



Figure 1: Ultra-High resolution functional MRI allowing layer-specific investigation of human brain activation (0.8 mm<sup>3</sup>). Superficial layers have been shown to respond more to internally generated cortical feedback. These human fMRI experiments will be linked to brain atlas, layer specific neurophysiology and layer specific computational modelling.



Project Number:	720270	Project Title:	Human Brain Project SGA1
Document Title:	SP3 Systems and Cognitive Neuroscience - Results for SGA1 Period 1		
Document Filename:	SP3 D3.5.1 FINAL		
Deliverable Number:	SGA1 D3.5.1		
Deliverable Type:	Report		
Work Package(s):	WPs 3.1, 3.2, 3.3, 3.4, 3.6		
Dissemination Level:	PU		
Planned Delivery Date:	SGA1 M12 / 31 3 2017		
Actual Delivery Date:	SGA1 M12 / 31 05 2017		
Authors:	Cyriel PENNARTZ, UvA (P98), Lars MUCKLI (P87), Pier Stanislao PAOLUCCI (P92), Johan STORM (P81)		
Compiling Editors:	Ingar SEEMANN, UvA (P98)		
Contributors:	<p>Nikolaus KRIEGESKORTE, MRC (P88)</p> <p>Christiaan LEVEL, KNAW (P91)</p> <p>Brigitte Röder, UHAM (P89)</p> <p>Matthew LARKUM, UBER (P90)</p> <p>Maurizio MATTIA, ISS (P96)</p> <p>Marcello MASSIMINI, UMIL (P94)</p> <p>Pau GOROSTIZA, IBEC (P95)</p> <p>Maria V. SANCHEZ-VIVES, IDIBAPS (P93)</p> <p>Emrah Duzel, DZNE (P99)</p> <p>Francesca CACUCCI, UCL (82)</p> <p>Tony PRESCOTT, USFD (P100)</p> <p>Martin PEARSON, UWE (P101)</p> <p>Steven Laureys, ULG (P97)</p>		
SciTechCoord Review:	<p>EPFL (P1): Jeff MULLER, Martin TELEFONT, Marie-Elisabeth COLIN</p> <p>UHEI (P47): Martina SCHMALHOLZ, Sabine SCHNEIDER</p>		
Editorial Review:	EPFL (P1): Guy WILLIS, Colin McKINNON		
Abstract:	<p>After a delayed onset, SP3 has been successfully setting up experimental and modelling research at the individual labs. This initial work includes data analyses, building setups and experimental design. Moreover, SP3 members have been very actively engaged in seeking and setting up collaborations with virtually all other SPs, also working via several CDPs (mainly CDP4 and CDP5). SP3 management was heavily involved in dissemination and outreach activities, as well as to support</p>		



the coordinator, Cyriel PENNARTZ, with the internal communication and physical WP- and SP-based meetings, and his contribution to main HBP organisational and planning activities (SIB meetings, DPIT-work, etc.). First manuscripts were submitted and published, including several papers in top journals, with more manuscripts in preparation.

Keywords:

Object recognition, learning, slow-wave activity, episodic memory, consciousness, multi-scale approaches



## Table of Contents <Title>

<b>1. SP Leader's Overview</b> .....	<b>7</b>
1.1 Key Personnel.....	7
1.2 Introduction.....	7
1.3 WP3.1 (incl. CDP support).....	7
1.4 WP3.2. (incl. CDP support).....	7
1.5 WP3.3. (incl. CDP support).....	7
1.6 WP3.4 (incl. CDP support).....	8
1.7 Deviations.....	8
1.8 Impact of work done to date.....	8
1.9 Priorities for the remainder of the phase.....	9
<b>2. WP3.1 Context-Sensitive Multisensory Object Recognition</b> .....	<b>10</b>
2.1 Key Personnel.....	10
2.2 WP Leader's Overview.....	10
2.3 Priorities for the remainder of the phase.....	10
2.4 Milestones.....	11
2.5 T3.1.1 Deep Learning Network Constrained by Human Brain Imaging.....	13
2.6 T3.1.2 Identifying Mouse (and Monkey) Cortical Regions Involved in Invariant Object Recognition Learning.....	15
2.7 T3.1.3 Visual Deprivation and Recovery- Studies with Cataract-Reversal Individuals.....	18
2.8 T3.1.4 Animal Model for Context-Sensitive Amplification - Dendritic Mechanisms of Feedback Interactions.....	19
2.9 T3.1.5 Context Varying Amplification of Expectation and Task Specification.....	21
<b>3. WP3.2 Wave Scaling Experiments and Simulations</b> .....	<b>23</b>
3.1 Key personnel.....	23
3.2 WP Leader's Overview.....	23
3.3 Priorities for the remainder of the phase.....	23
3.4 Milestones.....	25
3.5 T3.2.1 Slow-Wave Activity Changes Under Sleep/Anaesthesia-Wake Transition.....	26
3.6 T3.2.2 Slow-Waves and Complexity: from the Microscale to the Bedside.....	28
3.7 T3.2.3 Slow-Wave Activity in Murine Transgenic Models of Neurological Disease.....	32
3.8 T3.2.4 Modulation of Slow-Wave Activity with Optopharmacology.....	34
3.9 T3.2.5 Slow-Wave Simulation Platforms.....	36
<b>4. WP3.3 Episodic Memory as Multisensory Reconstruction</b> .....	<b>42</b>
4.1 Key Personnel.....	42
4.2 WP Leader's Overview.....	42
4.3 Impact of work done.....	42
4.4 Priorities for the remainder of the phase.....	42
4.5 Milestones.....	44
4.6 T3.3.1 Human Brain Imaging of Multisensory Episodic Memory.....	45
4.7 Task 3.3.2: Rodent Physiology: Pattern Completion in Episodic Memory.....	46
4.8 T3.3.3 Rodent Physiology and Optogenetics: Multisensory Integration in Episodic Memory.....	47
4.9 T3.3.4. Computational Modelling of Multisensory Episodic Memory.....	48
4.10 T3.3.5 Robotic Systems: Hardware Implementation of Multisensory Episodic Memory.....	50
<b>5. WP3.4. Experimental and Computational Exploration of Consciousness Mechanisms and Methods in Mice and Humans</b> .....	<b>53</b>
5.1 Key Personnel.....	53
5.2 WP Leader's Overview.....	53
5.3 Impact of work done.....	54
5.4 Priorities for the remainder of the phase.....	54
5.5 Milestones.....	55
5.6 T3.4.1 Mouse Experiments: Test PCI, ERP methods.....	56



5.7	T3.4.2 Multilevel Computational Modelling .....	58
5.8	T3.4.3 Loss and Recovery of Consciousness Pathophysiological Insights .....	60
5.9	T3.4.4 Develop and Compare Methods for Assessing Consciousness (Anaesthesia, Sleep, DOC) 63	
5.10	T3.4.5 Test Consciousness Theories in Wada Test .....	66
<b>6.</b>	<b>WP3.5 Scientific Coordination, Project Management and Communication .....</b>	<b>68</b>
6.1	Key Personnel .....	68
6.2	WP Leader's Overview .....	68
6.3	Impact of work done .....	68
6.4	Priorities for the remainder of the phase .....	69
6.5	Milestones .....	70
6.6	T3.5.1 Subproject Coordination and Management, Communication, Ethics and Innovation (Resource Allocation and Use, Quality Control, Performance and Risk Management, Internal Review and Reporting) .....	71
6.7	T3.5.2 - Management, Communication, Innovation, Preparation of Grants and Report Documents .....	71
6.8	T3.5.3 - Communication and Innovation .....	72
<b>7.</b>	<b>WP3.6 SP3 Contributions to Co-Design Projects and Infrastructure .....</b>	<b>74</b>
7.1	Key Personnel .....	74
7.2	WP Leader's Overview .....	74
7.3	Impact of work done .....	74
7.4	Priorities for the remainder of the phase .....	74
7.5	Milestones .....	76
7.6	T3.6.1 Large-scale Network Modelling of Multiscale, Multispecies Data to Model Prediction Error .....	77
7.7	T3.6.2 SP3 Contributions to the Development of the Infrastructure and CDPs of HBP: WaveScales .....	78
7.8	T3.6.3 SP3 Contributions to the Development of the Infrastructure and CDPs of HBP: SP3- CDP&I Episense .....	80
7.9	T3.6.4 - SP3 Contributions to the Development of the Infrastructure and CDPs of HBP: SP3- CDP&I ConsciousBrain .....	81
<b>8.</b>	<b>Publications .....</b>	<b>84</b>
<b>9.</b>	<b>Dissemination .....</b>	<b>90</b>
9.1	Participation in dissemination and outreach events: .....	90
9.2	Organisation of dissemination and outreach events: .....	90
<b>10.</b>	<b>Education .....</b>	<b>91</b>
<b>11.</b>	<b>Ethics .....</b>	<b>91</b>

## List of Figures

Figure 1: Ultra-High resolution functional MRI allowing layer-specific investigation of human brain activation (0.8 mm <sup>3</sup> ). Superficial layers have been shown to respond more to internally generated cortical feedback. These human fMRI experiments will be linked to brain atlas, layer specific neurophysiology and layer specific computational modelling. .....	1
---	---

## List of Tables

Table 1: Milestones for WP3.1. - Context-Sensitive Multisensory Object .....	11
Table 2: Milestones for WP3.2. - Wave Scaling Experiments and Simulations .....	25
Table 3: Milestones for WP3.3. - Episodic memory as multisensory reconstruction .....	44



---

Table 4: Milestones for WP3.4. - Experimental and Computational Exploration of Consciousness Mechanisms and Methods in Mice and Humans .....	55
Table 5: Milestones for WP3.5. - Scientific Coordination, Project Management and Communication .....	70
Table 6: Milestones for WP3.6. - SP3 Contributions to the Development of the Infrastructure and CDPs of HBP .....	76
Table 7: List of publications .....	84



## 1. SP Leader's Overview

### 1.1 Key Personnel

Subproject Leader: Cyriel PENNARTZ (UvA)

Subproject Deputy Leader: Johan STORM (UiO)

Subproject Manager: Ingar SEEMANN (UvA)

### 1.2 Introduction

Despite the delayed onset of the actual funding for the SGA1 phase, SP3 has been able to make an excellent start following the approval of four proposals in the Open Call and review phase to found a new Systems and Cognitive Neuroscience Subproject in the Human Brain Project (HBP). In addition to setting up experimental and theoretical research at the individual labs, SP3 members have been very actively engaged in seeking and setting up collaborations with virtually all other SPs, also working via several CDPs (mainly CDP4 and CDP5). SP3 has set up a structure for internal meeting and communication (e.g. monthly videoconferences), has organised and held many physical WP- and SP-based meetings, and contributed to main HBP organisational and planning activities (e.g. SIB Board meetings, Data Planning and Implementation Team (DPIT)-mediated reform of SP5, etc.). Most of these activities took place since September 2016 (when actual funding came through), and for the SGA1 year we aim to make the established collaborative ties productive for scientific work and further development of the HBP research infrastructure.

### 1.3 WP3.1 (incl. CDP support)

WP3.1 is conducting planned experiments to investigate context-dependent feedback in the cortex. The team has produced five publications including one in *Science* (Takahashi, et al. 2016). It is linking experiments across mice, humans and modelling. It developed experimental setups investigating somatosensory cortical responses arising from visual stimulation. These experiments will be conducted in mice (Larkum lab) and humans (Muckli lab, high-resolution fMRI). Further experiments record non-stimulated visual cortex receiving contextual information via feedback from other visual areas, to be conducted in mice (Levelt lab) and humans (Muckli lab). These data, and data from visually deprived human patients (Röder lab), will be compared to context-sensitive computational models of vision developed by the Kriegeskorte and Wibrals labs.

### 1.4 WP3.2. (incl. CDP support)

In SGA1, Work Package 3.2 focused on the following activities: (A) acquisition on human subjects of intracortical LFP and scalp high-density EEG evoked by intracerebral SPES, during wakefulness and sleep, and on TMS/scalp-EEG on healthy (awake and sleeping) and vegetative subjects; (B) preliminary analysis of local and global complexity and cortical bistability; (C) acquisition in anaesthetised mice of spontaneous and evoked slow waves using multi-electrode ECoG; (D) development of a common analysis pipeline for experimental and simulated waves in progress; (E) development of slow-wave simulations on high-resolution models of cortical areas including millions of neurons and billions of synapses progressing in strict cooperation with the NEST team; (F) design of several photoswitching molecules, which are now under chemical testing, before proceeding to tests on slices.

### 1.5 WP3.3. (incl. CDP support)

In collaboration with several other SPs (mainly SP4, SP5, SP9, SP10, SP12) Work Package 3.3 made much progress in the examination of neural systems mechanisms of multisensory



episodic memory, as well as in modelling and robotic implementations of such systems. In humans, high-resolution fMRI data were acquired, elucidating subregional BOLD correlates of pattern separation and pattern completion in the hippocampal-medial temporal lobe system. In rodents, we studied hippocampal place cell and entorhinal grid cell behaviour during 2-dimensional navigation in virtual reality, informing models of pattern completion and separation. We set up new behavioural tasks for visual-tactile objection recognition and multisensory integration, to be followed up next by multi-area ensemble recordings. The previously developed hardware robotic platform (Shrewbot) was extended to combine visual and whisking inputs (new Whiskeye robot) and this work was complemented by computational modelling of episodic memory using latent variable spaces, and of predictive coding in the sensory cortical-hippocampal hierarchy. The latter system was tested by embedding with control systems for the iCub robot. Real-time operation was shown for two forms of synthetic episodic memory retrieval.

## 1.6 WP3.4 (incl. CDP support)

The WP3.4 team made progress toward the WP3.4 objectives: (1) testing and improving methods for assessing consciousness; and (2) contributing to testing relevant theories of consciousness, in humans, rodents, and models. Thus, we established methods and obtained data (four papers published, some submitted), including calibration and validation of a measure of brain complexity (PCI) on a large benchmark population, using EEG and magnetic brain stimulation (TMS/ES), and investigated function-structure interaction in healthy subjects using TMS-EEG and diffusion magnetic resonance imaging tractography. We also successfully transferred the Hill-Tononi thalamocortical model for wake-sleep simulations into NEST, the Neural Simulation Tool used within HBP's High Performance Analytics and Computing (HPAC) Platform, thus providing a basis for HBP collaborations and future simulations of states of consciousness.

## 1.7 Deviations

The delayed onset of the actual funding for the SGA1 phase led to a late start of many of the Tasks and Components in SP3, which was felt throughout the Subproject. In many instances, no 'bridging' funds were available because the SP3 members in the SGA1 phase had not been part of HBP before. In general, corrective actions were actions to anticipate on the consequences of the delay and to minimise the delays in research work (e.g. in some cases, SP3 members were allowed by their institutions to start recruitments in view of upcoming funding). No changes were made to the DoA workplan because SP3's prevalent attitude was and is to try to compensate for the delays incurred, aiming to achieve as many of the original goals at the end of SGA1 as possible. Hence, we can hopefully minimise the consequences of the deviations.

## 1.8 Impact of work done to date

Although the work done to date was performed across a relatively short period, it is already beginning to have a considerable impact in several areas: (i) publications in both specialised and more general, high-ranked journals; (ii) posters and talks at international conferences, workshops, Open Days, and other outreach events, together with (iii) significant leadership and visibility in organising these events. Many of these events were open to non-HBP scientists. Both within the HBP and outside, research by SP3 members is gaining increasing recognition, and members are being contacted more often in relation to collaborations in the analyses of datasets, modelling, simulations etc. Within the HBP, the impact of SP3's work can be summarised by the large set of interactions and collaborations which have already been initiated and are ongoing, or are planned to be started soon, e.g. (i) joint modelling work with SP4 groups; (ii) setup and use of first data pipelines with SP5; (iii) ongoing NEST simulations in various projects with SP6; (iv) use of high-performance computing and collaboration to expand data analytics toolkits with SP7; (v) incorporation of



cognitive tasks, neuroscience principles in neuromorphic devices and models, with SP9; (vi) integration of SP3 robotics work with the Neurorobotics Platform, in particular virtual rodent musculoskeletal models; (vii) collaborations and data exchange with non-platform SPs, viz. SP1, SP2 and SP12.

## 1.9 Priorities for the remainder of the phase

One of our general top priorities is to make up for the time lost during the initial (non-funded) phase of SGA1. Because the new SP3 was set up via an Open Call and four winning proposals, we will also prioritise increased collaboration between these four new groups, which is feasible because of many technical and conceptual commonalities. One mechanism to reinforce collaborations further - also with other SPs, e.g. SP10 - is to prepare to integrate models produced in SP3 into a more comprehensive cognitive architecture, which will be used (in SGA2 and later) to control robot ("Mammalbot") behaviour in a more versatile, flexible, biologically plausible and smart manner. Similar integrative efforts are going on in the study of Brain states (sleep/wake cycle, conscious/unconscious states). We will furthermore prioritise work part of, or contributing to, CDPs and thereby strengthen interactions with Platform SPs and related work in Neuroscience and Theory. Finally, work to get Neuroscience data curated and processed via the Neuroinformatics Platform (SP5) will receive high priority, because this will create a gateway for more and deeper collaborations with other SPs (including SP7, SP8, SP9, SP10).



## 2. WP3.1 Context-Sensitive Multisensory Object Recognition

### 2.1 Key Personnel

Work Package Leader: Lars MUCKLI (University of Glasgow, UGLA)

Task Leader (T3.1.1): Nikolaus KRIEGESKORTE (Medical Research Council, MRC)

Task Leader (T3.1.2): Christiaan LEVELT (University of Amsterdam, UVA)

Task Leader (T3.1.3): Brigitte ROEDER (University of Hamburg, UHAM)

Task Leader (T3.1.4): Matthew LARKUM (Humboldt University, UBER)

Task Leader (T3.1.5): Lars MUCKLI (University of Glasgow, UGLA)

### 2.2 WP Leader's Overview

WP3.1 is currently running planned experiments in all Tasks and will begin reporting results from many experiments in the M13-M18 period of SGA1. Additionally, WP3.1 has produced 15 publications (from Tasks T3.1.2, T3.1.3, and T3.1.5, see *Publications* section of this report) during the M1-M12 period including one *Science* paper (Takahashi, et al. 2016). Recruitment for postdoctoral and PhD positions has been finalised across the Work Package. WP3.1 members have attended HBP meetings and workshops throughout the M1-M12 period to develop and enhance strong collaborations within SP3 and have developed connections with SPs 1-10. These meetings have encouraged and solidified many new connections for planning the SGA2 project phase.

WP3.1 contributes to CDP4 and CDP5 via T3.6.1, contributing multi-species functional data and models to implementations of visuomotor integration and large-scale simulations.

### 2.3 Priorities for the remainder of the phase

We have begun recording experiments planned for the SGA1 phase. Since experiments span mouse, human and modelling work, we are working to unite these experimental paradigms within WP3.1. We have developed experiments to investigate changes in somatosensory cortical responses arising from visual stimulation (from feedback connections between visual and somatosensory cortex). These experiments will be conducted in mice by the LARKUM lab (single unit, multiunit activity, local field potentials and calcium imaging of layer 5 cortical pyramidal neurons) and in humans by the MUCKLI lab (high-resolution ultra high-field functional MRI). Further experiments will span mouse and human recordings in non-stimulated visual cortex receiving contextual information via feedback from other visual areas. These experiments will be conducted in mice by the LEVELT lab (multiunit activity and calcium imaging of layer 5 cortical pyramidal neurons) and again in humans by the MUCKLI lab. These data, as well as data from visually deprived human patients from the RÖDER lab, will be compared to and used to improve context-sensitive computational models of vision developed by the KRIEGESKORTE and WIBRAL labs using Representational Similarity Analysis and information theoretic analyses.

In addition to currently planned and running experiments, we are developing experiments that expand on our SGA1 themes by incorporating temporal predictions for the SGA2 phase. Temporal predictions contextualise cortical processing, and it is a central challenge to understand this temporal contextualisation in a closed loop approach - i.e. from sensory processing to motor response, with changing sensory inputs. The closed loop challenge is essential for designing and informing robotic research. We will continue to develop experiments and collaborations within SP3 and with other Subprojects during the second half of this phase.



## 2.4 Milestones

Table 1: Milestones for WP3.1. - Context-Sensitive Multisensory Object

MS No.	Milestone Name	Leader	Task(s) involved	Expected Month	Achieved Month	Comments
MS3.1.1	Finalisation of Project implementation proposal for WP3.1	UGLA	T3.1.1 T3.1.2 T3.1.3 T3.1.4 T3.1.5	M01	M01	The milestone "Finalisation of Project implementation proposal" has been discussed and concordantly agreed on during a SP3 VC on 4 May 2016.
MS3.1.2	Construction of recording setups, initial experiments, data analysis tools, models	UGLA	T3.1.1 T3.1.2 T3.1.3 T3.1.4 T3.1.5	M12	M12	We have begun recording experiments planned for the SGA1 phase. Since experiments span mouse, human and modelling work, we are working to unite these experimental paradigms within WP3.1. We have developed experiments to investigate changes in somatosensory cortical responses arising from visual stimulation (from feedback connections between visual and somatosensory cortex). These experiments will be conducted in mice by the Larkum lab (single unit, multiunit activity, local field potentials and calcium imaging of layer 5 cortical pyramidal neurons) and in humans by the Muckli lab (high-resolution ultra high-field functional MRI). Further experiments will span mouse and human recordings in non-stimulated visual cortex receiving contextual information via feedback from other visual areas. These experiments will be conducted in mice by the Levelt lab (multiunit activity and calcium imaging of layer 5 cortical pyramidal neurons) and again in humans by the Muckli lab. These data, as well as data from visually deprived human patients from the Röder lab, will be compared to and used to improve context-sensitive computational models of vision developed by the Kriegeskorte and Wibrall labs using Representational Similarity Analysis and information theoretic analyses.
MS3.1.3	Validation of protocols, performance of experiments, computational	UGLA		M24		Not yet achieved



---

	model testing, data analysis.					
--	-------------------------------	--	--	--	--	--



## 2.5 T3.1.1 Deep Learning Network Constrained by Human Brain Imaging

### 2.5.1 Key Personnel

Task Leader: Nikolaus KRIEGESKORTE (Medical Research Council, MRC)

### 2.5.2 SGA1 DoA Goals

- 1) Create a deep learning network: The KRIEGESKORTE lab has implemented an infrastructure for deep learning using graphics processing units (GPU). This infrastructure will be expanded and replicated to enable us to explore a wide range of neuroscientifically motivated deep neural network models.
- 2) Perform comparison using representational similarity analysis (RSA): Based on the initial success of using a deep neural network to explain inferior temporal representations in humans and monkeys, we will build a framework for using RSA to test the entire range of models and evaluate to what extent each layer of a model can explain the representational geometry in each cortical area.
- 3) Information theoretical analysis of human and animal data: We will quantify the Task dependence of local active information storage and local information transfer and modification using TRENTOOL and the Java Information dynamics toolkit on animal and human data and data from biologically plausible models, comparing the information processing footprints in these systems. Using partial information decomposition, we will investigate, at all of these levels, whether contextual information amplifies shared information between context and bottom up input or is used to fuse both inputs in a synergistic manner that fuses disparate information from both input types.

### 2.5.3 Component Progress

#### 2.5.3.1 Model representational-space RDMs (DoA Goal 2)

Description of Component: Representational dissimilarity matrices (RDMs) characterising representational spaces in computational models, including deep neural network models trained with stochastic gradient descent and, in certain cases, with brain data acquired in previous published studies.

CDP Contributions: The model contributes to the advanced object recognition component of CDP4.

Progress: The KRIEGESKORTE lab has developed a range of deep learning architectures, including recurrent and stochastic architectures, for context-sensitive computations. The lab has also developed and published a method for driving the internal representational spaces in such networks into alignment with brain-representational spaces (McClure & Kriegeskorte, *Frontiers in Computational Neuroscience* 2016). The key model class for this component, recurrent convolutional neural networks, has been implemented. These models incorporate lateral (L) and top-down (T) connections, in addition to the typical feedforward bottom-up (B) connections found in neural networks for visual recognition. The lab has performed a detailed comparison between B, BL, BT and BLT architectures, using established benchmark stimulus sets. These tests have shown performance improvements on difficult recognition tasks (under extreme clutter and partial occlusion). A manuscript (Spoerer & Kriegeskorte) is about to be submitted for publication.

#### Quality Control

##### *Upstream Components:*

- SP2 - Computational architecture of the functional organisation in visual and auditory processing streams in human and macaque monkey



- SP2 - Ultra-high field fMRI of sub-units in higher-level visual areas and face areas in human and monkey
- Connections to areas for object learning
- SP2 - Selective attention in perception and learning in humans and monkeys
- SP2 - Brain atlas of visuo-motor integration
- T3.1.3 - Visual deprivation and recovery- studies with cataract-reversal individuals
- T3.1.5 Layer-specific fMRI to measure feedback
- T3.1.4 Information Theoretic Network Model of Layer 5 Pyramidal Cells
- T3.1.4 Dendritic mechanisms of feedback
- T3.1.1 Human ventral-stream object RDMs (3T or 7T fMRI)

*Downstream Components:*

- Ultra-high field fMRI of sub-units in higher-level visual areas and face areas in human and monkey
- Selective attention in perception and learning in humans and monkeys SP2 - Brain atlas of visuo-motor integration
- SP2 - Computational architecture of the functional organisation in visual and auditory processing streams in human and macaque monkey

### 2.5.3.2 Human ventral-stream object RDMs (3T or 7T fMRI) (DoA Goal 1)

Description of Component: Representational dissimilarity matrices (RDMs) characterising representational spaces in human cortical areas along the ventral visual stream acquired with fMRI at 3T or 7T while subjects view a wide range of natural object images. These datasets serve to test and constrain computational models of the ventral-visual pathway that explain object recognition.

CDP Contributions: None

Progress: The KRIEGESKORTE lab has begun the open-science assembly (which will be made available to the HBP once it is completed) of a rich set of about 1,000 visual stimuli for acquisition of brain-activity data in humans, using 3T and 7T fMRI in humans. The staff for the fMRI acquisition could not be hired yet because of the funding delay and the move of the KRIEGESKORTE lab. Data acquisition will therefore begin in the next period.

### Quality Control

*Upstream Components:*

- SP2 - Ultra-high field fMRI of sub-units in higher-level visual areas and face areas in human and monkey
- SP2 - Selective attention in perception and learning in humans and monkeys SP2 - Brain atlas of visuo-motor integration
- SP2 - Computational architecture of the functional organisation in visual and auditory processing streams in human and macaque monkey

*Downstream Components:*

- Ultra-high field fMRI of sub-units in higher-level visual areas and face areas in human and monkey
- Selective attention in perception and learning in humans and monkeys
- Brain atlas of visuo-motor integration



- SP2 - Computational architecture of the functional organisation in visual and auditory processing streams in human and macaque monkey
- T3.1.1 Model representational-space RDMs

### 2.5.3.3 Information Theoretic Network Model of Layer 5 Pyramidal Cells (DoA Goal 3)

Description of Component: Recurrent multilayer neural network on the NEST platform, with local, information theoretic learning rules and Kay-Phillips types of neurons with two distinct types of synapses - modulatory and driving.

CDP Contributions: CDP4 and CDP5

Progress: The KRIEGESKORTE lab has developed an abstract rate-coding model of context-dependent computations that is expected to scale to real-world tasks such as recognition of natural images. The model is currently being tested on standard benchmark of visual recognition.

The WIBRAL lab has ported its TRENTOOL toolbox to python/OpenCL to align with the HBP infrastructure. The resulting new toolbox (IDTxI) has been released under an open source license on github and will be added to the HBP software catalogue. We have produced a manuscript (submitted and available on bioRxiv, Brodski et al.) showing that task-related changes in active information storage are detectable in human MEG data in task-specific brain areas, and that they are related to internal models.

We plan to analyse the following datasets with the toolbox during the next period:

- 1) Data from layer 5 pyramidal neurons from the LARKUM lab (T3.1.4).
- 2) A large dataset of intracortical recordings from macaque monkeys performing a visual working memory task (from the lab of Charles Gray, U Montana). This dataset provides >150 simultaneously recorded channels covering a whole cortical hemisphere.

These analyses of task dependence of information storage and transfer in this are currently running on the supercomputer LOEWE-CSC in Frankfurt.

### Quality Control

#### *Upstream Components:*

- Single-compartmental models of cortical cells, including non-linear IF models and GLM
- Plasticity: Two-compartment neuron
- Multi compartmental reconstructed cortical cells: their input-output transfer properties
- NEST - The Neural Simulation Tool
- T3.1.4 Dendritic mechanisms of feedback - *Received dataset of L5 neuronal recordings*

#### *Downstream Components:*

- T3.1.1 Model representational-space RDMs

## 2.6 T3.1.2 Identifying Mouse (and Monkey) Cortical Regions Involved in Invariant Object Recognition Learning

### 2.6.1 Key Personnel

Task Leader: Christiaan LEVELT (Netherlands Institute for Neuroscience, KNAW)

### 2.6.2 SGA1 DoA Goals

The aim of this Task is to identify cortical circuits involved in object recognition learning. First, we will identify mouse cortical regions for object recognition learning by wide field



imaging of calcium signals while mice learn to recognise specific objects. Second, we will investigate the neuronal interaction during object learning, by chronically recording activity of excitatory and inhibitory neurons in neuronal ensembles during the same task. Third, we will study responses of inputs from other brain regions to V1 during the task, and modulate their activity to study their role. Finally, we will carry out learning experiments in mice and image changes in synaptic bouton loss and formation in the long-range connections undergoing neuronal plasticity. (This last goal is a replacement of our original goal to study in monkeys how neurons in auditory cortex receive visual input and task-related signals from different cortical sources.)

### **2.6.3 Component Progress**

#### **2.6.3.1 Mouse cortical regions for object recognition learning**

Description of Component: Wide field calcium imaging data of whole cortex measured in awake mice during object learning (ROELFSEMA).

CDP Contributions: None

Progress: We have established all the necessary techniques to perform the planned experiments, including skull clearing for wide field imaging in mice with cortical GCaMP6 expression, behavioural paradigms and the related hardware, and data analysis tools. Experiments are being executed. Furthermore, we are currently implementing new tools to map out the retinotopy and receptive field sizes in multiple visual cortical areas of the mouse.

#### **Quality Control**

*Upstream Components:*

- SP4 - SGA2 - Plasticity: multi-factor rule for deep networks
- Multi-area model of cortical network at neuronal resolution
- Web Atlas viewer

*Downstream Components:*

- Connections to areas for object learning
- important - data - Neuronal interactions during object learning

#### **2.6.3.2 Neuronal interactions during object learning**

Description of Component: Database of chronically recorded calcium responses of identified subsets of inhibitory and excitatory neurons in the visual cortex during object learning (LEVELT).

CDP Contributions: None

Progress: A two-alternative forced choice behavioural paradigm for head-fixed mice, in which mice learn to differentiate between two visual stimuli, has been established which is used in combination with chronic two-photon calcium imaging. We are able to chronically image responses of different neuronal subsets in visual cortex. We are continuously improving our data analysis pipeline. We have implemented and tested existing tools for image registration and segmentation but are also developing novel software tools that will be added to the HBP software catalogue. Actual experiments are currently running.

#### **Quality Control**

*Upstream Components:*

- T3.1.5 Layer-specific fMRI to measure feedback
- T3.1.4 Dendritic mechanisms of feedback



- Mouse cortical regions for object recognition learning
- GABAergic interneuron classifier
- 3D reconstructions of cortical neurons in primary visual and motor cortices from brain slices

*Downstream Components:*

- Connections to areas for object learning
- Parvalbumin interneurons distribution
- SOFTWARE > Data Factory > Workflow tools > Neuroimaging software > Compilation of Matlab Scripts

### 2.6.3.3 Connections to areas for object learning

Description of Component: Calcium imaging data of projections of relevant brain regions during object learning (LEVELT).

CDP Contributions: None

Progress: For these experiments, we make use of the experimental paradigm/setup developed for our Component, 'Neuronal interactions during object learning'. We have set up intrathalamic viral vector injections to express GCaMP6 in dLGN and LP, and can successfully image these inputs to V1. We have also established chronic *in vivo* GRIN lens imaging allow us to perform two photon imaging in thalamic nuclei. Our data analysis tools can be used for bouton imaging data, but we are also developing more powerful tools for this purpose. Experiments using this approach have been initiated.

#### Quality Control

*Upstream Components:*

- Mouse cortical regions for object recognition learning
- Neuronal interactions during object learning
- Neuronal activity profile across the cortical layers during figure-ground perception

*Downstream Components:*

- T3.1.1 Model representational-space RDMs
- added value - software - SOFTWARE > Data Factory > Workflow tools > Neuroimaging software > Compilation of Matlab Scripts

### 2.6.3.4 Synapse turnover in long-range projections

Description of Component: Data of bouton turnover in a pathway undergoing plasticity (ROELFSEMA).

CDP Contributions: None

Progress: The original subtask "Cortical interactions of audiovisual recognition in awake behaving monkeys has been replaced with the task: "Understand task-specific changes in synaptic bouton turnover in long-range connections undergoing neuronal plasticity". In mice carrying out a visual learning task, chronic *in vivo* two-photon imaging will be performed on sparsely labelled long-range connections relaying task-related and visual signals between different cortical areas." SP2-derived data from multi-contact depth probes in monkeys could be used to make important comparisons between the situation in the primate brain and mouse data we obtain in T3.1.2 a-c (a. mouse cortical regions for object recognition learning. b. neuronal interactions during object learning c: connections to areas for object learning). This frees up personnel time, allowing us investigate the anatomical changes of



long-range corticocortical connections underlying learning in visual tasks as described in T3.1.2a-c. This change will strengthen the coherence and impact of the Task.

This project has recently started. We have established basic techniques necessary for this task, including the labelling of long-range connections, chronic imaging of bouton turnover using two-photon microscopy and data analysis methods. The current challenge is to selectively label connections in one direction (e.g. the feedforward direction) without labelling the connections in the opposite direction (e.g. the feedback direction). To that aim we use the CAV virus, which is selectively transported in the retrograde direction. We are currently developing protocols to use optogenetics to induce plasticity in selective axonal projections.

## **2.7 T3.1.3 Visual Deprivation and Recovery- Studies with Cataract-Reversal Individuals**

### **2.7.1 Key Personnel**

Task Leader: Brigitte ROEDER (University of Hamburg, UHAM)

### **2.7.2 SGA1 DoA Goals**

- 1) Category specific representations in cataract-reversal individuals: Acquire data on object representations following a transient period of congenital vs. late lesions. We will use representational similarity analysis to compare cortical representations of cataract reversal individuals to sighted subjects and deep brain models. A variant of this will reveal the difference in feedback-related representational similarity analysis.
- 2) Structural measures (cortical thickness/volume, DTI) will be used to analyse structural constraints. We hypothesise that if visual input is lacking after birth, the setting up of hierarchical object representations does not take place. We assume that this learning is linked to sensitive phases, and limits the recovery of object processing even after restoring vision after congenital blindness. By contrast, individuals who have acquired object representations before blindness may show greater recovery after cataract removal.
- 3) Convolutional learning deep brain models of object recognition will inform which neural systems involved in object recognition develop experience dependence during a sensitive phase. We aim to understand the neural basis of the "sleeper effect"; why the lack of visual input during the first months results in permanent impairments of object perception even though these skills and neural circuits mature late in childhood.

### **2.7.3 Component Progress**

#### **2.7.3.1 Visual deprivation and recovery- studies with cataract-reversal individuals**

Description of Component: Functional and structural MR raw data (40 subjects).

CDP Contributions: None

Progress: hired a postdoc and PhD student (start December and November 2016 respectively), worked out details of the research plan for 1 and 2, submitted project specific ethical proposal. We received ethical approval for our studies both in Germany and in Maastricht; documents were submitted to the ethical office of the HBP.

A Skype meeting was held, during which all involved researchers discussed details of paradigms and stimuli to use for the first studies in cataract-reversal individuals. Stimuli have been identified, and software for presenting them was clarified. A project plan for the first data acquisition phase was agreed on.

In addition, existing structural data sets of visually impaired individuals and normally sighted controls are currently being segmented, each hemisphere taking ~5 hours to be segmented. Currently 30 datasets have been segmented.



## Quality Control

### *Upstream Components:*

- SP2 - Ultra-high field fMRI of sub-units in higher-level visual areas and face areas in human and monkey
- SP2 - Selective attention in perception and learning in humans and monkeys
- Web Atlas viewer

### *Downstream Components:*

- SP2 - Ultra-high field fMRI of sub-units in higher-level visual areas and face areas in human and monkey
- SP2 - Selective attention in perception and learning in humans and monkeys
- T3.1.1 Model representational-space RDMs
- Human visual/ auditory

## **2.8 T3.1.4 Animal Model for Context-Sensitive Amplification - Dendritic Mechanisms of Feedback Interactions**

### **2.8.1 Key Personnel**

Task Leader: Matthew LARKUM (Humboldt University, UBER)

### **2.8.2 SGA1 DoA Goals**

This Task deals with the dendritic mechanisms involved in integrating feedforward / feedback.

- 1) The Larkum lab will determine how feedback interacts with perceptual behaviour using electrical stimulation of neurons or populations of neurons in a primary sensory region while imaging effects of feedback from cortical and subcortical areas on large-scale populations in a cortical column. Using methods developed by Levelt/Roelfsema, we will train animals in object recognition. We will train animals in a go/no-go perceptual task, where animals report perception of single cell or microstimulation in visual and somatosensory cortex by licking. The effect of long range input on the ability to detect intracortical stimulation will be measured with optogenetic stimulation of inputs. The effect of single cell stimulation and microstimulation on cortico-cortical circuit activation will be measured by imaging calcium signals in implanted microprisms with 2-photon imaging throughout a column. The temporal and spatial pattern of local activity and the detectability of activity by the animal will be manipulated via pharmacological and optical stimulation and blockage of feedback to somatosensory cortex.
- 2) We will use information theoretic methods to measure information transfer and storage in spike trains and to identify a cell's computational role.

### **2.8.3 Component Progress**

#### **2.8.3.1 Dendritic mechanisms of feedback (DoA Goal 1)**

Description of Component: The effect of single cell stimulation and microstimulation on cortico-cortical circuit activation will be measured by imaging calcium signals in implanted microprisms with 2-photon imaging throughout a column.

CDP Contributions: CDP 5

Progress: We are currently collaborating with the group of Lars MUCKLI to use their human stimulus set in mice (rather than the stated goal of using the LEVELT/ROELFSEMA approach for training animals in object recognition). Our goal is to develop a mouse model for the human fMRI studies. In human studies, visual stimuli can generate changes in BOLD signal in



somatosensory cortex. The current hypothesis is that these changes in somatosensory cortex arise from feedback connections between visual and somatosensory cortex. But the BOLD signal does not directly measure action potentials, or field potentials, or mechanism, so animal models are necessary. We have established the same visual stimuli that are used in human fMRI studies, and are training mice on a go / no-go task to ensure that animals recognise the presence of the stimuli. We have established passive visual stimulation and discrimination tasks, and will next record single unit, multiunit activity and local field potentials to establish whether visual stimuli delivered passively (while animals perform a whisker task or a microstimulation detection task) generates a local field potential or drives neurons in somatosensory cortex. In addition, we have an ongoing study as part of CDP5 where we use optogenetic stimulation of somatostatin neurons together with microstimulation to establish the role of these neurons in sensory detection. Finally, we will use these two tasks (whisker or microstimulation) and image from layer 5 neurons and dendrites in somatosensory cortex while visual stimuli are delivered.

### Quality Control

#### *Upstream Components:*

- T3.3.3 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1
- SP2 - Selective attention in perception and learning in humans and monkeys
- SP2 - Morphological cortical connectivity profiles of neocortical pyramidal neurons
- SP2 - Maps of different human neuronal circuits
- Maps of neuronal activation of whole mouse brain
- Images of neuronal activation of whole mouse brain
- 3D reconstructions of 300 pyramidal neurons from the mouse somatosensory cortex across layers II-VI
- Immunocytochemical detection of excitatory and inhibitory terminals in the mouse neocortex (somatosensory cortex) by confocal microscopy
- Densities and 3D distributions of synapses using FIB/SEM imaging in the mouse neocortex (somatosensory cortex)
- Workflow for labelling, reconstruction, quantification and indexing of Long-range projection neurons
- Rodent physiology: pattern completion in episodic memory
- Web Atlas viewer

#### *Downstream Components:*

- T3.1.1 Model representational-space RDMs
- T3.1.4 Information Theoretic Network Model of Layer 5 Pyramidal Cells
- Neuronal interactions during object learning
- Non-conscious short-term memory
- SP6-T6.4.3-SGA1-Model representations for cellular and network models
- Detailed models of human cortical neurons



### 2.8.3.2 Information Theoretic Network Model of Layer 5 Pyramidal Cells (DoA Goal 2)

Description of Component: Implement a recurrent multilayer neural network on the NEST platform (CDP4), with local, information theoretic learning rules and Kay-Phillips types of neurons with two distinct types of synapses - modulatory and driving.

CDP Contributions: CDP4, CDP5

Progress: We are continuing to establish the cortical circuits that contribute to the perception of microstimulation, i.e. the activation of a small number of cortical neurons in combination with deep imaging with and without microprisms. We have an ongoing study as part of CDP5, where we use optogenetic stimulation of somatostatin neurons to establish the role of these neurons in a learning and memory task. These datasets will be used by the WIBRAL lab for information theoretic modelling in the remainder of this phase.

#### Quality Control

##### *Upstream Components:*

- Single-compartmental models of cortical cells, including non-linear IF models and GLM
- Plasticity: Two-compartment neuron
- Multi compartmental reconstructed cortical cells: their input-output transfer properties
- NEST - The Neural Simulation Tool
- T3.1.4 Dendritic mechanisms of feedback - *Received dataset of L5 neuronal recordings*

##### *Downstream Components:*

- T3.1.1 Model representational-space RDMs

## 2.9 T3.1.5 Context Varying Amplification of Expectation and Task Specification

### 2.9.1 Key Personnel

Task Leader: Lars MUCKLI (University of Glasgow, UGLA)

### 2.9.2 SGA1 DoA Goals

This Task deals with cortical feedback in context-sensitive object recognition.

- 1) We will use high resolution fMRI to measure cortical feedback to non-stimulated areas of retinotopic visual cortex. Objects and scenes will be presented with one quarter-field occluded. Layer-specific voxel time courses in occluded cortex will be separated into stimulus-related activity (feedback) and stimulus-unrelated background activity, and we will identify which cortical layers feedback terminates in. We will use Representational Similarity Analysis to examine feedback. Cortical responses to movies will be used to align functional data between individuals using a method called Hyperalignment.
- 2) We will examine one of the most striking nonlinearities of image formation; occlusion of one object by another. Recognition of objects likely requires recurrent information flow to infer hidden objects from partial information. We will create controlled occlusion stimuli by superimposing two isolated objects and will investigate representations of both objects in brain data and computational models.

### 2.9.3 Component Progress

#### 2.9.3.1 Layer-specific fMRI to measure feedback (DoA Goals 1 & 2)

Description of Component: We are using high field fMRI to measure feedback to non-feedforward stimulated layers of retinotopic cortex. We are using movies will be used for



hyperalignment (HAXBY) and visual objects (KRIEGESKORTE) will have one quarter-field occluded.

CDP Contributions:

CDP3: Product 4 (Enrichment of the Human Brain Atlas)

Use Case (Encoding models of complex stimuli into local brain activity)

CDP4: Product (Comparative analysis of experimental and simulated data)

Progress: Ethical approval was given for our fMRI experiments (University of Glasgow, Ethics Application No. 300140111). We have recorded large fMRI scene-viewing datasets (3 subjects, ~50 hours total). Data are currently pre-processed and segmented into cortical depth-layers. We have preliminary results for our stimulus encoding models in individual subjects viewing large image sets. These results have been accepted to the 2017 Organization for Human Brain Mapping international conference (to be presented in June). We have begun testing hyperalignment methods to combine high-resolution datasets for model-building. We have recruited two postdoctoral research assistants at the University of Glasgow with start dates in April 2017.

### Quality Control

*Upstream Components:*

- SGA2\_T2.5.7 Attentional modulation of sensory processing in monkey and human
- SGA2\_T2.5.5 feedback interactions in monkey and human
- SP2 - Selective attention in perception and learning in humans and monkeys
- SP2 - Brain atlas of visuo-motor integration
- SP5 - Registration of human whole brain fMRI data

*Downstream Components:*

- T3.1.1 Model representational-space RDMs
- Neuronal interactions during object learning
- SP2 - Selective attention in perception and learning in humans and monkeys
- SP2 - Brain atlas of visuo-motor integration



## 3. WP3.2 Wave Scaling Experiments and Simulations

### 3.1 Key personnel

Work Package Leader: Pier Stanislao PAOLUCCI (Istituto Nazionale di Fisica Nucleare, INFN)

Task Leader (T3.2.1): Maurizio MATTIA (Istituto Superiore di Sanità, ISS)

Task Leader (T3.2.2): Marcello MASSIMINI (Universita Degli Studi Di Milano, UMIL)

Task Leader (T3.2.3): Maria V. SANCHEZ-VIVES (Consorci Institut d'Investigacions Biomediques August Pi i Sunyer, IDIBAPS)

Task Leader (T3.2.4): Pau GOROSTIZA (Fundacio Institut de Bioenginyeria de Catalunya, IBEC)

Task Leader (T3.2.5): Pier Stanislao PAOLUCCI (Istituto Nazionale di Fisica Nucleare, INFN)

### 3.2 WP Leader's Overview

During the first 12 months of SGA1 the five partners of WP3.2, experts in complementary fields (UMIL - human experiments, IDIBAPS - murine experiments, IBEC - photostimulation techniques, ISS - theoretical models, INFN - parallel computing/simulation) established strong cooperation links, both inside the WP, but also with other SP3 partners, thanks to the guidance of the SP3 coordinator, and, outside SP3, with the development team of the platforms of immediate interest for our WP (e.g. NEST, Elephant). On the technical side, a few highlights of WP3.2 during the first 12 months have been:

- The acquisition on human subjects of a) intracortical LFP and scalp hd-EEG evoked by intracerebral SPES, during wakefulness and sleep and, b) TMS/scalp-EEG on healthy (awake and sleeping) and vegetative subjects. A preliminary analysis of local and global complexity and cortical bistability on the same data.
- The acquisition in anaesthetised mice of spontaneous and evoked slow waves using multi-electrode ECoG.
- The start of a joint development (ISS-INFN-IDIBAPS) of a common analysis pipeline for experimental and simulated waves in progress, with an undergoing discussion on the feasibility of porting toward an Elephant based pipeline with the Platform developers in SGA2.
- The refinement of theoretical models of cortical areas expressing slow-waves and asynchronous states and high-resolution simulations of grids of cortical modules including millions of neurons and billions of synapses executed on thousand hardware cores, and the establishment of an effective cooperation with the NEST development team.
- The design of several photoswitching molecules that are now under chemical test, before proceeding to tests of activity on receptors on slices.
- The late signature of the SGA1 contract caused a delay in the hiring of the full team, that completed in October 2016. However, the teams are now operating at full power, and we do not foresee delay in the final SGA1 deliveries.
- The milestone "Finalisation of Project implementation proposal" has been discussed and concordantly agreed on during a SP3 VC on 4 May 2016: the Project Lifecycle Application (PLA) has been updated and captures the descriptions of all components produced by WP3.2 and their dependencies inside and outside SP3.
- T3.6.2 integrates the contribution of WP3.2 into CDP5, posing the ground for an exploration of interaction between sleep and plasticity.

### 3.3 Priorities for the remainder of the phase



The focus will be on a further strengthening of the collaboration, both inside and outside the WP, particularly on the development of the pipeline that aims to a match of the experimental data and simulation results on both human and mouse, posing solid grounds for SGA2 activities.



### 3.4 Milestones

Table 2: Milestones for WP3.2. - Wave Scaling Experiments and Simulations

MS No.	Milestone Name	Leader	Task(s) involved	Expected Month	Achieved Month	Comments
MS3.2.1	Finalisation of Project implementation proposal	INFN	T3.2.1, T3.2.2, T3.3.3, T3.3.4, T3.3.5	M12	M12	The milestone "Finalisation of Project implementation proposal" has been discussed and concordantly agreed on during a SP3 VC on 4 May 2016.
MS3.2.2	First release of Slow Wave Activity models; characterisation hd-EEG scalp responses	INFN	T3.2.1, T3.2.2, T3.3.3, T3.3.5	M18		Not yet achieved
MS3.2.3	Measurements of slow waves (in control and transgenic) and optopharmacologic modulation.	INFN	T3.2.1, T3.2.2, T3.3.3, T3.2.4, T3.3.5	M24		Not yet achieved



## 3.5 T3.2.1 Slow-Wave Activity Changes Under Sleep/Anaesthesia-Wake Transition

### 3.5.1 Key Personnel

Task Leader: Maurizio MATTIA (ISS, Istituto Superiore di Sanità)

### 3.5.2 SGA1 DoA Goals

The goal of this Task is to develop a theoretical description of a cortico-thalamic system matching the multiscale experimental measures of slow-wave activity (SWA) from rodents and humans performed in T3.2.2 and T3.2.3. First, we will develop theory-inspired analyses to characterise SWA at different scales (cortical columns and across the cortical surface) from the data provided by T3.2.2 and T3.2.3. Simplified (point-like spiking) neuron network models will be tuned to match the resulting features. Second, we will test models to reproduce SWA changes measured in experiments during sleep/anaesthesia-wake transition. Third, a density-based clustering of multi-electrode recordings will be implemented to infer effective coupling matrix between probed local networks. Forth, we will develop large-scale versions of the devised models to be simulated in T3.2.5.

### 3.5.3 Component Progress

#### 3.5.3.1 Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity

Definition and simulation of a model of cortical slice fitting activity measured from experiments *in vitro* both under spontaneous regimes and perturbational approaches.

No CDP contribution.

Progress on Component:

The paper "Capone C, Mattia M. 2017. Speed hysteresis and noise shaping of traveling fronts in neural fields: role of local circuitry and nonlocal connectivity. *Scientific Reports* 7:39611" has been published. In this work we theoretically investigated the excitability regimes of the cortical tissue underlying SWA. Results obtained have been instrumental to tune the parameters of the cortical slice model to be released at M18. Analysis tools to characterise SWA from experimental data provided by IDIBAPS (T3.2.2 and T3.2.3) are at an advanced stage of development and have been shared with both IDIBAPS (T3.2.2) and INFN (T3.2.5), and the plan is to make them available to the community during the SGA2 period thanks to the cooperation that has been established with the platform team developing the Elephant/python based pipeline. A scientific paper co-authored by IDIBAPS and ISS in which modelling and analysis results on the characterisation of SWA in cortical slices has been submitted for publication.

#### Quality Control

*Upstream Components:*

- Multi compartmental reconstructed cortical cells: their input-output transfer properties: received nothing (release planned at M24)
- Electrical perturbations on slices during sleep-like pattern before and after drug application
- Perturbation of thalamic nuclei and cortical layer activity

*Downstream Components:*

- Testing pathological conditions in the cortico-thalamic system model
- Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness



### 3.5.3.2 Modelling and analysis of slow-wave activity across a cortical area with laminar organisation

Starting from the cortical slice model of slow-wave activity, define and simulate a model of a layered cortical area based on the analysis of *in vivo* recording in rodents.

Models progressively resulting from this Component will be used in T3.6.2, which contributes to CDP5, to investigate how SWA shapes the connectivity matrix of the network when dynamic/plastic synapses are taken into account.

Progress on Component:

A scientific paper co-authored by IDIBAPS and ISS in which a mean-field model matches the laminar organisation of SWA at the columnar level in anaesthetised rodents (data provided by IDIBAPS, T3.2.2) is under review for publication. The developed analysis tools will be employed in collaboration with IDIBAPS to characterise the differences in the functional columnar circuitry underlying SWA in wildtype and transgenic mice (Fmr1KO). Model enrichment including synthetic local field potential and extended mean-field description of SWA in cortical columns is starting through the exchange of students and post-docs between CNRS (DESTEXHE) and ISS. The modelling and analysis results obtained here will be instrumental to define the multi-columnar structure of the cortical area model to be released at M24.

#### Quality Control

*Upstream Components:*

- Model of photostimulation of cortico-thalamic simulations
- Simplified model of local field potentials
- Cortical recordings from awake Fmr1KO mice
- Cortical recordings from anaesthetised Fmr1KO mice
- Perturbation of thalamic nuclei and cortical layer activity

*Downstream Components:*

- Collective behaviour of mean-field and neural population models: A comparative study
- Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness

### 3.5.3.3 Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness

Starting from the model of a layered cortical area, an extension will be developed based on the analysis of *in vivo* recordings during the transition from the slow-wave activity and the awake state. Analysis tools will be developed to provide a low-dimensional description of the brain state transition.

No CDP contribution.

Progress on Component:

In collaboration with IDIBAPS (T3.2.2 and T3.2.3), we studied the changes of the dynamical features of L5 activity in V1 of anaesthetised rats underlying the transition from SWA to wakefulness. A mean-field rate model describing the recorded multi-unit activity at different anaesthesia levels has been devised to uncover and characterising the nonlinear dynamic underpinnings. A scientific paper on this work is in preparation. Second, starting from our spiking neuron network model of a cortical slice (T3.2.1), we devised a large-scale cortical field model in which a transition from SWA to an asynchronous state emerges varying the local excitability of the cortical modules. This model has been used as a benchmark for the DPSNN simulator developed by INFN (T3.2.5). Third, a theory-inspired density-based



clustering of multiple intra-cortical recordings is at an advanced stage of development and is now described in a scientific paper under review for publication. As next step, we aim to test the effectiveness of such approach on *in vivo* multisite recordings available from UMIL and IDIBAPS (T3.2.2). Finally, we started a scientific exchange with EPFL (T4.1.3, GERSTNER) on the “population activity equations” topic with the aim to compare the effectiveness of different dynamic mean-field models in describing SWA at columnar level.

### Quality Control

#### *Upstream Components:*

- Population activity equations: Finite-N mean-field model for interacting populations (with adaptation)
- Photostimulation
- Modelling and analysis of slow-wave activity across a cortical area with laminar organisation
- Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity
- Testing pathological conditions in the cortico-thalamic system model

#### *Downstream Components:*

- Perturbation of thalamic nuclei and cortical layer activity
- Slow waves and complexity relationships explored by perturbations: definition of models
- Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states

## 3.6 T3.2.2 Slow-Waves and Complexity: from the Microscale to the Bedside

### 3.6.1 Key Personnel

Task Leader: Marcello MASSIMINI (UMIL, University of Milan)

### 3.6.2 SGA1 DoA Goals

The general goal of Task 3.2.2. is to employ a perturbative approach to characterise, at multiple scales (micro-, meso- and macroscale), the relationships between slow waves - and the underlying bistability in cortical neurons - on the ability of corticothalamic circuits to sustain complex patterns of interactions. To reach this aim, this Task involves different experiments in different preparations at different scales (from slice multiunit and LFP recordings to high-density scalp EEG recordings in humans) whereby perturbations, such as transcranial magnetic stimulation (TMS) TMS or single-pulse electrical stimulation (SPES) are directly applied to the cortex (or to the thalamus). The common denominator of this coordinated effort is the study of thalamocortical dynamics by a casual perspective in order to link local neuronal reactivity (i.e. excitability levels, bistability) to global dynamics of causal interactions as assessed in the human brain in different conditions (wakefulness, sleep and the vegetative state).

### 3.6.3 Component Progress

#### 3.6.3.1 Intracortical SPES recording combined with hd-EEG and intracortical recording (data)

Description of Component:

Intracortical SPES in humans (presurgical evaluation) combined, for the first time, with intracortical recordings and high-density scalp EEG (256 channels). Local SPES perturbation



allows studying bistable dynamics (downstates in LFP response) and effects on local cortico-cortical interactions. Simultaneous hd-EEG allows connecting mesoscale events to network connectivity and macroscale complexity.

#### *Progress on Component:*

We have received the approval from the Ethical Committee of the NIGUARDA Hospital (Milano Area C) - where the clinical procedure for the presurgical evaluation of epileptic patient is routinely carried out - for the novel protocol (specific for the goals of T3.2.2) submitted during the first 6 months of the Project. After the approval, we first produced the documents to formalise the cooperation between our two structures (UMIL and NIGUARDA) and then we extended the MATLAB-based analysis pipeline defined during the first 6 months of the Project, to a larger dataset and improved the MATLAB-based scripts for the processing of intracortical LFP responses and scalp hd-EEG evoked potentials to SPES, during both wakefulness and sleep, in order to detect downstates (on the LFP) and cortico-cortical interactions (based on hd-EEG). After data analysis, both raw data (structural and electrophysiological) and metadata (functional / effective connectivity measures) will be provided to T4.4.1, T4.1.4, T4.1.2, T3.2.5.

We published an article entitled "Global and local complexity of intracranial EEG decreases during NREM sleep" in the international peer-reviewed "*Neuroscience of Consciousness*" 2017 Jan; 3(1) by MM Schartner, A Pigorini, SA Gibbs, G Arnulfo, S Sarasso, L Barnett, L Nobili, M Massimini, AK Seth, AB Barrett. In this study, we analysed three measures of dynamical complexity on spontaneous depth electrode recordings from ten epilepsy patients during wakeful rest (WR) and different stages of sleep: Lempel-Ziv complexity, amplitude coalition entropy and synchrony coalition entropy. When computed across sets of channels that are broadly distributed across multiple brain regions, all three measures decreased substantially in all participants during early-night non-rapid eye movement (NREM) sleep (when the intracerebral activity is mainly characterised by slow waves). This decrease was partially reversed during late-night NREM sleep (reduced slow wave activity), while the measures scored similar to WR during rapid eye movement (REM) sleep (absence of slow waves). This global pattern was in almost all cases mirrored at the local level by groups of channels located in a single region. This paper represents a first attempt to link local and global dynamics (in intracerebral recordings). These results will be generalised by performing similar measures on simultaneous intracerebral and hd-EEG recordings.

We made contact with Jean-Philippe LACHAUX (SP2, Task 2.5.3) and Timo DICKSCHEID in order to establish cooperation within the HBP. We will contribute to a Use Case ("SP3-UC-005a A perturbation-based atlas") by developing a perturbational atlas based on simultaneous intracerebral and hd-EEG recordings and by providing both raw data (structural and electrophysiological) and metadata (functional / effective connectivity measures).

During the Project, UMIL participated to the meeting "Insights from inside, intracranial studies of the human brain" (Tel Aviv, from 30 November to 1 December 2016) to devise common intracranial recording protocols and to implement and share data analysis procedures together with other HBP members (JP LACHAUX and P ROELFSEMA).

#### **Quality Control**

##### *Downstream Components:*

- (important) Prototype software to estimate effective connectivity: We will provide both intracerebral and hd-EEG data (M18 release).
- (added value) Simplified model of local field potentials: We will provide intracerebral data both spontaneous and during SPES (M18 release).
- (added value) Simplified EEG models. We will provide hd-EEG data both spontaneous and during SPES (M18 release).



- (essential) Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2: We will provide both intracerebral and hd-EEG data (M18 release).

### 3.6.3.2 Investigating cortical bistability in vegetative patients with TMS-EEG recordings (data)

Description of Component:

Bedside non-invasive TMS/EEG perturbations/recordings in vegetative patients. Does sleep-like neuronal bistability disrupt cortico-cortical communication and network complexity after brain lesion?

Progress on Component:

We have performed TMS/EEG measurements in 16 vegetative state patients and we have developed an analysis pipeline aligned with the ones derived from slice and intracranial experiments. This pipeline allows detecting - based on macroscale, non-invasive stimulations (TMS) and recordings (scalp EEG) - bistable dynamics (as assessed by time-frequency analysis of TMS-evoked potentials) and their effects on causal interactions (as assessed by phase-locking analysis and source modelling of TMS-evoked activity).

#### Quality Control

*Upstream Components:*

- TMS-EEG data in DOC (M18)

### 3.6.3.3 Electrical perturbations on slices during sleep-like pattern before and after drug application (data)

Description of Component:

Measures of perturbed slow-wave activity on slices before and after drug application.

Progress on Component:

Recordings have been obtained of the perturbed cortical activity of WT animals *in vivo* and *in vitro*. Photostimulating tools (IBEC, T3.2.4) are being tested. We are working towards defining a pipeline for data analysis, in collaboration with ISS (T3.2.1) and INFN (T3.2.5). The first release planned will be a publication on the SWA of the WT vs Fragile X mouse model.

#### Quality Control

*Upstream Components:*

- Photostimulation (release at M18)

*Downstream Components:*

- Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity (release at M18)
- Simplified model of local cortical potentials

### 3.6.3.4 Perturbation of thalamic nuclei and cortical layer activity (data)

Description of Component:

Perturbations (e.g. L5 or L6 silencing/stimulation) and optopharmacological silencing/activation of thalamic nuclei to reveal changes in columnar dynamic and/or wave propagation. The measures allow investigating the roles of thalamus vs cortex on slow wave initiation.

Progress on Component:



Recordings have been obtained at IDIBAPS (SANCHEZ-VIVES) of the spontaneous and perturbed cortical activity of WT *in vivo* and *in vitro*. At UMIL, we are working towards defining a pipeline for data analysis, in continuous collaboration with ISS (T3.2.1) and INFN (T3.2.5). The first planned release will be a publication on the SWA of the WT vs Fragile X mouse model.

### Quality Control

#### *Upstream Components:*

- Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness, T3.2.1 (release at M24)

#### *Downstream Components:*

- Modelling and analysis of slow-wave activity across a cortical area with laminar organisation (release at M24)
- (essential) Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity (release at M18)

### 3.6.3.5 Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 (model)

#### Description of Component:

This Component, a product of Task 3.2.2, defines the simulations to be performed in T3.2.5 about slow-waves and complexity relationships explored by perturbations, starting from the micro-scale, with the long-term goal of bedside.

#### Progress on Component:

We have collected new data, both at the micro- (*in vitro*) and meso- (*in vivo* LFP) scales, to be used, in the next months, to set parameter for simulations of T3.2.5. To this purpose, the cooperation with Task T3.2.5 already started during M10, with the delivery of a first set of experimental data.

### Quality Control:

#### *Upstream Components:*

- (important) Large-scale modelling of TMS/EEG-PCI (release M12)
- (important) Simulation of brain lesion and cortical bistability on complexity (M24 release)
- (essential) TMS/EEG non-invasive perturbation recordings (M24 release)
- (essential) Combined optogenetic, two-photon imaging and electrophysiological recordings from cerebellar neurons (release at M24)
- (important) Cerebellum application model (release M18)
- (added value) Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness, T3.2.1 (release M24)
- (essential) Testing pathological conditions in the cortico-thalamic system model (release M24)
- (important) Model of photostimulation of cortico-thalamic simulations (release M18)
- (essential) Intracortical SPES recording combined with hd-EEG and intracortical recording, release M18)
- (important) NEST Requirements Management, (release M12, M21)
- (important) NEST Support for Providers, (release M12, M24)
- (important) NEST Support for Modellers, (release M12, M24)

*Downstream Components:*

- (important) Simulation of brain lesion and cortical bistability on complexity (release M24)
- (important) Cerebellum application model (release M18)
- (essential) TMS/EEG non-invasive perturbation recordings (release M24)
- (essential) Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1 (release M18, M24)
- (added value) Simplified model of local field potentials
- (essential) EEG in rodents (release M12, M24)

### 3.7 T3.2.3 Slow-Wave Activity in Murine Transgenic Models of Neurological Disease

#### 3.7.1 Key Personnel

Task Leader: Mavi SANCHEZ-VIVES (IDIBAPS, Consorci Institut d'Investigacions Biomediques August Pi i Sunyer)

#### 3.7.2 SGA1 DoA Goals

In this Task, an interdisciplinary effort will be pursued to understand how SWA is in wild type (WT), control mice, and how it is affected different transgenic models of neurological disease. We mention here the Fragile X model but the approach is applicable to other models and has been successful in our laboratory (IDIBAPS) in the Down Syndrome model.

- 1) Cortical multielectrode recordings from anaesthetised WT and transgenic rodents used as model of central nervous system disorders such as Fragile X model (mental retardation) (Fmr1 knockout). Detailed match of SWA properties in Fmr1KO versus WT mice. ISS will contribute novel theory-driven data analyses.
- 2) Synchronous multisite recordings in awake behaving mice (WT and Fmr1KO) from nodes relevant to estimate features of the brain's functional connectivity, in collaboration with SP4.
- 3) Testing which critical parameters of the modelled macroscopic cortico-thalamic system, like cortico-cortical connectivity or excitability of local circuits, reproduce the features of SWA under pathological conditions.

#### 3.7.3 Component Progress

##### 3.7.3.1 Testing pathological conditions in the cortico-thalamic system model

Description of Component:

Test which critical parameters such as cortico-cortical connectivity or excitability of local circuits reproduce the features of slow-wave activity under pathological conditions (e.g. Fragile X).

CDP to which Component contributes: None.

Progress on Component:

Recordings have been obtained of the spontaneous and perturbed cortical activity of WT and animal model of disease both *in vivo* and *in vitro*. Photostimulating tools (IBEC, T3.2.4) have been tested and evaluated. Data analysis is being carried out in collaboration with ISS (T3.2.1) and INFN (T3.2.5).

#### Quality Control

*Upstream Components:*



- Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity [essential] (T3.2.1 MATTIA): the release of this upstream Component is planned at M18-SGA1. Continuous cooperation runs between T3.2.1 and T3.2.3.
- Photostimulation [important] (T3.2.4 GOROSTIZA): intermediate release. Continuous cooperation runs between T3.2.4 and T3.2.3.
- Cortical recordings from awake Fmr1KO mice [essential] (T3.2.3 SANCHEZ-VIVES): the release of this upstream component is planned at M24-SGA1. Preliminary data from this Component in awake mice are used as a basis for recordings in mouse models of disease.
- Cortical recordings from anaesthetised Fmr1KO mice [essential] (T3.2.3 SANCHEZ-VIVES): the release of this upstream Component is planned at M24-SGA1. Preliminary data from this Component in anaesthetised mice are used as a basis for recordings in mouse models of disease.

#### *Downstream Components:*

- The release of this Component is planned at M24-SGA1 together with the downstream Components:
  - Slow waves and complexity relationships explored by perturbation: definition of models [essential] (T3.2.2 MASSIMINI)
  - Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness [essential] (T3.2.1 MATTIA)
  - Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states [important] (T3.2.5 PAOLUCCI)

### **3.7.3.2 Cortical recordings from awake Fmr1KO mice**

#### **Description of Component:**

Synchronous multisite recordings in awake behaving mice (wild-type and Fmr1KO) to estimate features of the brain's functional connectivity.

CDP to which Component contributes: None.

#### **Progress on Component:**

The technique for the recordings by means of chronic implants has been set up at IDIBAPS and we have been solving technical problems posted by the free moving mice. Some preliminary recordings have been obtained by IDIBAPS and new analytical techniques are being developed to sort out brain states and adapt our analysis tools.

#### **Quality Control**

#### *Upstream Components:*

- Cortical recordings from anaesthetised Fmr1KO mice [important] (T3.2.3 SANCHEZ-VIVES): the release of this upstream Component is planned at M24-SGA1. Preliminary data from this Component in anaesthetised mice are used as a basis for recordings in awake mice.

#### *Downstream Components:*

- The release of this Component is planned at M24-SGA1 together with the downstream Components:
  - Modelling and analysis of slow-wave activity across a cortical area with laminar organisation [essential] (T3.2.1 MATTIA)
  - Testing pathological conditions in the cortico-thalamic system model [essential] (T3.2.3 SANCHEZ-VIVES)



### 3.7.3.3 Cortical recordings from anaesthetised Fmr1KO mice

Description of Component:

Cortical multielectrode recordings from anaesthetised transgenic mice (Fmr1 knockout) used as model of Fragile X (mental retardation).

CDP to which Component contributes: None.

Progress on Component:

Recordings have been obtained of the spontaneous and perturbed cortical activity of WT and animal models of disease. Data analysis is being carried out in collaboration with ISS (T3.2.1) and INFN (T3.2.5). Perturbation data are being analysed in collaboration with UMIL (T3.2.2). The first release planned will be a publication on the SWA of the WT vs Fragile X mouse model.

#### Quality Control

*Downstream Components:*

- The release of this Component is planned at M24-SGA1 together with the downstream Components:
  - Modelling and analysis of slow-wave activity across a cortical area with laminar organisation [essential] (T3.2.1 MATTIA)
  - Testing pathological conditions in the cortico-thalamic system model [essential] (T3.2.3 SANCHEZ-VIVES)
  - Cortical recordings from awake Fmr1KO mice [important] (T3.2.3 SANCHEZ-VIVES)

## 3.8 T3.2.4 Modulation of Slow-Wave Activity with Optopharmacology

### 3.8.1 Key Personnel

Task Leader: Pau GOROSTIZA (IBEC, Fundacio Institut de Bioenginyeria de Catalunya)

### 3.8.2 SGA1 DoA Goals

The goal of this Task is (1) to design, (2) synthesise and (3) characterise compounds capable of controlling with light the slow wave activity (SWA) of the brain. The first and key step in the development of this Task is to identify neuronal receptors and signalling pathways that are important to trigger and inhibit SWA. They constitute target receptors to design photochromic ligands. These ligands are then obtained with a combination of several procedures, including rational design based on previously published strategies, and blinded screening based on binding and activity assays. Once the compounds capable of controlling SWA with light have been obtained, the next step is to fully characterise their biological properties (target selectivity, efficacy, kinetics) and photophysical properties (one- and two-photon activation spectra, photosensitivity, relaxation-bistability) in order to be prepared for *in vivo* experiments. Brain illumination methods will then be set up (DoA Goal 4) to photomanipulate neuronal circuits involved in SWA (DoA Goal 5). Finally, we will combine our experiments with computer-simulated photomanipulations on the cortico-thalamic system of Task T3.2.5 (DoA Goal 6).

### 3.8.3 Component Progress

#### 3.8.3.1 Photostimulation

Description of component:

A. Photostimulation: Set of bioactive and photosensitive molecules (“molecular toolbox”) to stimulate the activity of neurons with light pulses. It will be used to spatiotemporally control slow wave activity (SWA) in WaveScaleS project and other brain activity patterns in the HBP. This component relates with all DoA goals (design (DoA Goal 1), synthesis (goal 2) and



characterisation in cell lines and brain slices (DoA Goal 3), photomanipulation of neuronal circuits involved in SWA (DoA Goal 5) except those concerning brain illumination methods (DoA Goal 4), which must be set up in every partner laboratory once the molecular toolbox is made available. The three compounds obtained so far (DoA Goals 1-3) could be the first molecules of the toolbox if photocontrol of neuronal activity can be demonstrated in brain slices (ongoing activity).

CDP to which Component contributes: None.

Use Case to which component contributes: SP3-UC-005c Spontaneous and light-evoked slow wave activity recordings and simulations

Progress on Component:

We have designed light-regulated ligands of neuronal receptors involved in the initiation of slow wave activity in the brain cortex (DoA Goal 1). We have synthesised four ligands with diverse binding and photochromic properties (DoA Goal 2). After initial difficulties finding suitable synthetic routes, all of them have been purified and we have characterised their chemical and photochromic properties (DoA Goal 3). They display high purity, good solubility in aqueous buffer solutions (as required for biological applications), robust photoisomerisation using violet and white light, and slow thermal relaxation in the dark (days). We have set up *in vitro* protein binding assays (radioactive), enzymatic assays (acetylcholine esterase) and cell assays (calcium imaging) in order to characterise the biological responses of their target receptors (DoA Goal 3). We have performed assays in mammalian cell lines overexpressing the target receptors and three of the compounds behave as highly potent agonists (picomolar affinity). One of the compounds appears to display light-regulated activity in the enzymatic and cellular activity assays. We have also performed preliminary assays in brain slices in the laboratory of Maria Victoria SÁNCHEZ-VIVES where one of the compounds was capable of triggering SWA at concentrations several orders of magnitude higher than with carbachol. Complete chemical characterisation is underway and photomanipulation experiments are being performed both in cultured cells and in slices (DoA Goal 5).

## Quality Control

*Downstream Components:*

- Simplified model of local field potentials [DESTEXHE]: The photoswitchable compounds obtained in this component will be used to stimulate neuronal circuits and the measured activity via calcium imaging will be used to build simplified models of neuronal activation (changes in field potentials).
- Model of photostimulation of cortico-thalamic simulations [GOROSTIZA]: Photostimulation and imaging of neuronal activity is now under course to characterise slow wave activity in the cortex and thalamus, in order to produce models of neuronal activity and responsivity in these regions.
- Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness [MATTIA]: Photostimulation is especially suited to span multiple spatial and temporal scales due to the ease to manipulate light, and will be used to induce the transition between slow-wave activity to wakefulness and compared to the model predictions.
- Testing pathological conditions in the cortico-thalamic system model [SÁNCHEZ-VIVES]: Similarly, photostimulation increases excitability of neuronal circuits and may exacerbate or rescue certain pathological conditions where SWA is altered.
- Electrical perturbations on slices during sleep-like pattern before and after drug application [SÁNCHEZ-VIVES]: Electrical and optical perturbations of brain slices will be compared and their ability to alter SWA will be quantified.



### 3.8.3.2 Model of photostimulation of cortico-thalamic simulations:

Description of Component:

**B. Model of photostimulation of cortico-thalamic simulations:** This Component includes the experimental data obtained from photostimulation experiments (e.g. fluorescence recordings of the activity of single neurons or neuronal populations, in response to the presence and photoisomerisation of light-regulated compounds, DoA Goal 5). It also contains a mathematical model of photostimulation experiments that calculates the expected neuronal responses to light-induced activation and inhibition (DoA Goal 6). This model will be used in the simulation Task T3.2.5. Preliminary photostimulation recordings in neurons are ongoing with two compounds, and will be integrated in this repository in the next months.

CDP to which Component contributes: none.

Progress on Component:

Experiments are now ongoing in the laboratory of Maria Victoria SÁNCHEZ-VIVES with brain slices, electrophysiological recordings and optical stimulation, and the data produced will be used to elaborate a model of photostimulation in the cortico-thalamic regions.

#### Quality Control

*Upstream Components:*

- Photostimulation [GOROSTIZA]: Several compounds have been synthesised and tested that activate muscarinic receptors with high potency, with at least one displaying light regulated activity that is currently being characterised. These compounds constitute a pre-release of the Photostimulation toolbox to manipulate SWA.

*Downstream Components:*

- Simplified model of local field potentials [DESTEXHE]: The model of photostimulation of cortico-thalamic simulations will allow implementing spatiotemporal perturbations with light and the corresponding changes in field potentials in the simplified models of neuronal activation.
- Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity [MATTIA]: Cortico-thalamic simulations incorporating photostimulation will be taken into account to develop models of spontaneous and perturbed slow-wave activity in brain slices.

## 3.9 T3.2.5 Slow-Wave Simulation Platforms

### 3.9.1 Key Personnel

Task Leader: Pier Stanislao PAOLUCCI (INFN, Istituto Nazionale di Fisica Nucleare)

### 3.9.2 SGA1 DoA Goals

This Task deals with the distributed simulation of SWA on large-scale models of single and multiple areas. It will:

- 1) Use inter-areal connection to scale from single area SWA simulation to multiple cortical areas. Distributed simulation on thousands of MPI processes (spiking neurons).
- 2) Refine columnar, single area layered architecture.
- 3) Run the state-of-the-art DPSNN simulator on the SP7 HPAC Platform. Measure scalability for large numbers of MPI processes. Evaluate scalability on multiple cortical areas.
- 4) Set-up the tools needed to observe the wave propagation, the transition to higher consciousness states and to measure indexes of brain structural integrity.



- 5) Port the model to the NEST simulator.
- 6) Run on SP7 Platform (HPAC) both the NEST and DPSNN versions; compare performances and bottlenecks. Suggest possible improvements of SP7 distributed MPI simulators, specifically for SWA modelling.
- 7) Estimate efficacy of custom HPC interconnects vs standard SP7 interconnects.

The Components produced by this Task constitute a background for the Component produced by T3.6.2, which integrates the contribution of WP3.2 to CDP5.

### 3.9.3 Component Progress

#### 3.9.3.1 Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states

Description of Component:

This Component includes multi-scale software models of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1. Eventually they will be ported to NEST. The initial version will be coded using the proprietary DPSNN simulation engine, used as a starting point by the WaveScaLES experiment (i.e. SP3 WP3.2 in SGA1). This Component relates with Task goals: 1, 2, 3, 4, 7.

Progress on Component:

At M12, as per the SGA1 plan of releases, this Component made its “First release of slow waves simulation engine, DPSNN version, starting point for porting to NEST”. DPSNN is a Distributed and Plastic Spiking Neural Network simulation engine used to implement the multi-scale software model expressing Slow Wave Activity (SWA) and asynchronous irregular states (AW). The neural network is described as a bi-dimensional grid of cortical modules, each module composed of point-like neurons (80% excitatory, 20% inhibitory neurons), based on a Leaky Integrate and Fire (LIF) neuronal model with spike-frequency adaptation (SFA) due to calcium- and sodium-dependent after-hyperpolarisation (AHP) currents. The neurons are connected among them with both intra- and inter-columnar connections. The connectivity can be varied according to the simulation needs, leading to configurations with different numbers of synapses per neuron. The neural network can be distributed over a set of MPI processes, and the simulations can be run on HPC server platforms.

The model expressing SWA and AW states have been simulated on grids of cortical modules with 1250 neurons per module and about 1200-1500 synapses per neuron, depending on the specific selected connectivity law. At the end of the first year of activity, using DPSNN we are able to simulate up to 36864 cortical modules (organised in a bi-dimensional grid of 192 x 192 cortical columns) composed of about 70G synapses and 46M neurons, distributing the problem over up to 1024 MPI software processes. The server platform used to run the simulations of SWA and AW states is GALILEO, a cluster of 516 IBM nodes provided by the CINECA consortium. Each 16-core dual-socket computational node contains two Intel Xeon Haswell 8-core E5-2630 v3 processors, clocked @2.40GHz.

The model expressing SWA and AW states based on the DPSNN simulation engine is the starting point for the implementation of the same model on the NEST simulator. The porting activity initiated in M6, in strict cooperation with the NEST development team.

In M9, starting from a pre-existing Matlab code developed by ISS, INFN and ISS have initiated the joint development of an improved data analysis pipeline (WAP - WaveScaLES Analysis Pipeline) to be applied both to the experimental data acquired by IDIBAPS during SGA1 experiments as well as to the simulation results produced by this and other simulation components of WaveScaLES. The first application of WAP will be the analysis of spontaneous and perturbed ECoG data recorded *in vivo* on mice. During M12, we started some preliminary application of the WAP on IDIBAPS data, for the recognition and the analysis of spontaneous and evoked SWA recorded on mouse under deep anaesthesia.



## Quality Control

### *Upstream Components:*

- Model of photostimulation of cortico-thalamic simulations [important] - T3.2.4 (the release of this upstream Component is planned at M18-SGA1, and will contribute to the third release of simulations released by this Component, planned at M24-SGA1)
- Multiscale cortico-thalamic model of the transition from slow-wave activity to wakefulness, T3.2.1 [essential] (This upstream Component is the theoretical counterpart of the third release of the simulations delivered by the Component here described. A continuous cooperation runs between T3.2.1 and T3.2.5. The formal delivery date of both are planned at M24 -SGA1)
- Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 [essential] (the release from this upstream Component is planned at M24 - SGA1, this upstream Component contributes to requirements of SGA2 WaveScalES simulations)
- Simulation of brain lesion and cortical bistability on complexity [important] - T3.4.3 (NOTE: LINK TO BE REMOVED. This is a Component related to Conscious Brain specific simulation activities. We suppose this link should be removed)
- Testing pathological conditions in the cortico-thalamic system model, T3.2.3 [important] (the release of this Component is planned at M24 - SGA1. Continuous cooperation runs between T3.2.3 and T3.2.5).

### *Downstream Components:*

- Single-area non-laminar model generating cortical slow waves - NEST flavour - WaveScalES SP3 SGA1 T3.2.5 [essential]. We are already using pre-releases of the Component here described, and it has been already used as the starting point for a pre-release of this NEST coded downstream component (planned at M18 - SGA1) available. A strict cooperation with the NEST development team has been established.
- Co-design of interconnects and simulators [essential] - T3.2.5. The first release of the component here described has been delivered, and is currently used for the study of advanced interconnect techniques for the acceleration of large scale simulations of spiking neural networks. The release of this downstream Component is planned at M24 - SGA1.
- Laminar single-area model generating cortical slow waves - NEST flavour - WaveScalES SP3 SGA1 T3.2.5 [essential] - The release from the Component here described to this downstream Component is the "second release" planned at M18-SGA1, and the release of the downstream Component is planned at M24 -SGA1.
- Multi-area model generating cortical waves - NEST flavour - WaveScalES SP3 SGA1 T3.2.5 [essential] - The release from the Component here described to this downstream Component is the "second release" planned at M18-SGA1, and the release of the downstream Component is planned at M24-SGA1.

### **3.9.3.2 Single-area non-laminar model generating cortical slow waves - NEST flavour - WaveScalES SP3 SGA1 T3.2.5 (model)**

#### Description of Component:

This is one of the Components delivered by SP3 SGA1 Task 3.2.5 in the WaveScalES experiment (WP3.2) - It is a single-area non-laminar model of a two-dimensional grid of cortical modules generating cortical slow waves. There are two flavours of this model: the first running on the NEST simulator (this Component), the second running on the DPSNN simulator

#### Progress on Component:



The first release of this Component is planned at M18-SGA1. During the first 12 Months of SGA1, we started implementing the single-area non-laminar model of a two-dimensional grid of cortical modules expressing SWA. The model is a porting of the one implemented in DPSNN (component of T3.2.5 described in the previous section of this report) whose first release (“First release of slow waves simulation engine, DPSNN version, starting point for porting to NEST”) is delivered at M12-SGA1.

The implementation of this component in NEST is being carried on in strict cooperation with the NEST development team. Actually, the Component is considered as a source of requirements for the NEST simulator development, requirements that we widely discussed with the NEST team in different occasions: key-note talk about requirements delivered at HBP Young Researchers Event (Budapest - April 2016), talk at the Nest User Workshop (Karlsruhe - November 2016), several conference calls and emails (mainly with H.E. Plesser).

For the Component implementation, we used the NEST simulator version 2.10.0 first, and 2.10.12 later, installed on our local servers. Moreover, in order to implement the specific neuron model required for our Component, we used NESTML, a modelling language for spiking neurons, and NESTML Tool Support, for the automatic code generation. For both activities, we received a full support from the NEST development team, in particular from H.E. Plesser for what concern NEST, and from D. Plotnikov for NESTML.

In the next months, this Component will go through a prototyping phase during which we need to perform benchmarks and scaling measures running the Component on an HPC server platform. During this phase, two of the upstream Components will become essential: the HPC system at Cineca for the simulations of the model, as well as the Federated HPAC Computing Services for the data archive and cloud services.

## Quality Control

### *Upstream Components:*

- Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1 [essential]
- NEST - The Neural Simulation Tool [essential]
- NEST Support for Modellers
- SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations [important]
- HPC systems at Cineca [essential]
- SP7 Federated HPAC Computing Services [essential]

### *Downstream Components:*

- NEST Requirement Management [essential]

### **3.9.3.3 Laminar single-area model generating cortical slow waves - NEST-like - WaveScalES SP3 SGA1 T3.2.5 (model)**

#### Description of Component:

This is one of the Components delivered by SP3 SGA1 Task 3.2.5 in the WaveScalES experiment (WP3.2) - It is a single-area laminar model of a two-dimensional grid of cortical modules generating cortical slow waves. There are two flavours of this model: the first running on the NEST simulator (this Component), the second running on the DPSNN simulator

#### Progress on Component:

The first release of this Component is planned at M24-SGA1. The activity on this Component has not yet started, because it depends on the second release, planned at M18-SGA1, of the Component “Multi-scale software model of cortical structures expressing slow waves and the



transition to other consciousness states, T3.2.5 SP3 SGA1", that delivers the prototype of a laminar model, coded in DPSNN, to be ported to NEST.

### Quality Control

Note: the activity producing this component is planned to start at M18, see progress above. Therefore, we report below only the list of Upstream and Downstream Components without additional details of deliveries.

#### *Upstream Components:*

- Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1 [essential]
- NEST - The Neural Simulation Tool [essential]
- NEST Support for Modellers
- SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations [important]
- NEST Requirement Management [essential]

#### *Downstream Components:*

- NEST Requirement Management [essential]

### 3.9.3.4 Multi-area model generating cortical waves - NEST-like - WaveScalES SP3 SGA1 T3.2.5 (model)

#### Description of Component:

This is one of the Components delivered by SP3 SGA1 Task 3.2.5 in the WaveScalES experiment (WP3.2) - It is a multiple-area model of interconnected two-dimensional grids of cortical modules generating cortical waves. There are two flavours of it, the NEST one (this Component) and the version running on the DPSNN simulator

#### Progress on Component:

The first release of this Component is planned at M24-SGA1. The activity on this component has not yet started, because it depends on the second release, planned at M18-SGA1, of the Component "Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1.

### Quality Control:

Note: the activity producing this component is planned to start at M18, see progress above. Therefore, we report below only the list of Upstream and Downstream Components without additional details of deliveries.

#### *Upstream Components:*

- Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1 [essential]
- NEST - The Neural Simulation Tool [essential]
- NEST Support for Modellers [essential]
- NEST Requirement Management [essential]

#### *Downstream Components:*

- T3.2.5 (4) Multi-area simulation scaling analysis on a human like model (SGA2 component) [essential]
- NEST Requirement Management [essential]





## 4. WP3.3 Episodic Memory as Multisensory Reconstruction

### 4.1 Key Personnel

Work Package Leader: Cyriel PENNARTZ (Universiteit van Amsterdam, UvA)

Task Leader (T3.3.1): Emrah DUZEL (Deutsches Zentrum fuer Neurodegenerative Erkrankungen EV, DZNE)

Task Leader (T3.3.2): Francesca CACUCCI (University College London, UCL)

Task Leader (T3.3.3): Cyriel PENNARTZ (Universiteit van Amsterdam, UvA)

Task Leader (T3.3.4): Tony PRESCOTT (University of Sheffield, USFD)

Task Leader (T3.3.5): Martin PEARSON (University of the West of England, Bristol, UWE)

### 4.2 WP Leader's Overview

DZNE (DÜZEL) completed a 7T fMRI study on pattern completion in episodic memory in collaboration with SP4, and developed a new virtual reality task with 3D scenes and 3D objects. UCL (CACUCCI) made progress with behavioural training, electrophysiological recordings and finalising hardware for our rodent Virtual reality system. Data analysis has also progressed. UvA (PENNARTZ) made substantial progress in behavioural training and electrophysiological recording setups, acquisition of ethical approvals and data analysis. Prescott (USFD) developed an initial model of human episodic memory (Synthetic Autobiographical Memory) which as attractor properties operating in a latent variable space. This model has been integrated in control systems for the iCub and Miro robot platforms, and complementary work on multisensory integration has taken place in the rodent (Shrewbot) robot platform. UWE (Pearson) designed robot processing architecture and built a whisker sensory array for the SP3-Shrewbot++ robot platform, and is working to build a visual-tactile robot from this. The group has met several times and has built up contacts with many other SPs, most notably SP5, SP10, SP9, SP4, SP2 and SP7. The milestones M1 and M12 were both achieved (i.e. Construction of recording setups, initial experiments, data analysis tools, models, robotic platform).

Due to the delayed availability of HBP funding, recruitment of personnel went slower than anticipated. For instance, UCL had problems recruiting personnel due to the delayed availability of HBP funding (which reached UCL at the end of September 2016). Dr. Guifen CHEN has been in place since 1 October, but has made good progress in recording electrophysiological data from place cells and grid cells in mice navigating in virtual reality environments. Due to new legislation on animal experiments in the Netherlands, ethical approvals took longer to acquire than expected (UvA).

### 4.3 Impact of work done

UCL has had discussion with other HBP partners on PLA model components 984 'Hippocampal and striatal model of spatial navigation, with extension to planning and episodic memory (model)' (linked to SP4 T4.4.4) and 2449 'Temporal dynamics of rodent spatial memory (model)' (linked to SP3 T3.3.4), with added value for constraining modelling. Analysis of a dataset recently acquired at the UvA, closely related to the planned experiments, resulted in the discovery of novel neural correlates of spatial cognition (Bos et al., Nature Comm., in press), and is leading collaborative impact in HBP and outside. The work at USFD has impact not only via publications, but also via public events (e.g. STOA, open days) and interacts with SP10. UWE published an IEEE conference paper on the RatSlam model with integrated whisker sensors. The joint work had further impact via conference talks, posters and workshops (organised by HBP or external).

### 4.4 Priorities for the remainder of the phase



DZNE will prioritise MR-PET measurements in a memory recall task using reward associations, tapping into dopamine function in the human brain. UCL will give priority to continue electrophysiological data acquisition of grid and place cells in rodents navigating in the virtual reality system we recently developed, with a view to understand the neural basis of spatial and memory properties of hippocampal network. We will also continue to forge new collaboration within HBP, and continue work with those already established. We will be recruiting another researcher for 6 months to ensure that the M24 milestone will be met. UvA will give priority to behavioural training of rats and mice on multisensory and episodic memory tasks, ensemble recordings from multiple cortical areas during these tasks, optogenetic manipulation and data analysis, thereby collaborating with several other SPs. USFD will pay particular attention to further Shrewbot development and to implementation of hippocampal and multisensory models in robot simulators. UWE will next focus on the visual-tactile robotic platform (WhiskEye) and using a 48X node SpiNNaker board for spike-based robotic control. In this respect, activities via CDP5 and with SP10, SP4, SP5 and other SPs will gain further prominence.



## 4.5 Milestones

Table 3: Milestones for WP3.3. - Episodic memory as multisensory reconstruction

MS No.	Milestone Name	Leader	Task(s) involved	Expected Month	Achieved Month	Comments
MS3.3.1	Finalisation of Project implementation proposal for WP3.3	UvA		M02	M02	Finalisation of Project implementation proposal, including definition of project objectives, methods, collaborative actions including those in CDPs, policy on dataset management, sharing and publications
MS3.3.2	Construction of recording setups, initial experiments, data analysis tools, models, robotic platform	UvA		M12	M12	Construction of recording setups, initial experiments, data analysis tools, models, robotic platform
MS3.3.3	Validation of protocols, performance of experiments, computational model testing, data analysis	UvA		M24		Not yet achieved



## 4.6 T3.3.1 Human Brain Imaging of Multisensory Episodic Memory

### 4.6.1 Key Personnel

Task Leader: Emrah DUEZEL, (DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen EV)

### 4.6.2 SGA1 DoA Goals

The goal of this Task is to identify the circuit-level mechanisms of hippocampal-neocortical interactions during episodic reinstatement of multisensory experiences, object-scene associations and reward. First, we will study CA3 pattern-completion associated with episodic memories in relation to input and output activity of the EC. Second, we will examine fMRI correlates of recollection of object-scene associations, including a test of whether laminar input and output activity of EC follows a topographic organisation. We will furthermore examine whether hippocampal-cortical mappings are preserved across input-output operations. Third, we will study, using truly simultaneous MR-PET, the functional regulation of hippocampal dopamine release during retrieval of multisensory information including reward associated with objects or scenes. This includes testing whether associative retrieval at CA3 leads to dopamine release.

### 4.6.3 Component Progress

#### 4.6.3.1 7 Tesla human fMRI of object-scene associations in hippocampus and EC

Study of recollection of object-scene associations, including a test of whether laminar input and output activity of EC follows a topographic organisation.

No CDP contribution

Progress: We completed our first Milestone and finished a 7T fMRI pattern-completion in episodic memory study in collaboration with T.3.3.2 and SP4 (N. Burgess). The results show how hippocampal-subfield activation is related to neocortical reinstatement of categorical information. In the last 6 months, we completed the ultrahigh-resolution manual segmentation of hippocampal and medial temporal subfields. We are now completing all analyses and plan to complete a manuscript in 6 months.

#### Quality Control

##### *Upstream Components:*

- SGA2\_T2.5.5 feedback interactions in monkey and human

#### 4.6.3.2 7Tesla fMRI of CA3 pattern-completion

Human 7 Tesla fMRI study of CA3 pattern-completion associated with episodic memories in relation to input and output activity of the EC and in relation to cortical reinstatement.

No CDP contribution

Progress: We created virtual reality 3D scenes with embedded virtual reality rendered 3D objects. We have piloted a task in which the scenes are presented with the embedded objects. After delays of 10 minutes, 30 minutes, 6 hours, 24 hours or 7 days, participants were presented with the scenes only and had to select which objects belonged to a particular location. This Task will now be used for 7T imaging.

#### Quality Control

##### *Upstream Components:*

- SP3.3.4 iCub episodic memory system
- SP3.3.4 Attractor networks for episodic memory



#### 4.6.3.3 MR-PET of dopamine release regulated by the hippocampus

Study using truly simultaneous MR-PET to investigate the functional regulation of hippocampal dopamine release during retrieval of multisensory information including reward associated with objects or scenes.

No CDP contribution: NA

Progress: We will start recording the simultaneous MR-PET measurements in 3 months using the task developed in the fMRI part in conjunction with a reward association of recalled objects.

### 4.7 Task 3.3.2: Rodent Physiology: Pattern Completion in Episodic Memory

#### 4.7.1 Key Personnel

Task Leader: Francesca CACUCCI (UCL, University College London)

Other Researcher: Guifen CHEN (UCL, University College London)

#### 4.7.2 SGA1 DoA Goals

To investigate place and grid cell firing patterns in virtual reality (VR) and the dynamics of their responses to changes in the virtual environment.

To understand how changes in the sensory input relate to changes in neural firing patterns of hippocampal spatial neurons.

To inform models of attractor dynamics in the hippocampus and their role in episodic memory encoding and retrieval.

#### 4.7.3 Component Progress

##### 4.7.3.1 Rodent physiology: pattern completion in episodic memory

Spatial cells in the hippocampal formation integrate landmark information (predominantly visual, but also from other modalities) and self-motion information in order to encode position (place cells), direction (head direction cells) and distance travelled (grid cells).

Our aim is to study the integration of landmark and self-motion input streams in grid cells, making use of our newly developed VR setup.

We intend to manipulate the gain between motor output and visual input whilst mice navigate in 2D virtual environments. This will allow us to determine: a) the relative influence of visual and self-motion inputs on grid cell firing and b) whether such influence will be the same across the whole population of sampled grid cells or rather each cell will show a bias towards visual and/or self-motion input modulation.

Previous work from Guifen CHEN (Chen et al PNAS, 2013) has established that the relative weight of self-motion vs visual information varies widely across hippocampal place cells. Our hypothesis is that grid cells, contrary to place cells, will all show a constant visual/self-motion weighting across the whole population of co-recorded cells. We therefore hypothesise that gain modulations will induce a mismatch between place and grid cell codes. This provides us with the opportunity of improving our current understanding of attractor dynamics in hippocampal networks.

#### Quality Control

##### *Upstream Components:*

- T4.4.4 Hippocampal and striatal model of spatial navigation, with extension to planning and episodic memory

##### *Downstream Components:*



- T3.3.4 (1) Temporal dynamics of rodent spatial memory
- SP3.3.4 Attractor networks for episodic memory
- T3.1.4 Dendritic mechanisms of feedback
- T4.4.4 Hippocampal and striatal model of spatial navigation, with extension to planning and episodic memory

## **4.8 T3.3.3 Rodent Physiology and Optogenetics: Multisensory Integration in Episodic Memory**

### **4.8.1 Key Personnel:**

Task leader: Cyriel PENNARTZ (UvA, University of Amsterdam)

### **4.8.2 DoA Goal(s):**

The goal of T3.3.3 is to uncover the neural mechanisms underlying multisensory integration during the formation and the retrieval of memory. This is done at multiple scales: cells, within-area and multi-area ensembles.

Firstly, we will study multisensory memory encoding and retrieval using cell-resolution, multi-area recordings simultaneously from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampus (CA1).

Secondly, using Bayesian decoding of spike patterns from ~100 simultaneously recorded neurons, we will test how neural ensembles in cortex and hippocampal formation perform multimodal scene representation.

Thirdly, we will apply optogenetic manipulation of episodic encoding and retrieval by (in) activating activity of hippocampal, parahippocampal and mesencephalic dopamine cells.

To sum up, T3.3.3 will build experimental setups, methods and data analysis tools of the behavioural and neural processes involved in episodic memory formation and retrieval from multisensory integration. On top of that, we will establish key relations with other tasks, WPs and SPs (SP1, SP2, SP4, SP5, SP6, SP9, SP10) to enable theoretical analyses, large-scale simulations, neuromorphic and robotic implementations.

### **4.8.3 PLA Components:**

#### **4.8.3.1 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1**

Description: We will investigate episodic memory formation as a result of multisensory integration by conducting cell-resolution and multi-area recordings simultaneously from visual and somatosensory cortices, hippocampus CA1 region and entorhinal and perirhinal cortices, while the animal is performing a spatial memory task requiring the integration of visual and tactile information.

#### **4.8.3.2 Decoded spike patterns of neural ensembles in cortex and hippocampus during multimodal scene representation**

Description: Using Bayesian decoding of spike patterns from ~100 simultaneously recorded neurons (from experiment in C1), we will test how neural ensembles in cortex and hippocampal formation perform multimodal scene representation.

#### **4.8.3.3 Optogenetic manipulation of hippocampal, parahippocampal and mesencephalic dopamine cells in relation to episodic encoding and retrieval**

Description: Multisensory integration during the formation and retrieval of episodic memory is studied by optogenetically manipulating the activity of hippocampal, parahippocampal and mesencephalic dopamine cells.



CDP Contributions: This Task contributes to CDP5.

Our three components contribute empirical data to CDP5.

Progress:

In July 2016, a successful WP3.3 meeting on tactile-visual integration was held in which researchers and administrative staff of EPISENSE exchanged their ideas and made concrete plans for rodent and robot experiments and complementary modelling. In a meeting in November/December 2016, T3.3.3 members presented and discussed experimental approaches and results to HBP members of SP3 and other SPs. Furthermore, the Task Leader of T3.3.3 (C. PENNARTZ) paid very productive work visits in January to members of SP9 (University of Heidelberg) and SP10 (Technical University of Munich). Finally, together with J. STORM, K. EVERS and A. DESTEXHE, PENNARTZ co-organised the first HBP-based workshop on neural mechanism of consciousness (held in Paris, EITN, March 9-10, 2017). This workshop was a big success.

On 1 September, two PhD students started their work on the UvA EPISENSE project. They have now finished setting up their behavioural experiments and the behavioural training of animals has started. Detailed Ethical work protocols have been approved (by the Dutch CCD, the Central Authority for Scientific Procedures on Animals of the Netherlands), and data analyses on datasets from recent experiments are proceeding well. Further analyses of neural correlates of spatial cognition in rodent perirhinal cortex have resulted in the acceptance of a major publication (*Nature Communications*). Optogenetic manipulation experiments, combined with electrophysiology in rodent cortex or ventral tegmental dopamine neurons, have been expanded. Several other papers have been submitted or are being prepared for submission. Collaboration with members in e.g. SP4, SP5 and CDP5 has started.

## 4.9 T3.3.4. Computational Modelling of Multisensory Episodic Memory

### 4.9.1 Key Personnel

Task Leader: Tony PRESCOTT (USFD, University of Sheffield)

### 4.9.2 SGA1 DoA Goals

Our goal is to implement a computational model of episodic memory incorporating (a) multisensory encoding of signals in superficial entorhinal cortex (EC), (b) projection of these signals to a latent variable space in Dentate Gyrus and CA3, (c) role of recurrent connections in CA3 in pattern separation/completion and sequence generation, (d) role of CA1 and deep layers of EC in decoding, and (e) involvement of wider sensory areas (e.g. somatosensory, visual cortices) in reconstruction of remembered events. Models to be tested on the iCub robot, and Whiskey platform (T3.3.5).

### 4.9.3 Component Progress

#### 4.9.3.1 SP3.3.4 Attractor networks for episodic memory

Description: Model of CA3 attractor dynamics relevant to episodic memory and spatial navigation matching constraints on pattern separation/completion identified in the mammalian hippocampus and instantiating capability for hippocampal replay.

Progress on Component: We have developed an initial model of human episodic memory, termed SAM (Synthetic Autobiographical Memory) that treats memory as an attractor network operating in a 'latent' (hidden) variable space whose dimensions encode salient characteristics of the physical and social world. The current model uses a machine learning approach (Gaussian Processes) and demonstrates properties of compression, pattern completion, and pattern separation. An open-source version of the generic SAM system is



being prepared for release. Ongoing work will use fMRI data to constrain model development.

This Task contributes to CDP5.

### Quality Control

#### *Upstream Components:*

- (essential) Rodent physiology: pattern completion in episodic memory - T3.3.2 - awaiting results
- (important) 7Tesla fMRI of CA3 pattern-completion - T3.3.1 - awaiting results
- (essential) T Multisensory integration for spatial navigational and episodic memory - T.3.3.4 - awaiting model

#### *Downstream Components:*

- (Essential) Temporal dynamics of rodent spatial memory - T3.3.4 - nothing provided yet
- (Essential) iCub episodic memory system - T3.3.4 - intermediate release provided
- (essential) SP3-Shrewbot++ robot platform - T3.3.5 - nothing provided yet

#### 4.9.3.2 SP3.3.4 iCub episodic memory system

Description: Integration of the episodic memory system into the control architecture of the iCub robot. Emulation of episodic memory for short human-robot interactions, including user-action-object recognition.

Progress on Component: The SAM episodic memory model (see above) has been integrated into control systems for the iCub and demonstrated across a range of memory tasks. The current version encodes memory of faces, voices, actions. We are working to develop user-action-object memory, and tools for visualising stored memory, and integration with the Neurorobotics Platform. The code is available for use by other researchers developing with the iCub platform.

No CDP contribution

### Quality Control

#### *Upstream Components*

- (important) 7Tesla fMRI of CA3 pattern-completion - T.3.3.1 - awaiting results
- (essential) Attractor networks for episodic memory - T.3.3.4 - intermediate release received - good
- SP3-Shrewbot++ robot platform [*essential*]

#### *Downstream Components:*

- T3.3.4 (2) Episodic memory dynamics for mental time travel
- SP3-Shrewbot simulation

#### 4.9.3.3 SP3.3.4 Multisensory integration for spatial navigation and episodic memory

Description: Model of integration of somatosensory and visual sense data based on entorhinal cortex and suited to implementation on robot platforms (iCub, Whiskeye).

No CDP contribution.

Progress on Component: Since the Whiskeye platform is under development we are working on model components using the MiRo robot and its simulator (MiRo-Sim). Current work has translated components of the Becker, Byrne, and Burgess (2007) model of hippocampus into the robot simulator and we are beginning to develop models of grid, place, and border cell



firing. Work is also underway to integrate the MiRO-Sim into the Neurorobotics Platform, evaluate implementation in the rodent body model.

### Quality Control

#### *Upstream Components:*

- (essential) Decoded spike patterns of neural ensembles in cortex and hippocampus during multimodal scene representation - T3.3.3 - awaiting results
- (essential) Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1 - T3.3.3 - awaiting results
- (important) Rodent Body Model for the Neurorobotics Platform - T10.3.1 - nothing provided yet

#### *Downstream Components:*

- (essential) - Attractor networks for episodic memory - T3.3.4 - nothing provided yet
- (important) - Shrewbot++ robot platform - T3.3.5 - nothing provided yet
- (important) - Shrewbot++ simulation - T3.3.5 - nothing provided yet

## 4.10 T3.3.5 Robotic Systems: Hardware Implementation of Multisensory Episodic Memory

### 4.10.1 Key Personnel

Task Leader: Martin PEARSON (UWE, University of the West of England, Bristol)

### 4.10.2 SGA1 DoA Goals

This Task will provide a strong test, using robotic systems, for computational theories of brain function and initiate novel autonomous technologies. We will evaluate Task 3.3.4 model of episodic memory using two robot platforms. First; integrate vibrissal sensing in robot model of freely-moving rodents with binocular vision. The new hippocampal model will be interfaced to a model superior colliculus mediating orienting to stimuli. The system will include a visuo-tactile saliency map enabling orienting to multisensory stimuli, which connects to temporal cortex. This work will emulate the behavioural experiments from Tasks 3.3.2 and 3.3.3. Second; we will integrate the episodic memory system into the control architecture of the iCub robot, building on models exploiting deep neural networks. This system implements motivation, attention, language and planning. We will emulate episodic memory for short human-robot interactions, including user-action-object recognition.

### 4.10.3 Component Progress

#### 4.10.3.1 SP3-Shrewbot++ robot platform

##### Description of Component:

A physical robotic platform that incorporates binocular vision and whisker based tactile sensing analogous to rat morphology to demonstrate models of sensory integration and spatial memory operating in the real-world.

##### Progress on Component:

Whisker sensor array has been built, all hardware/computing components sourced, and processing architecture designed. The morphology of the whisker array is being prototyped using the Gazebo robot simulation software adopted for the Neurorobotics Platform. RatSLAM hippocampal model has been integrated with whisker sensors and conference paper published in IEEE reporting importance of biomimetic placement strategies for whiskers. Flexible bodied whisker model has been developed for integration with Neurorobotics



Platform simulation platform. 48x node Spinnaker board is being evaluated for spike based robotic control in preparation for SGA2.

### Quality Control

#### *Upstream Components:*

- SP6-T6.2.5 Models of Basal Ganglia (received nothing)
- SP6-T6.2.4 Circuit model of rat hippocampus (received nothing)
- SP9-SpiNNaker small-scale NM-MC system (received nothing)
- SP4-Hippocampal and striatal model of spatial navigation, with extension to planning and episodic memory (received nothing)
- SP10-NRP -mobile robot model (received nothing)
- SP9-SpiNNaker next generation system (NM-MC2) (received nothing)
- SP3.3.4 Attractor networks for spatial navigation and episodic memory (intermediate release)
- SP4 -Motor control model (received nothing)

#### *Downstream Components:*

- T3.5.5 (1) Mammalbot layered control architecture (intermediate release)
- SP3.3.4 iCub episodic memory system (provided nothing)
- SP10 NRP -Robot designer in the NRP cockpit (intermediate release)
- SP3-Shrewbot simulation (intermediate release)

#### **4.10.3.2 SP3-Shrewbot simulation**

##### Description of Component:

The existing tactile whiskered robot platform "Shrewbot" will be instantiated into the Neurorobotics Platform as a placeholder for the Visual-Tactile robotic platform being developed, and for prototyping models of sensory integration and spatial memory.

##### Progress on Component:

The Shrewbot platform has been rendered in CAD and ported to SDF compatible with Gazebo simulation environment. Simple controllers have been written for each DoF and flexible bodied whisker model demonstrated by TruPhysics (SP10). Now awaiting upload to NRP robot library.

### Quality Control

#### *Upstream Components:*

- SP3.3.4 iCub episodic memory system (intermediate release)
- SP3.3.4 Multisensory integration for spatial navigation and episodic memory (intermediate release)
- NRP sensor model library (finished Component)
- NRP Physics simulation (finished Component)
- NRP Robot designer in the NRP cockpit (intermediate release)
- SP3-Shrewbot++ robot platform (intermediate release)
- SP2 - Selective attention in perception and learning in humans and monkeys (received nothing)

*Downstream Components:*

- T3.3.3 Decoded spike patterns of neural ensembles in cortex and hippocampus during multimodal scene representation (provided nothing)
- T3.3.3 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1 (provided nothing)



## 5. WP3.4. Experimental and Computational Exploration of Consciousness Mechanisms and Methods in Mice and Humans

### 5.1 Key Personnel

Work Package Leader: Johan STORM, (UIO, Universitetet I Oslo)

Task Leader (T3.4.1): Johan STORM, (UIO, Universitetet I Oslo)

Task Leader (T3.4.2): Johan STORM, (UIO, Universitetet I Oslo)

Task Leader (T3.4.3): Marcello MASSIMINI (UMIL, University of Milan)

Task Leader (T3.4.4): Steven LAUREYS (ULG, Universite de Liege)

Task Leader (T3.4.5): Johan STORM, (UIO, Universitetet I Oslo)

### 5.2 WP Leader's Overview

We have made progress toward the WP3.4 objectives: (1): Testing and improving methods for assessing consciousness; and (2): Contributing to testing relevant theories of consciousness. The two Milestones planned for the period at M1 and M12 were both achieved ("Finalisation of Project implementation proposal for WP3.4" and "Construction of recording setups, initial experiments, data analysis tools, models"). Thus, we have obtained experimental results from humans and rodents, and developed computational models for testing methods, principles and theories of consciousness.

T3.4.1 (mouse/rodent experiments): We successfully established methods and collaborations, including essential electrophysiology methods in mice and rats (EEG, ECoG; electrical stimulation methods, etc).

T3.4.2 (modelling): We successfully transferred the Hill-Tononi (2005) thalamocortical model for wake-sleep simulations into NEST.

T3.4.3 (modelling and human experiments): We calibrated and validated a measure of brain complexity (PCI) on a large (n=150) benchmark population (article: Casarotto et al. 2016. *Annals of Neurology*).

T3.4.4 (human experiments): Our report components went well. We investigated function-structure interaction in healthy subjects and patients using TMS-EEG and diffusion magnetic resonance imaging tractography (article: Amico et al. 2017, published in *Brain Connectivity* 7:84-97, Bodart et al, 2016, published in *Neuroimage: Clinical*. 2017 Feb 6;14:354-362.). More acquisition and preliminary analyses are on their way.

T3.4.5 (Wada test): We have successfully prepared for these tests, and development of a novel, more rapid method for continuously monitoring consciousness (Juel et al., 2017; article under revision in *Clinical Neurophysiology*), and compared this method to the established PCI method under different kinds of general anesthesia (collaboration Oslo-Milan-Liege; Juel et al., manuscript in preparation)

So far, the main obstacle to fulfilling our plans within WP3.4 has been the large HBP-related administrative burden, which has delayed scientific work.

T3.4.1 (mouse/rodent experiments). Some scientific work was delayed by administrative tasks.

T3.4.2 (modelling): Some delays, partly due to administrative tasks.

T3.4.3 (modelling and human experiments): Everything went according to plan.

T3.4.4 (human experiments): Acquisition of TMS-EEG in patients with disorders of consciousness (DOC) is more difficult than expected. We had to exclude half of the patients (due to active epilepsy, massive craniotomy, medical instability).



T3.4.5: Fewer Wada-test patients than expected were available in this period. 1-2 are planned for May/June, but some preparations were delayed by HBP-related administrative demands.

### 5.3 Impact of work done

T3.4.1 (mouse/rodent experiments): The established methods and collaborations provide a basis for much of the future experimental work on consciousness in rodents within WP3.4. Thus, the electrophysiology methods that were established in mice and rats (EEG, ECoG; electrical stimulation methods, etc) will be used for much of the future work in T3.4.1. The collaboration with WP3.4 has been particularly valuable, since they have much previous experience with such methods.

T3.4.2 (modelling): Our NEST version of the Hill-Tononi model that we have now established is much faster than the original Hill-Tononi (2005) model and can be run on larger computers. The collaboration within HBP, particularly with Hans E. Plesser, has been very important, since NEST is The Neural Simulation Tool that is used within HBP's HPAC Platform. Thus, this model provides a basis for stronger future collaborations within the HBP and future simulation work on states of consciousness within WP3.4.

T3.4.3 (modelling and human experiments): The calibration and validation of PCI represents a basic step towards the generalisation of brain complexity measures to other conditions and computational models.

T3.4.4 (human experiments): Our work on the structure-function relationship show that it is reduced following TMS within each frequency band at the whole-brain network level, pointing to the importance of different oscillations for integration and segregation of information in the human brain. Sharing of neuroimaging data within HBP for future use (e.g., improving brain atlases, data software, collaboration with MIP and SP7 storage).

T3.4.5 (Wada test): We are now almost ready (pending ethical approval) for data acquisition from the first Wada-test, which will provide a unique opportunity for testing methods and theories of consciousness.

### 5.4 Priorities for the remainder of the phase

T3.4.1 (mouse/rodent experiments): Improving methods. Data acquisition.

T3.4.2 (modelling): Testing, tuning, and developing the HT/NEST model.

T3.4.3 (modelling and human experiments): Systematically assessing the impact of cortical lesions (from focal to multifocal) on the complexity of cortical interactions.

T3.4.4 (human experiments): Continuing data acquisition and going further into analyses.



## 5.5 Milestones

Table 4: Milestones for WP3.4. - Experimental and Computational Exploration of Consciousness Mechanisms and Methods in Mice and Humans

MS No.	Milestone Name	Leader	Task(s) involved	Expected Month	Achieved Month	Comments
MS3.4.1	Finalisation of Project implementation proposal for WP3.4	UiO	T3.4.1-5	M02	M02	Finalisation of Project implementation proposal, including definition of project objectives, methods, collaborative actions including those in CDPs, policy on dataset management, sharing and publications
MS3.4.2	Construction of recording setups, initial experiments, data analysis tools, models	UiO	T3.4.1-5	M12	M12	Construction of recording setups, initial experiments, data analysis tools, models
MS3.4.3	Validation of protocols, performance of experiments, computational model testing, data analysis	UiO		M24		Not yet achieved



## 5.6 T3.4.1 Mouse Experiments: Test PCI, ERP methods

### 5.6.1 Key Personnel

Task Leader: Johan STORM (UIO, Universitetet i Oslo)

### 5.6.2 SGA1 DoA Goals

This Task aims to test mechanisms of connectivity and consciousness, and principles for assessing consciousness in rodents, by:

- 1) Developing and testing the following methods: (i) A Perturbational Complexity Index (PCI)-like measure of integration and differentiation in the cortex of rodents (mice, rats). We will use direct electrical/optogenetic stimulation of neural circuits, rather than magnetic stimulation (TMS) as applied in humans. This will result in an electrical PCI ("ePCI"), which can be computed with a similar methodology as the TMS-based PCI in humans. (ii) Mechanistic analysis of ERP in mice, using EEG, LFP, Ca<sup>2+</sup> imaging, pharmacology, and optogenetics.
- 2) Testing mechanisms: The roles of prefrontal (PFC) vs. parietal cortex (PC), ascending activation systems, and thalamus in wakefulness will be tested by transient inactivation and lesions and quantified with ePCI and multi-modal ERP. Functional connectivity and its impact on integration, differentiation and PCI will also be tested.

### 5.6.3 Components Progress

#### 5.6.3.1 PCI-like measure in rodents

Description: Develop and test a PCI-like measure of integration and differentiation in rodents. (No CDP contribution.)

Progress on component:

As already reported in M6, we obtained the necessary ethical permissions for the animal experiments needed for T3.4.1.

In M16-M12 we completed building most of the experimental setups (except the setup for calcium imaging, which is in progress) and are now establishing and developing the necessary *in vivo* rodent experimental methods for this Task. This includes high-density EEG and ECoG in mice and rats, using three different methods, anaesthesia, etc.

The established methods and collaborations provide a basis for much of the future experimental work on consciousness in rodents within WP3.4. Preliminary data and test results have been obtained, but no publishable data set has been acquired yet. As expected, it is a demanding task to develop experimental and analysis methods for a reliable PCI-like index for rodents. We are in contact with M. MASSIMINI's and M. SANCHES-VIVES groups in Milan and Barcelona, and other experts abroad, and will get together for a joint effort for developing reliable PCI-like index/indices for rodents.

#### Quality Control

*Downstream Components:*

- (added value) - T3.3.3 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1

#### 5.6.3.2 ERP in rodents

Description: Report on ERP in rodents.

Progress on Component:

We have obtained visual event-related potentials (ERPs) from rodents and continue to improve the method.



Work on this report will start once sufficient data on ERP have been gathered and preliminary analyses have been conducted.

### Quality Control

#### *Upstream Components:*

- (important) - Mechanistic analysis of ERP in rodents

#### *Downstream Components:*

- (added value) - T3.3.3 Decoded spike patterns of neural ensembles in cortex and hippocampus during multimodal scene representation
- (added value) - T3.3.3 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1

### 5.6.3.3 Mechanistic analysis of ERP in rodents

Description: Mechanistic analysis of ERP in rodents, for understanding of ERP assessment in humans.

#### Progress on Component:

As already reported in M6, we obtained the necessary ethical permissions for the work in T3.4.1, and are now establishing and developing the necessary *in vivo* rodent experimental methods for this Task (EEG, ECoG, anaesthesia etc.)

In M16-M12 we completed construction of the experimental setup and are now establishing and developing the necessary *in vivo* rodent experimental methods for this Task. We have obtained preliminary data and test results from visual event-related potentials (ERPs) in rodents, but no publishable data set has been acquired yet.

Work on this report will start once sufficient data on ERP have been gathered and preliminary analyses have been conducted.

### Quality Control

#### *Downstream Components:*

- (important) - ERP in rodents
- (important) - SP12-SGA1 Philosophy briefing report 1
- (important) - SP12-SGA1 Philosophy briefing report 2

### 5.6.3.4 EEG in rodents

Description: Large scale multi-channel EEG in rodents.

#### Progress on Component:

As stated above, we obtained the necessary ethical permissions for the animal experiments needed for all Components of T3.4.1.

In M16-M12 we completed construction of the experimental setups and are now establishing and developing the necessary *in vivo* rodent experimental methods for low-high-density EEG in mice and rats, using three different methods.

### Quality Control

#### *Upstream Components:*

- (essential) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2

#### *Downstream Components:*

- (important) - SP12-SGA1 Philosophy briefing report 1



- (important) - SP12-SGA1 Philosophy briefing report 2

## 5.7 T3.4.2 Multilevel Computational Modelling

### 5.7.1 Key Personnel

Task Leader: Johan STORM (UIO, Universitetet i Oslo)

### 5.7.2 SGA1 DoA Goals

The goal of T3.4.2 is to test consciousness mechanisms and indices using computer models of cortical/thalamocortical networks implemented using NEST. We seek to determine factors affecting potential indices of consciousness to generate hypotheses regarding key theoretical principles and mechanisms for consciousness and modulation of brain states.

- 1) Using models of TMS and EEG implemented with large-scale modelling of cortical/thalamocortical networks, we will test how PCI depends on network properties.
- 2) Model TMS/EEG-PCI in cortical/thalamocortical networks in simulated states of wakefulness, sleep, and anaesthesia.
- 3) Compare simulated TMS/EEG-PCI with a novel index based on sensory stimuli ("sPCI").
- 4) Model measures of functional and effective connectivity proposed as consciousness indicators, and investigate how they relate to integration and differentiation in the networks, as well as corresponding PCI values.
- 5) Simulate how neuromodulatory effects impact the effectiveness of indicators of consciousness.

### 5.7.3 Components Progress

#### 5.7.3.1 Frequency-dependence and resonance-dependent functional connectivity

Description: Model frequency-dependence and resonance-dependent functional connectivity and its impact on integration, differentiation and PCI values. (CDP 5 contribution).

Progress on Component:

As already reported in M6, we have started collaboration with Dr. Hans Ekehart PLESSER in SP6 and received from him access to the GitHub repository for the Hill-Tononi model from 2005 (developed by Sean Hill, the previous leader of SP5; S. Hill and G. Tononi *Journal of Neurophysiology* 2005). From July 2016, we employed a post-doc (Ricardo MURPHY) on T 3.4.2.

In M7-12, WP3.4 scientist in Oslo (PhD student Andre S. NILSEN, postdoc Ricardo MURPHY, and PhD student Bjørn E. JUEL) in collaboration with the NEST expert Prof. Hans Ekehart PLESSER in SP6 (NMBU, Oslo), and postdoc Thierry NIEUS in MASSIMINI's group in Milan, have now successfully implemented the Hill-Tononi (2005) model in NEST, i.e. The Neural Simulation Tool that is used within the HBP's HPAC Platform.

This work, which was completed in March 2017, required the original Synthesis code to be ported to NEST, while also correcting some errors in the previous version, and making necessary adjustments and tuning. The current NEST version of the model includes all the needed synaptic and cellular elements from the original Hill-Tononi model (and some errors in previous have now been corrected), and key part of the results of the original paper have been replicated, although some further tuning is needed.

This first implementation of the Hill-Tononi model in NEST is an important milestone, as it provides a basis for our work in T3.4.2 and for HBP collaborations, since NEST is widely used within the HBP by SP6 and HBP's HPAC Platform, and future simulations of states of consciousness.



Since the NEST version of the Hill-Tononi model is much faster than the original Synthesis version, and the NEST version can be run on larger, faster computers (supercomputers), it opens the door for more rapid progress in further developing and using the model. In further steps, we will expand the model to simulate the dynamics of several cortical columns/areas, and duplicate these to simulate two “hemispheres” etc.

In particular, in relation to this Component, the model will be developed to include electrical resonance at the cellular level, in order to simulate and study the effects of frequency-dependence and resonance-dependent functional connectivity. In collaboration with MASSIMINI’s group, the model will also be used to simulate cortical lesions and bistable dynamics.

### Quality Control

#### *Upstream Components:*

- (important) - NEST Support for Modellers
- (important) - NEST - The Neural Simulation Tool

#### **5.7.3.2 TMS/EEG-PCI in wakefulness, sleep and anaesthesia**

Description: Model frequency-dependence and resonance-dependent functional connectivity and its impact on integration, differentiation and PCI values. (CDP 5 contribution)

Progress on Component:

Please see the progress described for the component above: Frequency-dependence and resonance-dependent functional connectivity. The same applies here, for this Component:

This first implementation of the Hill-Tononi model in NEST provides the basis for nearly all our future work in T3.4.2.

### Quality Control

#### *Upstream Components:*

- (important) - NEST Support for Modellers
- (important) - NEST - The Neural Simulation Tool

#### *Downstream Components:*

- (important) - Structure-function in healthy subjects

#### **5.7.3.3 Large-scale modelling of TMS/EEG-PCI**

Description: Model how PCI depends on network properties using large-scale modelling of TMS/EEG-PCI in NEST.

Progress on Component:

Please see the progress described for the component above: Frequency-dependence and resonance-dependent functional connectivity. The same applies here, for this Component:

This first implementation of the Hill-Tononi model in NEST provides the basis for nearly all our work in T3.4.2 in the future.

### Quality Control

#### *Upstream Components:*

- (important) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2
- (important) - SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations
- (important) - NEST Support for Modellers



- (essential) - NEST - The Neural Simulation Tool

*Downstream Components:*

- (important) - Simulation of brain lesion and cortical bistability on complexity
- (important) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2
- (important) - SP12-SGA1 Philosophy briefing report 1
- (important) - SP12-SGA1 Philosophy briefing report 2

## 5.8 T3.4.3 Loss and Recovery of Consciousness Pathophysiological Insights

### 5.8.1 Key Personnel

Task Leader: Marcello MASSIMINI (UMIL, University of Milan)

### 5.8.2 SGA1 DoA Goals

This Task aims to study the effects of cortical lesions on the complexity of cortical interactions as assessed by the perturbational Complexity Index (PCI) and on sensory event-related potentials (ERPs). Through human experiments on brain-injured patients and large-scale simulation of the thalamocortical system we will test whether and how structural lesions (ranging from focal to diffuse sparing only cortical islands) may drive the rest of the brain into a state of low-complexity and/or sensory disconnection. The first aim is to explore the relationships - and the possible dissociations - between behavioural responsiveness (as assessed by behavioral scales), sensory-motor connectedness to the external environment (as assessed by ERPs) and the brain's capacity for consciousness (as quantified by PCI). The second aim is to understand the mechanisms by which structural lesions may drive the rest of the cortex into a disconnected and/or low complexity state (a reappraisal of the classic notion of diaschisis).

### 5.8.3 Components Progress

#### 5.8.3.1 TMS/EEG non-invasive perturbation recordings (data)

Description: Non-invasive TMS-EEG recordings in patients affected by focal cortical and sub-cortical level lesions (strokes) and traumatic brain injuries. To characterise the impact of structural lesions at different levels on brain reactivity, connectivity and complexity.

Progress on component:

We published an article "Stratification of unresponsive patients by an independently validated index of brain complexity" in collaboration with T3.4.4 (LAUREYS). Here, a cohort of 81 patients (43 in a vegetative state; VS and 38 in a minimally conscious state MCS) was analysed and stratified by means of a PCI cut-off derived from a previous validation on a benchmark of 150 subjects who could confirm the presence or absence of consciousness through subjective reports. This cut-off resulted in a sensitivity of 94.7% in detecting MCS (outperforming current existing metrics). Most important, this approach revealed three possible TMS-EEG patterns in clinically VS patients; when directly perturbed, the patients' cerebral cortex may: (i) fail to engage in any significant response; (ii) engage in a low-complexity response similar to the one observed in NREM sleep and anaesthesia unconsciousness; (iii) engage in a complex spatiotemporal dynamics similar to the one observed in conscious awake or dreaming subjects. Notably, TMS-EEG allowed identifying a number of behaviourally unresponsive VS patients (9 out of 43) with high values of PCI, overlapping with the distribution of the benchmark conscious condition. This subgroup of VS patients may retain a capacity for consciousness that is not expressed in behaviour. Overall, this stratification (no-response, low-complexity, and high-complexity) represents a first step



towards a pathophysiological reframing of unresponsive patients by means of perturbational complexity measures.

Following up on this result we are working on an article titled "Sleep-cortical bistability disrupts brain complexity in vegetative state patients". In this study, conducted in collaboration with T3.4.4 (LAUREYS), by means of TMS/EEG we investigate the role of bistable dynamics in producing low-complexity responses to TMS in a group of 16 brain-injured, VS patients. Results show that low-complexity responses are associated with the presence of a sleep-like slow wave in response to TMS that is underpinned by the occurrence of high frequency (>20 Hz) suppression (the extracranial marker of cortical downstates). Importantly, the occurrence of such sleep-like phenomenon is temporally associated with the time at which PCI ceases to grow. This observation points toward a targetable neurophysiological mechanism (sleep-like bistability) for the recovery of consciousness, will be complemented by structural analysis, by the analysis of ERPs (to be delivered at M24) and that will inform models of cortical function after brain injury.

In a separate series of preliminary experiments, we assessed the effects of focal lesions on the overall complexity and have performed TMS-EEG experiments in 18 fully conscious patients who are affected by focal cortical lesions (stroke). Preliminary results, show that in these patients, PCI is high, except when TMS is delivered directly on the peri-lesional area. In this case, TMS elicits a local sleep-like, low-complexity response, suggesting that bistability may play a role in disabling part of the cortex also after stroke and that local changes in cortical reactivity may affect the emergence of large-scale, global complex responses. We also performed the same TMS-EEG experiments on 16 stroke patients with subcortical lesions. In this case PCI attained high values across all the stimulated sites, regardless of whether the stimulation was performed over the healthy or the affected hemisphere, thus further confirming the specific role of cortical lesions in determining such changes.

### Quality Control

#### *Upstream Components:*

- (important) - Combined optogenetic, two-photon imaging and electrophysiological recordings from cerebellar neurons (release at M24)
- (essential) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 (release at M24)

#### *Downstream Components:*

- (added value) - The TMS/EEG-PCI and P3b response for assessment of consciousness - We have provided training on TMS/EEG experiments and data analysis procedures (release at M24).
- (essential) - TMS-EEG data in sleep and anesthesia - (release at M18)
- (essential) - TMS-EEG data in DOC patients - Provided nothing (release at M18)
- (essential) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 (release at M24)
- (essential) - Structure-function in DOC patients
- (essential) - Structure-function in healthy subjects

### 5.8.3.2 Simulation of brain lesion and cortical bistability on complexity (model)

Description: In a large-scale model of the thalamocortical system we will explore through simulations the possibility that: cortical lesions may induce bistable dynamics in the surrounding areas and through these dynamics impair cortical connectivity and complexity.

Progress on Component:



In order to simulate cortical lesions and bistable dynamics we adopted the thalamocortical model proposed by Hill & Tononi (Hill, Tononi *Journal of Neurophysiology* 2005). We target to expand this model to several cortical columns. After several discussions with our HBP partners we agreed that NEST would be the appropriate simulation ambient to perform these simulations. This requires porting the original Synthesis code to NEST and recently all the needed synaptic and cellular elements have been incorporated in the simulator. Thanks to the collaboration with J. STORM's group and the constant effort of H. PLESSER, part of the results of the original paper have been replicated. As a further step, we will expand the model to simulate the dynamics of several cortical columns.

### Quality Control

#### *Upstream Components:*

- (important) - Visual analysis tools (release at M18)
- (important) - NEST - The Neural Simulation Tool (release at M24)
- (important) - Combined optogenetic, two-photon imaging and electrophysiological recordings from cerebellar neurons (release at M24)
- (important) - Cerebellum application model (release at M18)
- (important) - Large-scale modelling of TMS/EEG-PCI (release at M12, M24)
- (important) - NEST Support for Modellers (release at M12, M24)
- (important) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 (release at M24)

#### *Downstream Components:*

- (important) - NEST Requirements Management (release at M12, M21)
- (important) - Cerebellum application model (release at M18)
- (important) - Simplified model of local field potentials
- (important) - Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states, T3.2.5 SP3 SGA1 (release at M12, M24, M36)
- (important) - Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 (release at M24)

### 5.8.3.3 SOP on Informed Consent (report)

Description: SOP providing guidance to researchers working with humans on principles of informed consent.

#### Progress on Component:

In the first 12 months of SGA1, we performed differential actions in order to warrant a full compliance of the Task experimental activity with the HBP requirements. Specifically: 1) we updated the ethical documentation in order to explicitly state that EEG and TMS/EEG data acquisition is funded by HBP; 2) we updated the ethical documentation in order to allow study participants to exercise the "right of not to know"; 3) we received the certification by the ethical committee of the University of Milan concerning the full compliance of the experimental activities to the European Guidelines for personal data protection. The local ethical committees of the Hospital San Gerardo in Monza and Hospital Sacco in Milan, where the recordings are taking place, have officially approved these updates. At present, we are waiting for the approval by these two ethical committees for the amendment concerning encrypting procedures of personal data and to the change of the recruiting procedure when the study participant wants to exert the "right of not to know".



## 5.9 T3.4.4 Develop and Compare Methods for Assessing Consciousness (Anaesthesia, Sleep, DOC)

### 5.9.1 Key Personnel

Task Leader: Steven LAUREYS (ULG, University of Liege)

### 5.9.2 SGA1 DoA Goals

This Task aims to develop methods for assessing consciousness in humans by 1) testing novel “PCI-like” indices of network integration and complexity based on sensory auditory or peripheral nerve stimulation; 2) Testing these methods in general anaesthesia, sleep and disorders of consciousness (DOC); 3) Comparing PCI, global P3b and brain connectivity measures in patients with DOC; 4) Investigating structure-function interactions using multimodal modelling of source reconstructed TMS/hd-EEG recordings and MRI diffusion tensor imaging (DTI) tractography in healthy subjects and DOC patients.

### 5.9.3 Components Progress

#### 5.9.3.1 Structure-function in healthy subjects (report)

Description: Scientific publication on structure-function interactions mapping the modulations of the information flow (DTF) following TMS to the underlying structural connectome assessed by MRI in healthy subjects.

Progress on Component:

We published an article entitled “Tracking dynamic interactions between structural and functional connectivity: a TMS/EEG-dMRI study” in the journal *Brain Connectivity* 2017 Mar; 7(2):84-97 by Amico E, Bodart O, Rosanova M, Gosseries O, Heine L, Van Mierlo P, Martial C, Massimini M, Marinazzo D, Laureys S.

See <https://www.ncbi.nlm.nih.gov/pubmed/28092972>.

#### Quality Control

*Upstream Components:*

- (important) - Elephant
- (important) - Visual analysis tools
- (important) - TMS/EEG-PCI in wakefulness, sleep and anaesthesia
- (essential) - TMS/EEG non-invasive perturbation recordings
- (essential) - EEG data in sleep and anaesthesia
- (essential) - TMS-EEG data in sleep and anaesthesia

*Downstream Components*

- (important) - MIP - DATA > Reference Data
- (important) - SP12-SGA1 Philosophy briefing report 1
- (important) - SP12-SGA1 Philosophy briefing report 2

#### 5.9.3.2 Structure-function in DOC patients (report)

Description: Scientific publication on structure-function interactions using multimodal modelling of source reconstructed TMS-EEG recordings and MRI diffusion tensor imaging (DTI) tractography in DOC patients.

Progress on Component:

We are working on an article entitled “Structural and effective connectivity in patients with chronic disorders of consciousness” by Bodart O, Amico E, Wannez S, Heine L, Thibaut A,



Annen J, Gomez F, Casarotto S, Rosanova M, Casali A, Gosseries O, Laureys S, Massimini M. In this study, we demonstrated that structure supports effective connectivity in brain-injured patients. Increased structural damage level decrease effective connectivity, which prevents the emergence of consciousness. This may be the first step in unveiling the role of specific structural-effective networks in the emergence and loss of consciousness.

### Quality Control

#### *Upstream Components:*

- (important) - Elephant
- (important) - Visual analysis tools
- (essential) - The TMS/EEG-PCI and P3b response for assessment of consciousness
- (essential) - TMS/EEG non-invasive perturbation recordings
- (essential) - EEG data in DOC patients
- (essential) - TMS-EEG data in DOC patients

#### *Downstream Components:*

- (important) - MIP - DATA > Reference Data
- (important) - SP12-SGA1 Philosophy briefing report 1
- (important) - SP12-SGA1 Philosophy briefing report 2

### 5.9.3.3 TMS-EEG data in sleep and anaesthesia (data)

Description: acquisition of TMS-EEG data in healthy subjects during sleep and general anaesthesia.

#### Progress on Component:

We are collecting TMS-EEG data in healthy volunteers during Dexmedetomidine (an agonist of  $\alpha_2$ -adrenergic receptors) infusion using neuronavigated TMS stimulator and EEG. We target the superior frontal and parietal lobule. We record four conditions: baseline, light sedation, deep sedation (loss of consciousness), and recovery of consciousness. Dexmedetomidine infusion rate is set-up automatically using a mathematical model to achieve the target plasmatic concentration. Blood samples are obtained to analyse and compare these putative concentrations with the real plasmatic level. Preliminary analyses are currently being performed.

### Quality Control

#### *Upstream Components:*

- (essential) - TMS/EEG non-invasive perturbation recordings

#### *Downstream Components:*

- (important) - Archive data repositories
- (essential) - Structure-function in healthy subjects
- (added value) - The TMS/EEG-PCI and P3b response for assessment of consciousness
- (important) - SP12-SGA1 Philosophy briefing report 2
- (important) - SP12-SGA1 Philosophy briefing report 1
- (essential) - Databases



#### 5.9.3.4 EEG data in sleep and anesthesia (data)

Description: acquisition of EEG and ERP data in healthy subjects during sleep and general anaesthesia.

Progress on component:

We are collecting resting state EEG data in healthy volunteers during Dexmedetomidine infusion. Five minutes recording are obtained in four conditions: awareness (baseline), light sedation, loss of consciousness and recovery of awareness (see TMS-EEG data in sleep and anaesthesia for more info).

#### Quality Control

*Downstream Components:*

- (important) - Archive data repositories
- (essential) - The TMS/EEG-PCI and P3b response for assessment of consciousness
- (essential) - Structure-function in healthy subjects
- (important) - SP12-SGA1 Philosophy briefing report 2
- (essential) - Databases

#### 5.9.3.5 EEG data in DOC patients (data)

Description: acquisition of EEG and ERP data in patients with disorders of consciousness.

Progress on Component:

We are collecting 30 minutes of resting state EEG data in patients with unresponsive wakefulness syndrome, minimally conscious state and emergence of minimally conscious state. In a subset of these patients (the ones in whom we can perform TMS-EEG, see below), we are also recording event related potentials (ERPs) with an auditory oddball paradigm (to measure auditory PCI). Preliminary analyses are being performed.

#### Quality Control

*Downstream Components:*

- (important) - Archive data repositories
- (essential) - The TMS/EEG-PCI and P3b response for assessment of consciousness
- (essential) - Structure-function in DOC patients
- (important) - SP12-SGA1 Philosophy briefing report 1
- (important) - SP12-SGA1 Philosophy briefing report 2
- (important) - DATA > Hospital Data
- (essential) - Databases

#### 5.9.3.6 TMS-EEG data in DOC patients (data)

Description: acquisition of TMS-EEG data in patients with severe brain injury and disorders of consciousness (i.e., vegetative state/unresponsive wakefulness syndrome, minimally conscious state).

Progress on Component:

We are collecting TMS-EEG data in patients with disorders of consciousness. We however had to exclude more than half of the patients enrolled at our hospital because of active epilepsy, craniectomy, or medical instability. Preliminary analyses are being performed including comparison with the auditory ERPs.



## Quality Control

### *Upstream Components:*

- (essential) - TMS/EEG non-invasive perturbation recordings

### *Downstream Components:*

- (important) - Archive data repositories
- (essential) - Investigating cortical bistability in vegetative patients with TMS-EEG recordings
- (essential) - The TMS/EEG-PCI and P3b response for assessment of consciousness
- (essential) - Structure-function in DOC patients
- (important) - SP12-SGA1 Philosophy briefing report 1
- (important) - SP12-SGA1 Philosophy briefing report 2
- (important) - DATA > Reference Data > TBI (Traumatic Brain Injury)
- (important) - DATA > Hospital Data
- (essential) - Databases

## 5.10 T3.4.5 Test Consciousness Theories in Wada Test

### 5.10.1 *Key Personnel*

Task Leader: Johan STORM (UIO, Universitetet i Oslo)

### 5.10.2 *SGA1 DoA Goals*

The goal of T3.4.5 is to test predictions from theories of consciousness using Wada tests. We shall test two leading theories of neural substrates of consciousness, while transiently anaesthetising one hemisphere (Wada test) in neurosurgery patients. Thus, we will for the first time use this paradigm to test two leading EEG-based methods for assessing consciousness: (1) TMS/EEG-PCI, and (2) Global P3b.

### 5.10.3 *Components Progress*

#### 5.10.3.1 *The TMS/EEG-PCI and P3b response for assessment of consciousness*

Description: Scientific publication on a test of two leading EEG-based methods for assessing consciousness.

#### Progress on Component:

As already reported in M6, we have employed a PhD student from August 2016, and are now establishing and developing the necessary experimental methods in humans (navigated TMS, high density EEG, etc.) for this Task, thus making progress towards MS3.4.3 (M24). In M1-M6 we already obtained some human EEG data and received data from M. MASSIMINI's group that we started analysing and obtained promising preliminary results.

In M7-12, WP3.4 scientist and students in Oslo (mainly PhD student Bjørn E. JUEL, and PhD student Andre S. NILSEN, with assistance from two psychology master students and others in the Oslo group), have further prepared for the Wada test experiments and methods development in several ways.

They have tested and improved the navigated TMS (nTMS) combined with high density EEG (hdEEG) methods and obtained more human nTMS-hdEEG data for PCI measurements, as well as spontaneous high-density EEG data for connectivity measures, from humans (healthy volunteers) under various conditions. The conditions include normal wake, sleep deprived, and different forms of anaesthesia: general anaesthesia with propofol, and partial



anaesthesia with low doses of ketamine. Many of these experiments and analyses were done in collaboration with the EEG expert Dr. Pål G. LARSSON (connectivity analysis), and the anaesthesiologist Dr. Luis ROMUNSTAD (for anaesthesia), both at Oslo University Hospital. Importantly, we have also been in close contact with M. MASSIMINI's group (Milan) who has provided expert help with the nTMS-hdEEG method for PCI measurements. Thus, Drs. Silvia CASAROTTO and Matteo FECCHIO from Milan came to Oslo in January 2017 and gave expert help with the nTMS-hdEEG /PCI methods.

In parallel, we have recently developed and tested a novel method for classifying states of consciousness in humans, based on connectivity analysis. This method has been developed and tested on clinical anaesthesia data by LARSSON, JUEL and others in the Oslo group, and has yielded promising results for propofol anaesthesia: more than 98% accuracy in classification of conscious vs. unconscious state, and the method is faster than the PCI method, requiring only a few seconds for each data point, and may thus be well suited for continuous monitoring of consciousness during anaesthesia, although further testing under other conditions are needed. A paper (Juel et al.) is revised and under review in *Clinical Neurophysiology*.

The Oslo group has also received nTMS-hdEEG /PCI data from MASSIMINI's group that we are currently analysing and already obtained promising preliminary results. In this study, we compare two methods for assessing consciousness during anaesthesia and other conditions: the PCI method developed by MASSIMINI's group, which has already been thoroughly tested (Casali et al. 2013; Casarotto et al. 2016), and our recently developed method based on connectivity analysis in Oslo. So far, the results from these two methods in classifying states of consciousness seem to correlate well, which is promising. Based on this, we plan a publication on the testing and comparison of these two EEG-based methods for assessing consciousness (Juel et al., ms. In preparation). We are also in the process of establishing the EEG/ERP-based P3b method using auditory local/global oddball paradigms (Beckenstein et al.), and will compare also this to PCI as planned, but this has been delayed by our work on the connectivity-based method.

All this work, while yielding different types of data as described above, also serve as preparation for our planned tests of consciousness theories and methods during Wada tests, which is a very interesting long-term goal, but also very challenging and requires that the methods are perfected beforehand in terms of data quality, safety, speed, and well-drilled personnel. Now, in March 2017, we are finally applying for ethical permission, based on all this experience from the past year, for performing our first experimental measurements in patients undergoing the Wada test.

### Quality Control

#### *Upstream Components:*

- (essential) - EEG data in sleep and anaesthesia
- (essential) - EEG data in DOC patients
- (essential) - TMS-EEG data in DOC patients
- (added value) - TMS-EEG data in sleep and anaesthesia
- (added value) - TMS/EEG non-invasive perturbation recordings

#### *Downstream Components:*

- (essential) - Structure-function in DOC patients



## 6. WP3.5 Scientific Coordination, Project Management and Communication

### 6.1 Key Personnel

Work Package Leader: Cyriel PENNARTZ (Universiteit van Amsterdam, UvA)

Task Leader (T3.5.1): Cyriel PENNARTZ, (Universiteit van Amsterdam, UvA)

Task Leader (T3.5.2): Johan STORM (UIO, Universitetet i Oslo)

Task Leader (T3.5.3): Cyriel PENNARTZ, (Universiteit van Amsterdam, UvA)

### 6.2 WP Leader's Overview

On 6 June 2016, an SP3 Project Manager, and on 1 September 2016 an Assistant Coordinator were accepted and appointed and are supporting the SP3 Coordinator Cyriel PENNARTZ in his leader tasks. Monthly SP3 VCs took place and strengthened the collaboration within SP3, as well as CDPs and WP-internal face-to-face (physical) meeting and ad-hoc meetings. Two SP3 face-to-face meetings took place and were open to invited speakers and other researchers; one during the Open Day at the Summit in Florence, 12 October 2016, and the second meeting took place in Amsterdam, 30 November and 1 December 2016. Besides meetings and regular email between the SP3 project office in Amsterdam and SP3 members, an SP3 WhatsApp group is successfully used for urgent requests. We coordinated Subproject reporting (semester report, periodic report) and writing of Deliverables. Dr. Wim GHIJSEN and Dr. Olivia GOSSERIES, ethical rapporteurs, coordinated ethical issues with the Ethics Rapporteur and with SP12. The internal SP3 project office at the UvA (Prof. Dr. Cyriel PENNARTZ, Katharina MÜLLER and Dr. Ingar SEEMANN) provided support to partners on issues related to administration, innovation; and acted as a point of contact with the HBP Project Coordination Office. So far, the feedback has been positive and permit to state that project coordination is going well.

### 6.3 Impact of work done

UvA has co-organised a Consciousness workshop; this workshop, held at the European Institute for Theoretical Neuroscience (EITN) in Paris is the first in a series on consciousness, and investigated the topic at different scales and approaches (EITN, Paris, France, 9-10 March 2017). A Lecture by Steven LAUREYS on Coma and altered states of consciousness was held at the University of Amsterdam (ABC lecture series, University of Amsterdam, Amsterdam, 13 December 2016). Steven LAUREYS presented on the vast body of research on altered states of consciousness collected in the last 15 years and its clinical applications. The University of Liege offered an Introductory hands-on Nilearn Workshop for engineers and other methods for people including PhD students and post-doctoral researchers. Neuroimaging datasets are constantly growing in sample size, resolution, and complexity. There is also an increasing interest in data-driven analysis methods. Nilearn is a scientific computing package in Python designed to address the aforementioned challenges in contemporary data analysis in imaging neuroscience. This workshop provided state-of-the-art machine-learning methods for convenient pre-processing, analysis, and visualisation of various types of neuroimaging results (i.e., experimental fMRI, VBM, and resting -state correlations).

Also, Steven LAUREYS organised a Coma Recovery Scale-Revised Workshop (Liege, 13-14 February 2017) to help assessors using the CRS-R in clinical practice. Theoretical background about consciousness was introduced and detailed theoretical and practical information about this scale was provided. In addition, UvA organised an international workshop on Neuronal Ensemble function in collaboration with the EBPS (European Behavioural Pharmacology Society) and the National Institute on Drug Abuse (NIDA), held in Amsterdam (September



2016). We prepared one more workshop and one large conference (with J. STORM). Further impact of the work in WP3.5 lies in (i) promotion of publicity of SP3 activities via websites, flyers, arranging interviews and generating media attention; (ii) the facilitation of scientific and ethical work within SP3, through contributing to the overall progress of SP3 and its collaboration with other HBP partners, and with partners outside HBP core (e.g. FLAGERA-NET, non-HBP participants in meeting). We have successfully achieved MS 3.5.1 (Report on potential Ethics issues in SP3, Innovation Plan and Plan for engaging the community).

## **6.4 Priorities for the remainder of the phase**

MS3.5.2 SP3 roadmap for SGA2 and MS3.5.3 Report on engagement with Ethics issues in SP3, outcome of commercialisation discussions and outcome.



## 6.5 Milestones

Table 5: Milestones for WP3.5. - Scientific Coordination, Project Management and Communication

MS No.	Milestone Name	Leader	Task(s) involved	Expected Month	Achieved Month	Comments
MS3.5.1	Report on potential Ethics issues in SP3, Innovation Plan and Plan for engaging the community	UvA		M06	M09	
MS3.5.2	SP3 roadmap for SGA2	UvA		M13		Not finished yet
MS3.5.3	Report on engagement with Ethics issues in SP3, outcome of commercialisation discussions and outcome	UvA		M24		Not achieved yet



## **6.6 T3.5.1 Subproject Coordination and Management, Communication, Ethics and Innovation (Resource Allocation and Use, Quality Control, Performance and Risk Management, Internal Review and Reporting)**

### **6.6.1 Key Personnel**

Task Leader: Cyriel PENNARTZ (Universiteit van Amsterdam, UvA)

### **6.6.2 SGA1 DoA Goals**

The goals of Task 3.5.1 are to coordinate Subproject reporting and writing of Deliverables; monitor scientific progress within the Subproject; organise SP-wide meetings; coordinate with the External Relations Team on issues related to innovation; coordinate with the Ethics Rapporteur and with SP12 on issues related to ethics; provide support to partners on issues related to administration, innovation and ethics; and, act as a point of contact with the HBP Project Coordination Office.

### **6.6.3 Component Progress**

#### **6.6.3.1 Subproject Coordination and Management, Communication, Ethics and Innovation**

Description: Coordinate Subproject reporting and writing of Deliverables; monitor scientific progress within the Subproject; organise SP-wide meetings; organise one SIB meeting; coordinate with the External Relations Team on issues related to innovation; coordinate with the Ethics Rapporteur and with SP12 on issues related to ethics; provide support to partners on issues related to administration, innovation and ethics; and act as a point of contact with the HBP Project Coordination Office.

Progress on Component:

Monthly SP3 VC and two SP3 face-to-face meetings were held; one in Florence at the HBP Summit, 12-15 October 2016 and another one in Amsterdam, 30 November and 1 December 2016. We successfully submitted a semester report and Deliverable M12, as well as Milestones reports. Successful participation at the STOA exhibition at the European Parliament, 29 November 2016. Several organised workshops and participation in workshops.

## **6.7 T3.5.2 - Management, Communication, Innovation, Preparation of Grants and Report Documents**

### **6.7.1 Key Personnel**

Task Leader: Johan STORM (UIO - Universitetet i Oslo)

Other Researcher: Iars MUCKLI (UGLA - University of Glasgow)

Other Researcher: Pier Stanislao PAOLUCCI (INFN - Istituto Nazionale di Fisica Nucleare)

### **6.7.2 SGA1 DoA Goals**

The goals of T3.5.2 are to co-lead Subproject reporting and writing of Deliverables; co-monitor scientific progress within the Subproject; coordinate on issues related to innovation and ethics; and co-organise SP-wide meetings, dissemination, outreach and industry events outreach and industry events.



### 6.7.3 Component Progress

#### 6.7.3.1 Management, Communication, Innovation, Preparation of grants and report documents

Description: Co-lead Subproject reporting and writing of Deliverables; co-monitor scientific progress within the Subproject; coordinate on issues related to innovation and ethics; co-organise SP-wide meetings, dissemination, outreach and industry events outreach and industry events.

CDP to which Component contributes (if relevant): No CDP contribution

Progress on Component:

Each of the WP leaders appointed an administrative representative to support the WP Leader in his co-leadership of SP3. These admin. representatives work in close collaboration with the Project Manager of SP3 and together they coordinated the booth at the Science Market at the 2016 HBP Summit, and organised SP3-wide meetings, including:

- the 2016 HBP Summit SP3-based meeting in Florence, 12-5 October 2016
- the SP3-based meeting in Amsterdam in November/December 2016.
- the HBP-based (SP3, SP5, SP6, SP12) workshop on consciousness at the European Institute for Theoretical Neuroscience in Paris, from 9-10 March 2017.

These administrative representatives also participated and helped organising several other dissemination events.

## 6.8 T3.5.3 - Communication and Innovation

### 6.8.1 Key Personnel

Task Leader: Cyriel PENNARTZ (Universiteit van Amsterdam, UvA)

### 6.8.2 SGA1 DoA Goals

Task 3.5.3 is responsible for supporting community activities in SP3. Such activities include dissemination, outreach, organising community workshops and industry events.

### 6.8.3 Component Progress

#### 6.8.3.1 Report on Ethics issues in SP3

Description: Report on Ethics issues in SP3, Innovation Plan and Plan for engaging the community

CDP to which Component contributes (if relevant): No CDP contribution

Progress on Component:

Participation in Ethical Committees:

- Member of the Belgian Advisory Committee on Bioethics (S. LAUREYS, ULG)
- Member of the "Società Italiana di Neuroetica" (M. MASSIMINI, UMIL)
- Member of the Institutional Board of Animal Welfare of the University of Amsterdam. (W. GHIJSEN, UvA)

#### 6.8.3.2 Participation in Workshops and Meetings:

- Presentation entitled: *Functional neuroimaging in patients with disorders of consciousness: What to care about?* Day on Ethics of Neuroscience and Neuroscience of Ethics, Aix-Marseille University, France, 20 May, 2016. (A. DEMERTZI, ULG)



- Attended an ethical workshop in the LUMINOUS meeting on Studying, Measuring and Altering Consciousness, Barcelona, Spain, October 2016. (O. GOSSERIES, ULG)
- Presentation entitled: *Neuroethical implications of clinician's attitudes toward the locked-in syndrome*, ICREA Conference on Personhood and the LIS, Barcelona, Spain, 18 November 2016. (A. DEMERTZI, ULG)
- Presentation entitled: *Situation de fin de vie chez les patients EVC-EPR: Quelles particularités?*, EVC-EPR 201- L'ETHIQUE, Paris, France, February 2017. (A. DEMERTZI, ULG)
- Attendance by PhD student of a course organised by EMBO on the research integrity in science, Milan, Italy, 23 February 2017 (lab of M. MASSIMINI, UMIL)
- Presentation at UNISTEM DAY 2017, involving seven European countries to make people aware about the risks of massive and fake scientific news, 17 March 2017. (M. MASSIMINI, UMIL))
- Attended the annual Workshop on Research, Ethics & Society organised by the Board for Ethics and Scientific Integrity of the ULG, 23 March 2017. (O. GOSSERIES, ULG)

#### 6.8.3.3 Giving Courses/Organising symposia:

- Symposium (chair): "Consciousness-meters" for assessing levels of consciousness: from research, to clinics and ethics, 20th ASSC, Buenos Aires, Argentina, June 2016. (A. Demertzi, ULG)
- Hosted the HBP Ethics Advisory Board-Ethical Management-Ethical Rapporteurs meeting by The Bristol Robotics Laboratory (UWE) 28-29 March 2016. (A. Winfield M. Pearson, UWE)



## 7. WP3.6 SP3 Contributions to Co-Design Projects and Infrastructure

### 7.1 Key Personnel

Work Package Leader: Cyriel PENNARTZ (Universiteit van Amsterdam, UvA)

Task Leader (T3.6.1): Lars MUCKLI (University of Glasgow, UGLA)

Task Leader (T3.6.2): Pier Stanislao PAOLUCCI (Istituto Nazionale di Fisica Nucleare, INFN)

Task Leader (T3.6.3): Cyriel PENNARTZ, (Universiteit van Amsterdam, UvA)

Task Leader (T3.6.4): Johan STORM (Universitetet I Oslo, UIO)

### 7.2 WP Leader's Overview

Setting up modelling and computer simulation components in relation to data gathered in other Tasks of SP3, and in relation to (mainly) CDP4 and CDP5, proceeded largely according to plan. In T3.6.1, MUCKLI, KRIEGESKORTE, WIBRAL and associates developed context-sensitive computational models of vision, including deep-learning networks. In T3.6.2, PAOLUCCI and MATTIA added synaptic plasticity as a key component to large-scale simulations of a corticothalamic model of slow-wave activity (SWA), which is also an explicit research aim of CDP5. Amongst others, this model will be made available in the NEST format. In T3.6.3, PENNARTZ and DORA (in collaboration with S. BOHTE, CWI, and W. SENN, SP4) developed a multi-layer firing-rate based, scalable network for predictive coding in a single modality (vision). T3.6.4 developed NEST-based computational models for simulation of neuromodulation and plasticity effects on different brain states (sleep/waking, conscious/unconscious). These SP3 teams have been interacting with other SP members, notably those involved in CDP4 and CDP5 (including e.g. R. GOEBEL, W. SENN, W. MAASS, H.E. PLESSER, K. MEIER).

Due to the delayed availability of HBP funding, recruitment of personnel went slower than anticipated. For instance, several labs were only able to appoint postdocs and PhD students engaging in CDP support activities by the fall of 2016.

### 7.3 Impact of work done

This work has been initiated very recently and therefore its final impact cannot be estimated at this time. However, preliminary work and results have been presented at various HBP-based and local meetings, including: (i) several meetings with HBP members participating in CDP4 and CDP5, and SP4; (ii) a first workshop on Theory and Research on Consciousness, featuring both HBP and non-HBP speakers and participants; (iii) SP3-based meeting in Florence, preceding the HBP Summit meeting, and various talks and poster contributions to the HBP Summit itself (October 2016); (iv) CDP5 workshops at EITN (Paris; with DESTEXHE) and at Fürberg (Austria, with W. MAASS). Further meetings relevant to the topics of study are being planned, such as the first, HBP-based, open conference on Neural Mechanisms of Consciousness (planned for Spring 2018) and a main SFN Symposium on Consciousness at SFN's Annual Meeting in Washington DC (Autumn 2017; with chairperson and speakers from SP3). Finally, SP3 (Muckli group, Glasgow) will host the next HBP summit meeting in Autumn 2017. The work obviously meets positive reactions and is expected to have significant impact through future publications and conferences. Furthermore, follow-up of this crucial, cross-SP activity is foreseen for SGA2.

### 7.4 Priorities for the remainder of the phase

Our first priority is to make up for the time lost during the initial (non-funded) phase of SGA1. Second, we prioritise collaboration between the current WP3.6 projects and other



projects contributing to CDPs, particularly CDP4 and CDP5. Third, we aim to design models produced in WP3.6 such that they can be integrated easily later on (SGA2) into a more comprehensive cognitive architecture, which will be used to control robot (“Mammalbot”) behaviour. Fourth, by upscaling simulations, we will be able to contribute to the development and use of Platforms supporting modelling (mainly SP6, SP7 and SP10 - NEST models, HPAC Platform, robotics). Finally, promoting the biological plausibility of the models, and hence their comparison to neurobiological data, is a priority.



## 7.5 Milestones

Table 6: Milestones for WP3.6. - SP3 Contributions to the Development of the Infrastructure and CDPs of HBP

MS No.	Milestone Name	Leader	Task(s) involved	Expected Month	Achieved Month	Comments
MS3.6.1	Finalisation of Project implementation proposal for WP3.6	UvA		M01	M01	The milestone "Finalisation of Project implementation proposal" has been discussed and concordantly agreed on during a SP3 VC on 4 May 2016.
MS3.6.2	Performance of initial data analyses, tool development, initial simulations	UvA		M12		Not achieved yet, foreseen date M14
MS3.6.3	Validation of data analyses, tools, network simulation models, test cases	UvA		M24	--	Not achieved yet



## 7.6 T3.6.1 Large-scale Network Modelling of Multiscale, Multispecies Data to Model Prediction Error

### 7.6.1 Key Personnel

Task Leader: Lars MUCKLI (University of Glasgow, UGLA)

Task Contributor: Michael WIBRAL (Johann Wolfgang Goethe Universität Frankfurt, UFRA)

### 7.6.2 SGA1 DoA Goals

- 1) We will investigate the role of prediction error processing during mismatch between feedforward and feedback signalling in mouse and humans. Specifically, we will model error signals when top-down projections do not match feedforward input using a NEST network model. We will record layer-specific fMRI data during a motion-induced blindness illusion. Top-down motion processes mask early visual cortex so that feedforward information flow is interrupted and top-down projections replace the feedforward stream. When motion-induced blindness ends, the feedforward signal breaks through again - described as prediction error. The neuronal differentiation between match and non-match stimuli is a challenge worthwhile to model in NEST simulation.
- 2) Mouse data will provide examples of multisensory contextual mismatch data. Information content of neuronal processing and network models of learning and visual motor integration will be compared. These Tasks will include modelling and theoretical analysis of experimental data acquired in animal electrophysiology and human brain imaging, and incorporate integrative work across different partners. For instance, models of cortical disamplification of feedforward processing will be tested for masking and enhancing interactions. Other examples will include multisensory integration and visuomotor integration. This goal involves large-scale network modelling in CDP4 and will accordingly contribute to Platform development & use (mainly SP7).

### 7.6.3 Component Progress:

#### 7.6.3.1 NEST/NRP eye movement simulation (DoA Goal 1)

Description of Component: We will develop a model of saliency-guided eye movements using the NEST Neural Network Simulation Tool and Neural Robotics Platform. The model can be continuously improved by comparing with recorded behavioural and neuroimaging data.

CDP Contributions: CDP4

Progress: The MUCKLI Lab has also begun contributions with experimental designs for a Motion Induced Blindness illusory paradigm, allowing for the examination of dissociated conscious perception and physical stimulation. In a previous 3T fMRI study, primary visual cortex (V1) activity was masked during motion-induced blindness, indicating that feedforward information is interrupted or overruled by top-down information. Using high-field fMRI at 7 Tesla we are investigating the V1 layer-specific information profile. We have collected one pilot dataset (3 sessions) and have produced preliminary results, which have been accepted to the 2017 Organization for Human Brain Mapping international conference (to be presented in June). We are currently planning to collect a full dataset using this experiment to be collected in the next reporting period.

### Quality Control

#### Upstream Components:

- SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations - *Available*
- NEST Support for Modellers - *Available*



- SP2 - Computational architecture of the functional organisation in visual and auditory processing streams in human and macaque monkey - *No delivery*
- NRP software packages - *Available*
- NEST - The Neural Simulation Tool - *Available*

*Downstream Components:*

- None

### 7.6.3.2 Information Theoretic Network Model of Layer 5 Pyramidal Cells (DoA Goal 2)

Description of Component: CDP4 Recurrent multilayer neural network on the NEST platform, with local, information theoretic learning rules and Kay-Phillips types of neurons with two distinct types of synapses - modulatory and driving.

CDP Contributions: CDP4 & CDP5

**Progress:** The WIBRAL lab has ported its TRENTOOL toolbox to python/OpenCL to align with the HBP infrastructure. The resulting new toolbox (IDTxI) has been released under an open source license on github and will be added to the HBP software catalogue. We have produced a manuscript (submitted and available on bioRxiv, Brodski et al.) showing that task-related changes in active information storage are detectable in human MEG data in task-specific brain areas, and that they are related to internal models.

We plan to analyse the following datasets with the toolbox during the next period:

- 1) Data from layer 5 pyramidal neurons from the LARKUM lab (T3.1.4).
- 2) A large dataset of intracortical recordings from macaque monkeys performing a visual working memory task (from the lab of Charles GRAY, U Montana). This dataset provides >150 simultaneously recorded channels covering a whole cortical hemisphere.

These analyses of task dependence of information storage and transfer in this are currently running on the supercomputer LOEWE-CSC in Frankfurt.

### Quality Control

*Upstream Components:*

- Single-compartmental models of cortical cells, including non-linear IF models and GLM - *available*
- Plasticity: Two-compartment neuron - *no delivery*
- Multi compartmental reconstructed cortical cells: their input-output transfer properties - *no delivery*
- NEST - The Neural Simulation Tool - *Available*
- T3.1.4 Dendritic mechanisms of feedback - *Received dataset of L5 neuronal recordings*

*Downstream Components:*

- T3.1.1 Model representational-space RDMs - *no delivery*

## 7.7 T3.6.2 SP3 Contributions to the Development of the Infrastructure and CDPs of HBP: WaveScales

### 7.7.1 Key Personnel

Task Leader: Pier Stanislao Paolucci (INFN)

Task Co-leader: Maurizio Mattia (ISS)



### 7.7.2 SGA1 DoA Goals

This Task will add synaptic plasticity to the simulations expressing Slow Wave Activity (SWA) developed by WP3.2 WaveScalES. The goal is to understand the interactions between SWA and synaptic plasticity during deep sleep. We will observe: (i) the differences between simulations of SWA with or without plasticity, and (ii) the effect of different plasticity models. Critical points are: a) the implementation of local synaptic plasticity, b) the control of the substantial increase of computational cost and c) the evaluation of the stability properties of the rhythmic multiscale activity patterns generated by the cortico-thalamic system with plastic synapses. This will also contribute to: (i) beta testing of inclusion of synaptic plasticity in large scale networks of point-like spiking neurons and configuration of low TRL features offered by the Platforms, and (ii) exploitation of parallel programming methodologies and HPC platforms. The Task contributes to CDP5, dedicated to synaptic plasticity.

### 7.7.3 Component Progress

#### 7.7.3.1 SP3 - Synaptic plasticity in Slow Wave Activity simulations as specified by CDP5 (model)

CDPs involved: CDP5

Description of component (from PLA):

In the framework of SGA1 CDP5, this cComponent adds synaptic plasticity to one of the key products of the SP3 WaveScalES WP: the large scale simulation of a cortico-thalamic system expressing SWA, modelled by a network of point-like spiking neurons. The model of synaptic plasticity will be selected according to the theoretical output of CDP5 partners. The model will be available both in the NEST simulation format and in the proprietary DPSNN format.

Progress on Component:

This Component has three releases planned during SGA1

- M1 - SGA1 - proposal of synaptic plasticity modelling for slow wave simulations as specified by CDP5.
- M12 - SGA1 - definition of synaptic plasticity models for slow wave simulations as specified by CDP5.
- M24 - SGA1 - Implementation in the simulator of synaptic plasticity models for slow wave simulations as specified by CDP5

M1 release: the proposal of synaptic plasticity modelling for slow wave simulations, planned for release at M1, has been presented and discussed during M2-SGA1 at the Paris, 12-13 May 2016 joint CDP5, SP4 and SP9 joint kick-off meeting by Maurizio MATTIA (Task Co-Leader), and discussed with CDP5 key-persons (Walter SENN, Wolfgang MAASS) and during several conference calls following the meeting.

A key cooperation event contributing to the progress of this task has been the Fuerberg CDP5 meeting (3-6 October 2016) "From experimental data on structure and plasticity to models and network function" attended by Pier Stanislaw PAOLUCCI (Task Leader), where all the Tasks participating to the plasticity theme had an opportunity for ample discussion of the individual approaches to the problem under investigation.

M12 release: a document defining the synaptic plasticity models for slow wave simulations to be implemented is under finalisation during M12. This document defines the target of the simulation model to be released at M24. In extreme synthesis, we will start from the simulation code released at M12 by the "Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states" Component of T3.2.5 (see the corresponding section of this document for details). The synaptic matrix of the above model will be modified to create a landscape with minima corresponding to memories



and during simulation of local deep sleep oscillations, the simulator will be improved to accommodate mechanisms for: 1) synaptic homeostasis, and 2) strengthening mechanism of the synaptic matrix storing the memories. A critical point will be the stability of the rhythms expressed by the simulator, notwithstanding the modification of the synaptic matrix.

### Quality Control

#### *Upstream Components:*

- NEST Support for Modellers (produced by T7.5.5-SGA1) - (release of documentation planned at M12).
- Rule- and data-based connectivity generation in NEST (produced by T7.1.4)- (release of prototype of the upstream component planned at M24, however the cooperation with the NEST development team already demonstrated an efficient start during the first 12 months in the framework of T3.2.5 that produces the starting point for the development of the simulation model here described)
- SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations essential] - (also this release is planned at M24, however see point above about the cooperation framework with the NEST development team)

#### *Downstream Components:*

- NEST Requirements Management - (Preliminary requirements report for SGA2 planning, schedule at M12). A set of requirements for WaveScaleS simulations has been discussed with the NEST development team during several presentations, in person meeting, mail exchanges and phone calls).
- T3.5.2 (1) Cortical spiking model of the interplay between sleep and plasticity (SGA2) This is a Component foreseen to start in SGA2 to continue the activity of the Component here described.

## **7.8 T3.6.3 SP3 Contributions to the Development of the Infrastructure and CDPs of HBP: SP3-CDP&I Episcense**

### **7.8.1 Key Personnel**

Task Leader: Cyriel PENNARTZ (UvA)

### **7.8.2 DoA Goal(s)**

The goal of T3.6.3 is to develop a multi-layer computational model illustrating the integration of multisensory information in the brain and to link this model to the memory system of the medial temporal lobe. This Task also includes analysis of the features learned by the higher layers in the network, the comparison to neurobiological and other modelling data and implementation of a NEST model.

The first sub-goal of this Task is to develop a scalable, deep, firing-rate based multi-layer computational model for processing of visual information. An important focus of this sub-goal would be to utilise only biologically plausible learning mechanisms for learning.

Subsequently, this model will be extended to process information from multiple modalities simultaneously. The purpose of developing this model is to show how the brain could achieve a unified abstract representation by utilising information perceived by multiple modalities, and how information in one modality can help recall information in a second modality.

The next significant step in this Task is to move towards a more biologically plausible framework of spiking neural networks, including a NEST implementation. In this step, the aim is to convert the firing-rate based model into a model that uses spikes for propagating information within the network.



To sum up, T3.6.3 will develop a framework for development of biologically plausible deep multi-layer networks that can be used to model the processes related to sensory information processing in the brain. The framework will be suitable for modelling processing of information from a single modality as well as integration of information from multiple modalities, and for comparison with data from neurobiological experiments, related computational models and robotic data, as well as other results from CDP5.

### **7.8.3 PLA Components**

#### **7.8.3.1 Modelling of network-level mechanisms from T3.6.3a**

Description: Computational modelling mimicking and integrating of experimental findings from T3.6.3a in a biologically realistic model of spiking neurons; to be followed up by HPC simulations, neuromorphic implementation and emulation in robotics.

#### **7.8.3.2 Analysis of network-level mechanisms constraining the in vivo implementation of learning rules and implementing integration, encoding and recall of multisensory memories**

Description: Augmenting the development of large-scale learning systems through experimental data analysis and modelling.

#### **7.8.3.3 CDP(5) Contributions:**

The computational model developed in this Task is used for analysis/comparison with the neurobiological data. The model provides a framework for studying various biological phenomena like hippocampal replay, etc.

### **7.8.4 Progress on components**

A multi-layer deep firing-rate based computational model has been developed for processing information received from a single modality. The model extends the existing predictive coding mechanisms by creating a systematic framework for development of scalable computational models. Further analyses of the characteristics of the input modality that are learned by the model is being conducted.

A prospective extension of adding lateral connections for episodic memory to the model is being discussed with Dr. Walter SENN (SP4).

## **7.9 T3.6.4 - SP3 Contributions to the Development of the Infrastructure and CDPs of HBP: SP3-CDP&I ConsciousBrain**

### **7.9.1 Key Personnel**

Task Leader: Johan STORM (UIO - Universitetet i Oslo)

### **7.9.2 SGA1 DoA Goals**

The goals of this Task are to develop tools for, and analyse suitable test cases of, network-level mechanisms of neuromodulation and plasticity involved in modulating consciousness in relation to cortical functional connectivity, integration, differentiation, and modulation of cortico-thalamic arousal levels and states. Including developing improved tools for implementing neuromodulated plasticity in large-scale network simulations, in NEST (SP6) and other simulators.

(a) Simulating roles of neuromodulation in setting the stage for large-scale connectivity/integration, and differentiation needed for conscious processing;

(b) Simulating roles of synaptic and other neural plasticity in permitting such connectivity, integration, and differentiation;

(c) Simulating interactions between neuromodulation.



### 7.9.3 Component Progress

#### 7.9.3.1 SP3-T3.6.4-SGA1-Analysis of neuromodulation and plasticity mechanisms

Description: Analyse test cases of simulated mechanisms of neuromodulation and neural plasticity involved in regulation of cortical functional connectivity, integration, differentiation, and cortico-thalamic arousal, and consciousness.

CDP to which Component contributes: CDP5 - Plasticity, Learning and Development: Modelling the Dynamic Brain

Progress on Component:

The Component progress here is much the same as described above under T3.4.2 - Multilevel computational modelling, since all of these components involve the development of infrastructure in the form of NEST-based computational models that are used for simulation of brain dynamics and mechanisms under various conditions, including neuromodulation and plasticity, conscious and unconscious brain states, wake and sleep, oscillations, TMS, etc.

Thus, the analysis of test cases of simulated mechanisms of neuromodulation and neural plasticity involved in regulation of cortical functional connectivity, integration, differentiation, and cortico-thalamic arousal, and consciousness, will come later, after the required version(s) of model is/are fully established and tested.

Therefore, the same progress report is repeated here as described above under T3.4.2 - Multilevel computational modelling, with small modifications in relation to this Component:

As already reported in M6, we have started collaboration with Dr. Hans Eckehart PLESSER in SP6 and received from him access to the GitHub repository for the Hill-Tononi model from 2005 (developed by Sean HILL, the previous leader of SP5; S. Hill and G. Tononi *Journal of Neurophysiology* 2005). From July 2016, we employed a post-doc (Ricardo MURPHY) on T 3.4.2.

In M7-12, WP3.4 scientist in Oslo (PhD student Andre S. NILSEN, postdoc Ricardo MURPHY, and PhD student Bjørn E. JUEL) in collaboration with the NEST expert Prof. Hans Eckehart PLESSER in SP6 (NMBU, Oslo), and postdoc Thierry NIEUS in MASSIMINI's group in Milan, have now successfully implemented the Hill-Tononi (2005) model in NEST, i.e. The Neural Simulation Tool that is used within HBP's HPAC Platform.

This work, which was completed in March 2017, required the original Synthesis code to be ported to NEST, while also correcting some errors in the previous version, and making necessary adjustments and tuning. The current NEST version of the model includes all the needed synaptic and cellular elements from the original Hill-Tononi model (and some errors in previous have now been corrected), and key part of the results of the original paper have been replicated, although some further tuning is needed.

This first implementation of the Hill-Tononi model in NEST is an important milestone, as it provides a basis for our work in T3.4.2 and for HBP collaborations, since NEST is widely used within HBP by SP6 and HBP's HPAC Platform, and future simulations of states of consciousness.

Since the NEST version of the Hill-Tononi model is much faster than the original Synthesis version, and the NEST version can be run on larger, faster computers (supercomputers), it opens the door for more rapid progress in further developing and using the model. In further steps, we will expand the model to simulate the dynamics of several cortical columns/areas, and duplicate these to simulate two "hemispheres" etc.

In particular, in relation to this Component, the model will be developed to include be used to for analysis of test cases of simulated mechanisms of neuromodulation and neural plasticity involved in regulation of cortical functional connectivity, integration, differentiation, and cortico-thalamic arousal, and consciousness.

#### Quality Control

*Upstream Components:*

- (important) - SP3-T3.6.4-SGA1-Neuromodulation and plasticity mechanisms

**7.9.3.2 SP3-T3.6.4-SGA1-Neuromodulation and plasticity mechanisms**

Description: Develop tools for simulating (using NEST and other simulators) mechanisms of neuromodulation and plasticity involved in regulation of cortical functional connectivity, integration, differentiation, and cortico-thalamic arousal states and consciousness

CDP to which Component contributes: CDP5 - Plasticity, Learning and Development: Modelling the Dynamic Brain

*Progress on Component:*

The Component progress here is much the same as described above, under 5.3.1, and under T3.4.2 - Multilevel computational modelling, since all of these components involve the development of infrastructure in the form of NEST-based computational models that are used for simulation of brain dynamics and mechanisms under various conditions, including neuromodulation and plasticity, conscious and unconscious brain states, wake and sleep, oscillations, TMS, etc.

Thus, the analysis of test cases of simulated mechanisms of neuromodulation and neural plasticity involved in regulation of cortical functional connectivity, integration, differentiation, and cortico-thalamic arousal, and consciousness, will come later, after the required version(s) of model is/are fully established and tested.

Therefore, please see the progress report above (5.3.1).

In particular, in relation to this Component, the model will be developed to be included and used to for analysis of neuromodulation and plasticity mechanisms.

**Quality Control***Upstream Components:*

- (important) - NEST Support for Modellers
- (essential) - NEST - The Neural Simulation Tool

*Downstream Components:*

- (important) - SP3-T3.6.4-SGA1-Analysis of neuromodulation and plasticity mechanisms



## 8. Publications

Table 7: List of publications

Author(s)	Title	Publication type	Number, date or frequency	Title of the periodical or series	Task involved	Relevant pages
Capone C, Mattia M	Speed hysteresis and noise shaping of traveling fronts in neural fields: role of local circuitry and nonlocal connectivity.	Article in Scientific Journal	7 (2017)	Scientific Reports	T3.2.1	39611
Rovira X, Trapero A, Pittolo S, Zussy C, Faucherre A, Jopling C, Giraldo J, Pin JP, Gorostiza P, Goudet C, Llebaria A	OptoGluNAM4.1, a Photoswitchable Allosteric Antagonist for Real-Time Control of mGlu4 Receptor Activity	Article in Scientific Journal	2016	Cell Chemical Biology	T3.2.2	23(8):929-34
Izquierdo-Serra M, Bautista-Barrufet A, Trapero A, Garrido-Charles A, Díaz-Tahoces A, Camarero N, Pittolo S, Valbuena S, Pérez-Jiménez A, Gay M, García-Moll A, Rodríguez-Eschrch C, Lerma J, de la Villa P, Fernández E, Pericàs MA, Llebaria A, Gorostiza P	Optical control of endogenous receptors and cellular excitability using targeted covalent photoswitches.	Article in Scientific Journal	2016	Nature Communications	T3.2.2	7:12221.
Gómez-Santacana X, Pittolo S, Rovira X, Lopez M, Zussy C, Dalton JA, Faucherre A, Jopling C, Pin JP, Ciruela F, Goudet C, Giraldo J, Gorostiza P, Llebaria A	Illuminating Phenylazopyridines To Photoswitch Metabotropic Glutamate	Article in Scientific Journal	25(3), 2017	ACS Central Science	T3.2.2	81-91



	Receptors: From the Flask to the Animals					
Nashaat M, Oraby H, Peña LB, Dominiak S, Larkum M, Sachdev R	Pixying behavior: a versatile real-time and post-hoc automated optical tracking method for freely moving and head fixed animals	Article in Scientific Journal	2017	eNeuro	T3.1.4	pii:ENEURO.0245-16.2017
Amico E, Bodart O, Rosanova M, Gosseries O, Heine L, Van Mierlo P, Martial M, Massimini M, Marinazzo D, Laureys S.	Tracking dynamic interactions between structural and functional connectivity: a TMS/EEG-dMRI study.	Article in Scientific Journal	2017	Brain Connectivity	T3.4.4/T3.4.3	in press
Casarotto S, Comanducci A, Rosanova M, Sarasso S, Fecchio M, Napolitani M, Pigorini A, G Casali A, Trimarchi PD, Boly M, Gosseries O, Bodart O, Curto F, Landi C, Mariotti M, Devalle G, Laureys S, Tononi G, Massimini M.	Stratification of unresponsive patients by an independently validated index of brain complexity.	Article in Scientific Journal	2016	Annals of Neurology	T3.4.4/T3.4.3	80(5):718-729
Bodart O, Gosseries O, Wannez S, Thibaut A, Annen J, Boly M, Rosanova M, Casali A.G, Casarotto S, Tononi G, Massimini M, Laureys S.	Measures of metabolism and complexity in the brain of patients with disorders of consciousness.	Article in Scientific Journal	2017	Neuroimage: Clinical	T3.4.4/T3.4.3	in press



Lansink CS, Meijer GT, Lankelma JV, Vinck MA, Jackson JC, Pennartz CM	Reward Expectancy Strengthens CA1 Theta and Beta Band Synchronization and Hippocampal-Ventral Striatal Coupling	Article in Scientific Journal	2016	Journal of Neuroscience	T.3.3.3	36(41), 10610. 10598-
Montijn JS, Meijer GT, Lansink CS, Pennartz CM	Population-level neural codes are robust to single-neuron variability from a multidimensional coding perspective.	Article in Scientific Journal	2016	Cell Reports	T.3.3.3	16(9), 2486-2498
Montijn JS, Olcese, U, Pennartz CM	Visual Stimulus Detection Correlates with the Consistency of Temporal Sequences within Stereotyped Events of V1 Neuronal Population Activity.	Article in Scientific Journal	2016	Journal of Neuroscience	T.3.3.3	36(33), 8624-8640.
Olcese U, Bos JJ, Vinck M, Lankelma JV, van Mourik-Donga LB, Schlumm F, Pennartz CM	Spike-based functional connectivity in cerebral cortex and hippocampus: loss of global connectivity is coupled to preservation of local connectivity during non-rem sleep	Article in Scientific Journal	2016	Journal of Neuroscience	T.3.3.3	36(29), 7676-7692.



Bos JJ, Vinck M, van Mourik-Donga LA, Jackson JC, Witter MP, Pennartz CMA	Perirhinal firing patterns are sustained across large spatial segments of an animal's environment	Article in Scientific Journal	2017	Nature Communications	T.3.3.3	in press
Takahashi N, Oertner TG, Hegemann P, Larkum ME	Active cortical dendrites modulate perception.	Article in Scientific Journal	2016	Science	T3.1.4	354(6319):1587-1590.
Zolnik TA, Sha F, Jochenning FW, Schreiter ER, Looger LL, Larkum ME, Sachdev RN	All-optical functional synaptic connectivity mapping in acute brain slices using the calcium integrator CaMPARI.	Article in Scientific Journal	2017	Journal of Physiology	T3.1.4	595(5):1465-1477
Petro LS, Paton AT, Muckli L	Contextual modulation of primary visual cortex by auditory signals.	Article in Scientific Journal	2017	Philos Trans R Soc Lond B Biol Sci.	T3.1.5	372(1714)
Petro LS, Muckli L	The laminar integration of sensory inputs with feedback signals in human cortex.	Article in Scientific Journal	2016	Brain and Cognition	T3.1.5	pii: S0278-2626(16)30114-2
Self MW, Mookhoek A, Tjalma N, Roelfsema PR	Contextual effects on perceived contrast: figure-ground assignment and orientation contrast	Article in Scientific Journal	2015	Journal of Vision	T3.1.2	15(2):2, 1-21



Lorteije JAM, Zylberberg A, Ouellette BG, De Zeeuw, CI, Sigman M, Roelfsema PR	The formation of hierarchical decisions in the visual cortex	Article in Scientific Journal	2015	Neuron	T3.1.2	87, 1344-1356
Roelfsema PR, de Lange FP	Early visual cortex as a multi-scale cognitive blackboard	Article in Scientific Journal	2016	Annual Review of Vision Science	T3.1.2	2, 131-151.
Jeurissen D, Self MW, Roelfsema PR	Serial grouping of 2D-image regions with object-based attention in humans	Article in Scientific Journal	2016	eLife	T3.1.2	5, e14320
Poort J, Self MW, van Vugt B, Malkki H, Roelfsema PR	Texture segregation causes early figure enhancement and later ground suppression in areas V1 and V4 of visual cortex	Article in Scientific Journal	2016	Cerebral Cortex	T3.1.2	26, 3964-3976
Self MW, Peters JC, Pospel JK, Reithler J, Goebel R, Ris P, Jeurissen D, Reddy L, Claus S, Baayen H, Roelfsema PR	The effects of context and attention on spiking activity in human early visual cortex.	Article in Scientific Journal	2016	PLoS Biology	T3.1.2	14 (3), e1002420
Christophel TB, Klink PC, Spitzer B, Roelfsema PR, Haynes J-D	The distributed nature of working memory.	Article in Scientific Journal	2017	Trends in Cognitive Sciences	T3.1.2	21, 111-124
Self MW, Roelfsema PR	Paying attention to the cortical layers.	Article in Scientific Journal	2017	Neuron	T3.1.2	93, 9-11



van Kerkoerle T, Self MW, Roelfsema PR	Layer specificity in the effects of attention and working memory on neuronal activity in primary visual cortex.	Article in Scientific Journal	2017	Nature Communications	T3.1.2	8:13804
--	---	-------------------------------	------	-----------------------	--------	---------



## 9. Dissemination

In the first year of SGA1, SP3 members have already succeeded in publishing HBP-related and HBP-sponsored research in many journals, including high-ranking ones such as *Science* and *Nature Communications*. Furthermore, several outreach events and meetings together with other SPs were organised: (i) several meetings with HBP members participating in CDP4 and CDP5, and SP4; (ii) an outreach event on Neural Ensemble activity, in collaboration with the European Brain and Pharmacology Society (EBPS) and the National Institute on Drug Abuse (NIDA), drawing about 100 participants; (iii) a first workshop on Theory and Research on Consciousness, featuring both HBP and non-HBP speakers and participants; (iv) SP3 made important contributions to several HBP-based public events, such as STOA (Brussels, November 2016) and the HBP Open Day at the HBP Summit in Florence (talks by MASSIMINI, MATTIA, PAOLUCCI). Furthermore, SP3 has been engaged in preparing further Open Events such as a first, HBP-based, open conference on Neural Mechanisms of Consciousness (planned for Spring 2018) and strongly contributes to a main SFN Symposium on Consciousness at SFN's Annual Meeting in Washington DC (Autumn 2017; with chairperson and speakers from SP3). Finally, SP3 (MUCKLI group, Glasgow) will host the next HBP summit meeting in Autumn 2017. Finally, SP3 invested a significant amount of its energy in developing connections with SPs 1-10. Meetings have solidified connections for SGA2 planning. Below are some highlighted dissemination and outreach events for SP3.

### 9.1 Participation in dissemination and outreach events:

- “20th Annual meeting of the Association for the Scientific Study of Consciousness (ASSC)” held in Buenos Aires, Argentina, 15-18 June 2016. In the context of the symposium titled “Consciousness-meters for assessing levels of consciousness: from research, to clinics and ethics” we presented our data on the stratification of unresponsive patients by means of PCI.
- “What is consciousness?” workshop held at the EITN in Paris, France, 9-10 March 2017. The workshop, organised by K. EVERS, C. PENNARTZ, J. STORM and A. DESTEXHE, aimed to bring together several communities, both within and outside HBP, interested in the biophysical and systems-level mechanisms by which brain circuits generate perception and other manifestations of awareness, as well as in bridging the gap between physiology, systems function, and the contents of subjective experiences. The workshop featured many HBP speakers such as, J-P. CHANGEUX, G. DECO, A. DESTEXHE, K. EVERS, S. LAUREYS, M. MASSIMINI, K. MEIER, C. PENNARTZ, T. PRESCOTT, F. RÖHRBEIN, M-V. SANCHEZ-VIVES, J. STORM.
- Advanced Course titled “Consciousness: From Theory to Practice” held in Novacella, Italy, 17-24 September 2016 and organised by the Neuroscience School of Advanced Studies (NSAS).
- National initiatives aimed at disseminating neuroscience research to high school students.
- “The Science of Consciousness” (TSC) annual meeting held in Tucson, Arizona, USA, 25-30 April 2016. Poster title: “Comparing Potential Objective Measures of Human Consciousness: the Perturbational Complexity Index and the Directed Transfer Function” (Bjørn E. JUEL, Thomas R. BREMNES).

### 9.2 Organisation of dissemination and outreach events:

- During 2016-April 2017 we organised six HBP-related public lectures on consciousness in our Forum for Consciousness Research in Oslo, chaired by J.F. STORM, in collaboration with the Norwegian Academy of Science and Letters, the University of Oslo, and the Scandinavian Physiological Society. The lecturers were:



- 8 Feb. 2016: Jean-Pierre CHANGEUX (Paris, and HBP/SP12)
- 21 April 2016: John Dylan HAYNES, Berlin
- 26 August 2016: Steven LAUREYS, Liege and HBP/SP3
- 26 August 2016: Nic. SCHIFF, New York
- 26 August 2016: Marzia DE LUCIA, Lausanne
- 10 October 2016: Rodolfo LLINAS, New York Medical School
- March 16, 2017, Johan F. STORM held a lecture on consciousness and HBP work at the annual psychiatry congress in Oslo (PSYKIATRIVEKA, Radisson Blu Scandinavia Hotel, Oslo)
- Concept of HBP Standard Operating Procedure for Informed Consent by Ethical Management, December 2016. (O. GOSSERIES, ULG, W. GHIJSEN, UvA, J. STORM, UIO)
- “Mathematical Modelling”, consists of an introduction to the computational neuroscience field, to the Python language and to the simulator NEST. During the first part of the course some dissemination about the main objectives of the HBP will also be given to the students. At the end of the course, the students will develop a project on one of the possible subjects proposed during the lessons. The course takes advantage of the interaction with H. PLESSER, who shared some teaching material (slides + Python notebook) with us (course is given by Thierry NIEUS, UMIL)

## 10. Education

On 12th April 2016, at the HBP Young Researcher Education Event in Budapest, Hungary, the keynote lecture “Requirements for a multi-scale simulation of the transition from deep-sleep to awakesness” was delivered by SP3 (PAOLUCCI).

Due to administrative failure, other SP3 members were only contacted by HBP Education Programme in October 2016 during the HBP Summit. Unfortunately, SP3 did not participate in any of the introduced HBP Education Programme activities until now.

## 11. Ethics

### Participation in Ethical Committees:

- Member of the Belgian Advisory Committee on Bioethics (S. LAUREYS, ULG)
- Member of the “Società Italiana di Neuroetica” (M. MASSIMINI, UMIL)
- Member of the Institutional Board of Animal Welfare of the University of Amsterdam. (W. GHIJSEN, UvA)

### Participation in Workshops and Meetings:

- Presentation entitled: *Functional neuroimaging in patients with disorders of consciousness: What to care about?* Day on Ethics of Neuroscience and Neuroscience of Ethics, Aix-Marseille University, France, 20 May 2016,. (A. DEMERTZI, ULG)
- Attended an ethical workshop in the LUMINOUS meeting on Studying, Measuring and Altering Consciousness in Barcelona, Spain, October 2016. (O. GOSSERIES, ULG)
- Presentation entitled: *Neuroethical implications of clinician’s attitudes toward the locked-in syndrome*, ICREA Conference on Personhood and the LIS, Barcelona, Spain, 18 November 2016. (A. DEMERTZI, ULG)
- Presentation entitled: *Situation de fin de vie chez les patients EVC-EPR: Quelles particularités?*, EVC-EPR 201- L’ETHIQUE. Paris, France, February 2017, (A. DEMERTZI, ULG)



- Attendance by PhD student of a course organised by EMBO on the research integrity in science, Milan, Italy, 23 February 2017 (lab of M. MASSIMINI, UMIL)
- Presentation at UNISTEM DAY 2017, involving seven European countries to make people aware about the risks of massive and fake scientific news, 17 March 2017. (M. MASSIMINI, UMIL)
- Attending the annual Workshop on Research, Ethics & Society organised by the Board for Ethics and Scientific Integrity of the ULG, 23 March 2017. (O. GOSSERIES, ULG)

#### **Giving Courses/Organising symposia:**

- Symposium (chair): "Consciousness-meters" for assessing levels of consciousness: from research, to clinics and ethics, 20th ASSC, Buenos Aires, Argentina, June 2016. (A. DEMERTZI, ULG)
- Hosting the HBP Ethics Advisory Board-Ethical Management-Ethical Rapporteurs meeting by The Bristol Robotics Laboratory (UWE), 28-29 March 2016. (A. WINFIELD M. PEARSON, UWE)

#### **Commenting on Ethical documents:**

- Concept of HBP Standard Operating Procedure for Informed Consent by Ethical Management, December 2016. (O. GOSSERIES, ULG, W. GHIJSEN, UvA, J. STORM, UIO)