innsbruck  
Austria

Tel: +43 512 507 3701  
Email: Guenther.Sperk@uibk.ac.at

Nelson SPRUSTON  
Dept Neurobio/Physiology  
Northwestern University  
2205 Tech Dr  
Evanston IL 60208  
United States

Tel: +1 847-467-2734  
Email: spruston@northwestern.edu

Mark STEWART  
Health Science Center  
Department Physiology  
SUNY Box 31  
450 Clarkson Avenue  
Brooklyn NY 11203  
United States

Tel: +1 718-270-1167  
Email: mstewart@downstate.edu

Susan TOTTERDELL  
Department of Pharmacology  
University of Oxford  
Mansfield Road  
Oxford OX1 3QT  
United Kingdom

(Local Organiser)

Tel: +44 186 527 1892

Email: [susan.totterdell@pharmacology.ox.ac.uk](mailto:susan.totterdell@pharmacology.ox.ac.uk)

Andrzej TRZEBSKI  
Polish Academy of Sciences  
Division of Medical Sciences  
Pl. Defilad 1  
00-901 Warsaw  
Poland

(ESF Representative:)

Tel: +48 22 620 33 32

Email: [Wydzial6@pan.pl](mailto:Wydzial6@pan.pl)

Thomas VAN GROEN  
Dept. Neuroscience and Neurology  
University of Kuopio  
P.O.Box 1627  
70211 Kuopio  
Finland

Tel: +358 17 162698

Email: [vangroen@messi.uku.fi](mailto:vangroen@messi.uku.fi)

Menno Peter WITTER  
Department of Anatomy  
Research Institute Neurosciences  
Vrije Universiteit, VU University Medical Center  
Room MF - G102c PO Box 7057  
1007 MB Amsterdam  
Netherlands

Tel: +31 204 448 048

Email: [mp.witter@vumc.nl](mailto:mp.witter@vumc.nl)

## Statistical information on ages and origins of participants:

Gender distribution	F	5
	M	15

Age distribution	31-35	3
	36-40	3
	41-45	5
	46-50	3
	51-55	4
	56-60	1
	60-65	1

Country of current position	Austria	1
	Finland	1
	France	3
	Germany	1
	Holland	3
	Ireland	1
	Spain	2
	UK	5
	US	3