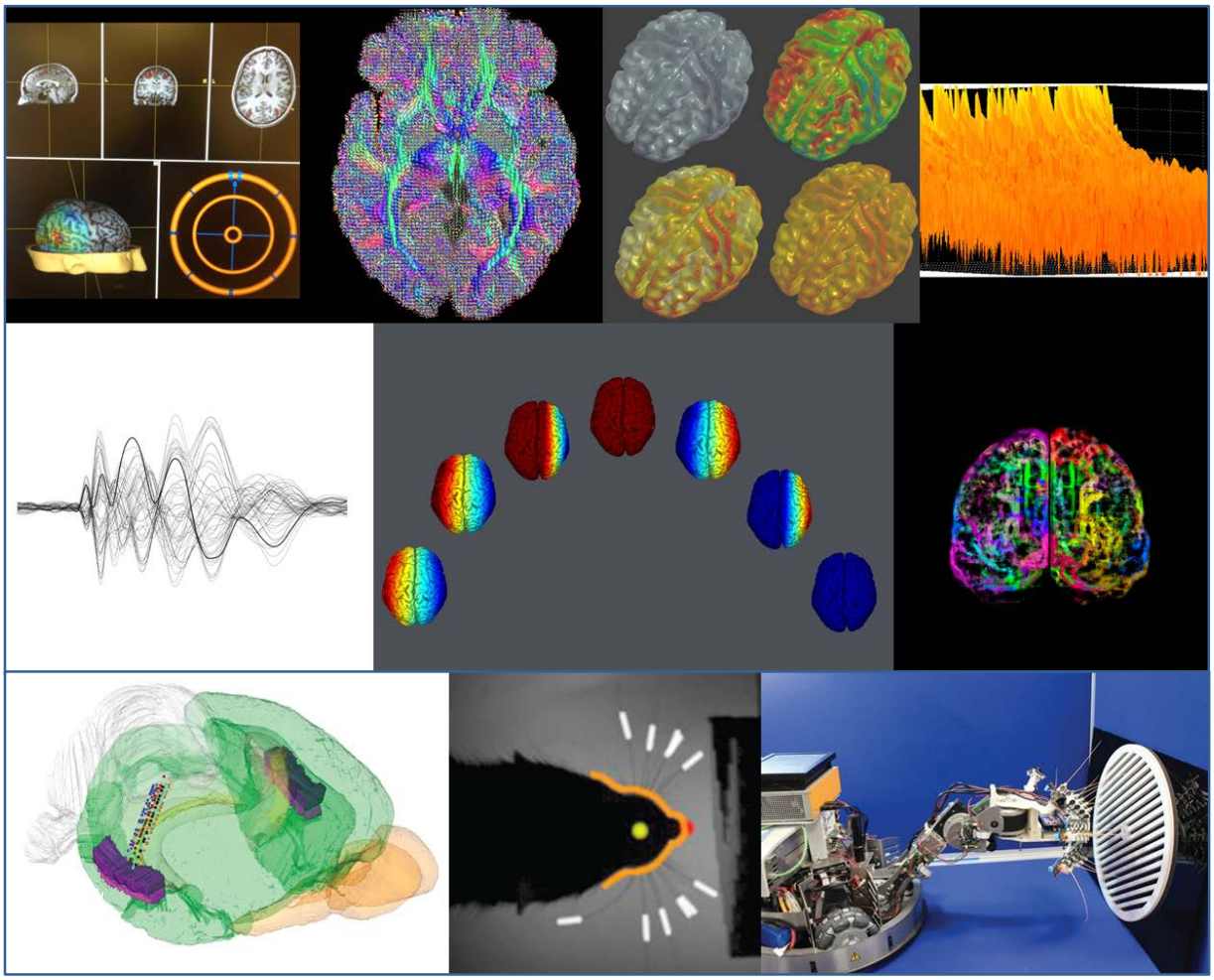
Grant Number:	720270	Grant Title:	Human Brain Project SGA1

Deliverable Title:	D3.5.2 (D17.2 D44) SP3 Systems and Cognitive Neuroscience - Results for SGA1 Period 2
Contractual Number and type:	SGA1 D3.5 2 (D17.2 D44)
Dissemination Level:	PUBLIC
Version / Date:	Submitted date: 24 Apr 2018; ACCEPTED 09 Jul 2018

Abstract:	This deliverable is the annual compound of HBP deliveries and results (outputs and outcomes) from SP3 – Systems and Cognitive Neuroscience. The live complete catalogue of HBP deliveries is accessible online at the HBP portal. The main deliveries from April 2017 to March 2018 are: Research on large-scale neural interactions and development of network models that integrate recurrent information processing in context-sensitive object recognition. Multi-scale exploration of spontaneous and perturbed slow wave activity (SWA) and underlying cortico-cortical interactions, local excitability and adaptation. Recordings in physiologic and pathologic humans and animal models, and cortical slices. Creation of the first chemical for SWA manipulation with light. Multi-scale SWA theoretical models. Design and implementation of innovative, distributed simulation techniques. Study of 7T fMRI pattern completion in episodic memory, the development of a 2D virtual reality system to investigate spatial cells in the hippocampus and recordings in place and grid cells in mice navigating this system. The development of multisensory object recognition tasks for rodents and collection of single unit and LFP recordings, and development of a computational model and associated robots to implement multi-sensory episodic memory. Development of new objective approaches to detect consciousness and unconsciousness in humans (both healthy subjects and brain-injured patients), applications in rodents, and evaluation in a large-scale computational model of thalamocortical networks, capable of transitioning between wake-like and sleep-like states. Investigation of the role of prediction error processing during mismatches between feedforward and feedback signalling, addition of plasticity to large-scale cortical models, training of biological deep neural networks and development of a large multilayer thalamocortical network model running with the neural simulation tool NEST to test and generate predictions about consciousness in humans.

Keywords:	cognition, neuroscience, processes, learning, object recognition, multisensory integration, perception, sleep, consciousness, systems, robotics, computational modelling, experimental, human brain, animal brain, brain state, episodic memory, plasticity



Targeted users/readers	Systems, clinical, molecular & theoretical computational neuroscientists; Parallel/distributed computer scientists; Colleagues in SP1, SP2, SP4, HBP ICT Platforms, SPs. Understanding the physiological and pathological roots of deep sleep has an impact for the general public and the students, as well.
Contributing Work-Package(s):	SGA1 WPs 3.1, 3.2, 3.3, 3.4, 3.6
Initially Planned Delivery Date:	SGA1 M24 / 31 Mar 2018

Authors:	Ingar Seemann, UvA (P98) Yasmin Mzayek, UvA (P98) Lars Muckli, UGLA (P87) Pier Stanislao Paolucci, INFN (P92) Johan Storm, UIO (P81) Cyriel Pennartz, UvA (P98)
Compiling Editors:	Ingar Seemann, UvA (P98) Yasmin Mzayek, UvA (P98)
Contributors:	Johan Storm, UIO (P81) Francesca Cacucci, UCL (P82) Maria V. Sanchez-Vives, IDIBAPS (P93) Pau Gorostiza, IBEC (P95) Emrah Duezel, DZNE (P99) Matthew Larkum, UBER (P90) Pier Stanislao Paolucci, INFN (P92) Maurizio Mattia, ISS (P96) Christiaan Levelt, KNAW (P91) Nikolaus Kriegeskorte, MRC (P88) Marcello Massimini, UMIL (P94) Steven Laureys, ULG (P97) Brigitte Roeder, UHAM (P89) Cyriel Pennartz, UvA (P98) Lars Muckli, UGLA (P87) Tony Prescott, USFD (P100) Martin Pearson, UWE (P101)
SciTechCoord Review:	Science and Tech Coordination (SP11)
Editorial Review:	EPFL (P1): Annemieke Michels

Table of Contents

List of Figures

1. Introduction

The goal of the Systems and Cognitive Neuroscience Subproject (SP3) of the Human Brain Project (HBP) is to uncover neural mechanisms underlying cognitive processes, such as learning, multisensory integration, perception, sleep, consciousness and associated systems phenomena. The results provide the constraints for the development of computational models of cognitive and systems-level processes, which will be implemented in robots and neuromorphic computing systems. SP3 addresses these issues at multiple levels (cells, groups, networks, brain systems) and works to integrate different disciplines.

Research in Context-Sensitive Multisensory Object Recognition involves work spanning multiple levels of systems neuroscience: neuronal signalling, interactions between cortical layers, within cortical columns, between neighbouring areas, and between remote cortical areas. One of our goals was to develop an increasingly sophisticated understanding of large-scale neural interactions and to develop network models that integrate recurrent information processing in context-sensitive object recognition. In the current funding phase, we showed that deep learning model architectures that incorporate bottom-up, lateral and top-down connections develop context sensitivity and recognise objects better in cluttered scenes. Furthermore, we showed that feedback to apical tufts of layer 5 pyramidal neurons is necessary for perception and that superficial layers of visual cortex receive predictive signals in absence of feedforward stimulation.

We also investigated slow-wave activity, (SWA) to reveal the multiscale organisation of cortical networks. The underlying relationships between cortico-cortical interactions, local excitability and adaptation were explored during spontaneous and perturbed activity from the microscale to the macroscale, with measurements in cortical slices, *in vivo* animal models, intracranial recordings in humans (presurgical epilepsy mapping and vegetative state patients). SWA expressed during physiological deep sleep, anaesthesia or in pathological models (Fragile X, Williams-Beuren Syndrome) was studied using techniques like hd-EEG, TMS, SPES, ECoG, microECoG, and photo-stimulation. We created the first compound that allows manipulating SWA with light: PhtalAzoIper (PAI), a light-regulated ligand of muscarinic acetylcholine receptors. Bridging different spatiotemporal scales, we developed theoretical models capable of matching and predicting experimental observations. Aiming at efficient simulations, innovative techniques of distributed computing on thousands of computing cores have been designed and implemented, thus contributing to the definition of key requirements (e.g. for interconnects) of future High Performance Analytics and Computing (HPAC) Platforms.

Brain mechanisms of episodic memory were investigated. Human 7 Tesla fMRI and MR-PET studies on episodic memory and multisensory integration were conducted. A 2D virtual reality system was developed to investigate spatial cells in the hippocampus, recording place and grid cells in mice navigating this system. We developed a visual-tactile object recognition task in rodents, to study the neural correlates of multisensory processing, and made ensemble recordings from four brain areas simultaneously. This work is supporting the ongoing development of a computational model of episodic memory that is modelled on the hippocampal system and the building of a physical robot in order to implement two key aspects of multisensory episodic memory: multisensory integration and spatial memory

Our work on the “Conscious brain” deals with understanding the mechanisms and nature of consciousness, by using theoretically inspired experimental approaches in both humans and animals, in combination with *in silico* models. Specifically, our efforts were focused on the development of new objective approaches to detect consciousness and unconsciousness in humans (both healthy subjects and brain-injured patients). Similar methods have also been tested and applied in rodents. They are evaluated in a large-scale computational model of thalamocortical networks, capable of transitioning between wake-like and sleep-like states.

Finally, the generation of prediction errors got a central role in models of biased competition, and in predictive coding models of cortical processing. We investigated the role of prediction error processing during mismatches between feedforward and feedback signalling and took steps to develop information-theoretical models of such mismatches, using the NEST simulator, thus informing models of visuo-motor integration. Learning is a key element in cognitive neuroscience

and sleep is believed to exert multiple influences on this process through several mechanisms that have to be replicated at the Neuromorphic Robotics Platform. We added plasticity to large-scale cortical models, capable of expressing deep sleep characteristics, developed at different level of abstractions by various team members. This opens the path for a quantitative investigation of the interaction between sleep and memory using the HBP Platforms. We also investigated the training of biological deep predictive coding networks using the idea of predictive coding. The architecture of the network is inspired by the connectivity observed in the cortical sensory areas. The trained model can infer hierarchical representations for a given stimulus. A large multilayer thalamocortical network model with detailed cellular properties, that can transition between wake- and sleep-like activity patterns, is developed for NEST. The model is in preparation for publication on the HBP Collaboratory and github, available for the public, and it is tested for compatibility with the SpiNNaker supercomputer.

2. Results

2.1 Incorporation of feedback and lateral connections in deep neural network models (BLT Networks) for visual recognition.

One of our goals is to develop an increasingly sophisticated understanding of large-scale neural interactions and to develop network models that integrate recurrent information processing in a new realistic theory of context-sensitive object recognition. This development is at multiple scales: neuronal interactions between cortical layers, within cortical columns, between neighbouring areas, and between remote cortical areas.

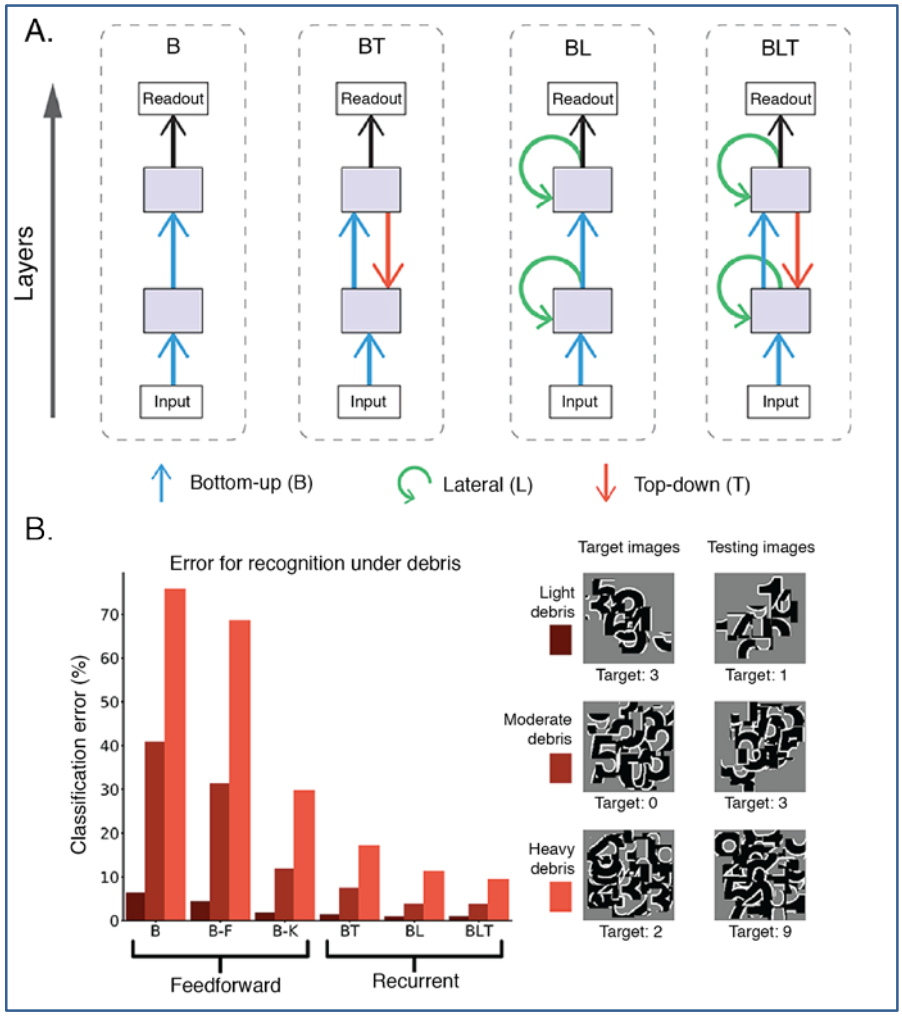


Figure 1: Recurrent convolutional neural networks are better models of biological object recognition.

Schematic diagrams for used architectures. (A) arrows indicate bottom-up (blue), lateral (green), and top-down (red) convolutions. (B) left: classification error for all models on single digit detection under varying levels of debris; right: examples of the images used to train and test the networks.

Deep learning network constraints to human brain imaging

The Kriegeskorte group extended deep learning networks with bottom-up, lateral and feedback connections to include control feedforward models with matched number of parameters (Figure 1). Model efficacy was tested using two novel occluded object recognition tasks (digit clutter, where multiple target digits occlude one another, and digit debris, where target digits are occluded by digit fragments). Recurrent neural networks outperformed feedforward models at

recognising objects, both in the absence of occlusion and in all occlusion conditions. Recurrent networks were also found to be more robust to the inclusion of additive Gaussian noise. Recurrent neural networks are better in two respects: 1) they are more neurobiologically realistic than their feedforward counterparts and 2) they are better in terms of their ability to recognise objects, especially under challenging conditions.

Identifying mouse cortical regions involved in invariant object recognition learning

The LevelIt team developed a two-alternative forced choice behavioural paradigm for head-fixed mice where animals learn to differentiate between two visual stimuli. This task is used in combination with chronic two-photon calcium imaging. With training, neurons in V1 begin to respond in anticipation of visual stimulation and during collection of the reward. Interestingly, there is a decrease in the number of neurons that respond to the visual stimulus. This sparseness of coding is highly task-dependent. The contribution of different cortical interneuron subsets is currently under investigation in the observed phenomena, whose responses are also measured using chronic calcium imaging. Novel software tools were developed to deal with the very large calcium imaging datasets associated with these experiments. These include novel approaches for isolating regions of interest (neurons or neurites showing calcium responses), image alignment and data visualisation.

In order to visualise feedback responses in V1, LevelIt has set up simultaneous calcium imaging of dendritic tufts and deep apical dendrites of layer 5 neurons. Novel data analysis approaches allow identification of dendritic arbors and apical dendrites that belong to the same neurons. Using visual stimulation paradigms that are known to engage feedback connections to V1 in awake, behaving mice, preliminary results show that dendritic tufts respond to stimuli that are not in the receptive field of the neuron and do not elicit somatic responses. This indicates that feedforward and feedback inputs are indeed separable using this approach. Additionally, genetic and chemogenetic approaches alter thalamic function, affecting cortical feedback responses.

Data have been collected using wide field imaging in mice with cortical GCaMP6 expression during a task that requires mice to distinguish between a figure and the background. Optogenetic silencing of V1 has been carried out during the figure-ground segregation task and while measuring the activity of different types of interneurons during the same task. Currently, the lab is also setting up the so-called "crystal skull" method where a large piece of the cranium is replaced by glass so that large regions of the cortex can be imaged at the mesoscopic, but also at the cellular resolution. In addition, new tools map out the retinotopy and receptive field sizes in multiple visual cortical areas of the mouse. We will apply this tool to determine the possible discrepancies between the brain atlases, obtained with wide-field imaging and previous tracing results in mice.

Visual deprivation and recovery- studies with cataract-reversal individuals

The Roeder group has received ethical approval for an amendment to the original ethical approval in order to run 3T and 7T MRI studies in visually impaired individuals and healthy controls. The contract for MRI studies in Maastricht with Scannexus was signed. Scanning protocols and experimental paradigms were piloted in Maastricht and adapted. An optician for a quick production of MRI compatible aids was searched and a contract was negotiated; first aids were produced and piloted. First cataract-reversal patients and controls were scanned.

Dendritic mechanisms of feedback interactions

In the Larkum lab, it was shown that activity in apical tufts of layer 5 pyramidal neurons is necessary for perception (Figure 2). This activity is related to cortical feedback. In experiments combining two-photon imaging, electrophysiology, optogenetics, and behavioural analysis in mice, calcium signals in apical dendrites of pyramidal neurons in the somatosensory cortex controlled the perceptual threshold of the mice's whiskers. Strong reduction of dendritic calcium signalling impaired perceptual detection so that an identical stimulus could no longer be noticed.

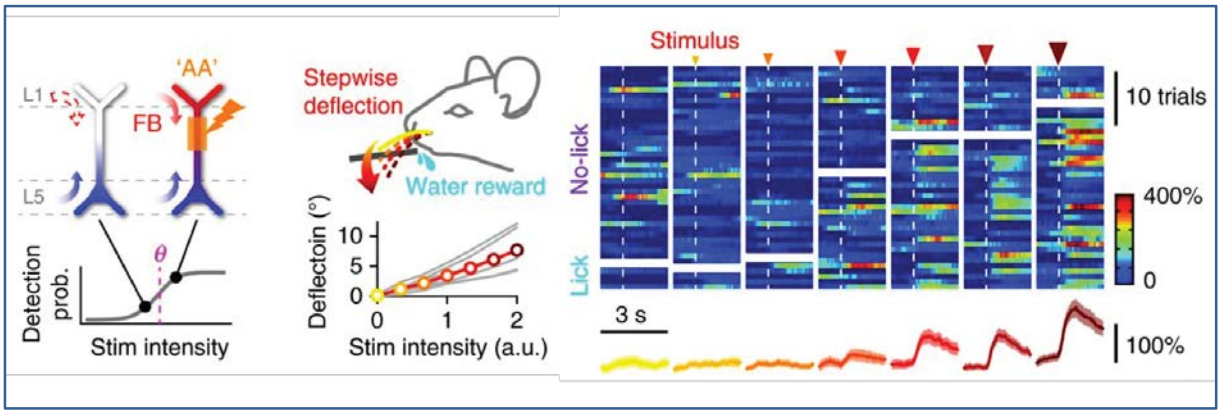


Figure 2: Apical cortical dendrites modulate perception.

Left: apical amplification hypothesis and behavioural task design. Deflection angle of the whisker is proportional to the stimulus intensity. Mean amplitude (colour) plotted with individual data (grey). Right: Ca2+ signals in an apical dendrite during the detection task organised according to increasing stimulus intensity (columns) and trials (rows), separated based on the behavioural response ("lick" or "no-lick") by a blank row. Bottom right: average and SEM of Ca2+ responses for all trials of a given stimulus intensity.

Larkum also showed the relationship between sleep spindles and dendritic activity, and the contribution of dendritic spikes to local field potentials. His team developed a multimodal sensory motor behavioural system called the "Air-track". They developed methods to track animal behaviour in this complex environment and characterised feedback effects on layer 2/3 and 5 pyramidal neurons using a novel calcium indicator.

Context varying amplification of expectation and task specification

Muckli showed that predictive information arrives at superficial layers of early visual cortex. Many experiments have improved our understanding of the feedforward features that modulate early sensory areas, but relatively little is known about the feature space that drives cortical feedback channels. Feedforward input was blocked to subsections of retinotopic visual cortex by occluding one quarter of the visual field while participants viewed 384 real-world scenes and recorded V1 responses using high-resolution 7T fMRI (0.8mm). V1 responses exhibited predictive and contextual response properties, in addition to feedforward orientation and spatial frequency properties typically associated with V1 responses. These predictive and contextual responses were primarily associated with superficial layers of the cortex (Figure 3). Our findings suggest that feedback connections terminating in superficial layers provide V1 neurons with contextual information, not available via localised feedforward input.

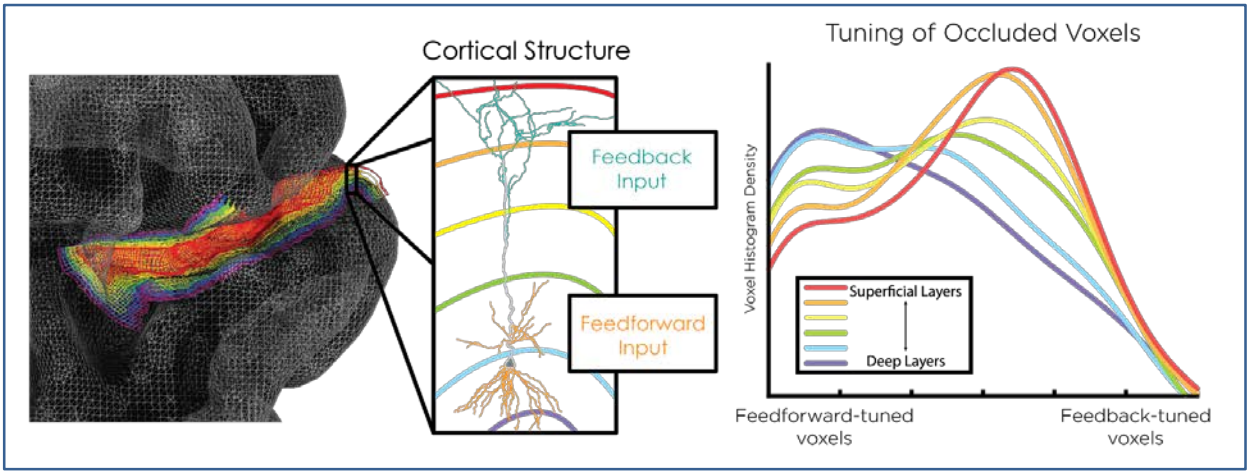


Figure 3: Superficial layers of V1 are tuned to predict missing visual information.

Left: high-resolution fMRI data were used to differentiate tuning properties to feedforward and feedback information sources between different depths in the primary visual cortex. Right: separate voxel tuning histograms for each cortical depth. Tuning was calculated by contrasting the unique information encoding of feedforward models to that of feedback models for each voxel.

2.1.1 Achieved Impact

- Kriegeskorte extended deep learning networks with bottom-up, lateral and feedback connections to include control feedforward models with matched number of parameters, which is now published (Spoerer *et al.,* "Recurrent Convolutional Neural Networks: A Better Model of Biological Object Recognition" doi:10.3389/fpsyg.2017.01551).
- Levelt published a paper, "Thalamic inhibition regulates critical-period plasticity in visual cortex and thalamus" in Nature Neuroscience (Sommeijer *et al*., 2017; doi:10.1038/s41593-017-0002-3), and this work has received feedback from the scientific community in the form of a News & Views article: "The underdog pathway gets a boost." Jeon BB, Kuhlman SJ. Nat Neurosci. (2017; doi: 10.1038/s41593-017-0019-7). He also formed new collaborations with Helmut Kessels (University of Amsterdam), Lars Muckli (University of Glasgow), and Wiesje van der Flier (VU Medical Center, Amsterdam - funded by ZonMW, to study how feedforward/feedback interactions are altered in Alzheimer's Disease).
- Roeder gave keynote addresses at the LV Prasad Eye Institute Eleventh Annual Champalimaud Symposium ("The neural basis of sight recovery after cataract surgery", Hyderabad, India, January 28, 2018), the German Society of Psychology 50th Anniversary Meeting ("Sensitive periods in human neuro-cognitive development", Leipzig, Germany, September 22, 2016), the Leibniz-Lecture ("Sensitive phases in human brain development", Hyderabad, February 3, 2016), and Hertie Stiftung/FAZ Reihe ("Hirnforschung, was kannst du?", Frankfurt, Germany). She also formed new collaborations with Bruno Rossion (Institute of Neuroscience, Université Catholique de Louvain, Belgium) and Jozsef Fiser (Central European University, Budapest, Hungary).
- Larkum published papers in Science (Takahashi *et al.*, 2016, doi:10.1126/science.aah6066), Nature Communications (Suzuki and Larkum, 2017, doi:10.1038/s41467-017-00282-4; Seibt et al., 2017, doi:10.1038/s41467-017-00735-w), the Journal of Physiology (Zolnik *et al.*, 2017, doi:10.1113/JP273116), eNeuro (Nashaat *et al.*, 2017, doi:10.1523/ENEURO.0245-16.2017), and the Journal of Neurophysiology (Nashaat *et al.*, 2016, doi:10.1152/jn.00088.2016). His work has received feedback from the scientific community in the form of a News & Views article: "New recipes with CaMPARI for 'snapshots' of synaptic circuit activity." (Chereau and Hotmaat, doi:10.1113/JP273733). New collaborations within the Human Brain Project include: Karl Heinz Meyer, Lars Muckli, and Martin Pearson. New external collaborations because of published papers, will include Adam Kepecs (Cold Spring Harbor), Lucy Palmer (University of Melbourne), Eric Schreiter (Janelia). Larkum has given many talks on HBP papers in the US, in Europe, and gave lectures during Barrel meetings (Los Angeles, 2016, and Johns Hopkins, 2017).
- Muckli published papers in Neuroimage (Revina *et al.,* "Cortical feedback signals generalise across different spatial frequencies of feedforward inputs." doi: 10.1016/j.neuroimage.2017.09.047), Nature Scientific Reports (Edwards *et al*., "Predictive feedback to V1 dynamically updates with sensory input" doi:10.1038/s41598-017-16093-y), Trends in Cognitive Sciences (Petro & Muckli "Forecasting faces in the cortex" doi:10.1016/j.tics.2017.12.001), and Philosophical Transactions of the Royal Society B (Petro, *et al*., "Contextual modulation of primary visual cortex by auditory signals" doi:10.1098/rstb.2016.0104). Muckli gave a keynote at the Dartmouth summer workshop on predictive coding; and the Jena, Spring School on cortical feedback. Muckli hosted the HBP summit and open day in 2017, in Glasgow. Recent results of the project were presented at CCN, New York 2017, the HBP Summit, and at the 2018 HBP Student Conference (Ljubljana, Slovenia; lab member Andrew Morgan won the best oral presentation). Muckli formed new collaborations with Christiaan Levelt (University of Amsterdam), Matthew Larkum (Humboldt University Berlin), Pieter Roelfsema (University of Amsterdam).

2.1.1.1 Highlighted Publications

Edwards, G., Vetter, P., McGruer, F., Petro, L. S., & Muckli, L. (2017). Predictive feedback to V1 dynamically updates with sensory input. *Scientific Reports*, *7*(1), 16538. https://doi.org/10.1038/s41598-017-16093-y

Nashaat, M. A., Oraby, H., Peña, L. B., Dominiak, S., Larkum, M. E., & Sachdev, R. N. S. (2017). Pixying Behavior: A Versatile Real-Time and Post Hoc Automated Optical Tracking Method for Freely Moving and Head Fixed Animals. *ENeuro*, *4*(1). https://doi.org/10.1523/ENEURO.0245-16.2017

Nashaat, M. A., Oraby, H., Sachdev, R. N. S., Winter, Y., & Larkum, M. E. (2016). Air-Track: a real-world floating environment for active sensing in head-fixed mice. *Journal of Neurophysiology*, *116*(4), 1542–1553. https://doi.org/10.1152/jn.00088.2016

Petro, L. S., & Muckli, L. (2018). Forecasting Faces in the Cortex. *Trends in Cognitive Sciences*, *22*(2), 95–97. https://doi.org/10.1016/j.tics.2017.12.001

Petro, L. S., Paton, A. T., & Muckli, L. (2017). Contextual modulation of primary visual cortex by auditory signals. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *372*(1714). https://doi.org/10.1098/rstb.2016.0104

Petro, L. S., & Muckli, L. (2017). The laminar integration of sensory inputs with feedback signals in human cortex. Brain Cogn. 112(54-57). https://doi.org/10.1016/j.bandc.2016.06.007

Revina, Y., Petro, L. S., & Muckli, L. (2017). Cortical feedback signals generalise across different spatial frequencies of feedforward inputs. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2017.09.047

Seibt, J., Richard, C. J., Sigl-Glöckner, J., Takahashi, N., Kaplan, D. I., Doron, G., … Larkum, M. E. (2017). Cortical dendritic activity correlates with spindle-rich oscillations during sleep in rodents. *Nature Communications*, *8*(1), 684. https://doi.org/10.1038/s41467-017-00735-w

Sommeijer, J.-P., Ahmadlou, M., Saiepour, M. H., Seignette, K., Min, R., Heimel, J. A., & Levelt, C. N. (2017). Thalamic inhibition regulates critical-period plasticity in visual cortex and thalamus. *Nature Neuroscience*, *20*(12), 1715–1721. https://doi.org/10.1038/s41593-017-0002-3

Spoerer, C. J., McClure, P., & Kriegeskorte, N. (2017). Recurrent Convolutional Neural Networks: A Better Model of Biological Object Recognition. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.01551

Suzuki, M., & Larkum, M. E. (2017). Dendritic calcium spikes are clearly detectable at the cortical surface. *Nature Communications*, *8*(1), 276. https://doi.org/10.1038/s41467-017-00282-4

Takahashi, N., Oertner, T. G., Hegemann, P., & Larkum, M. E. (2016). Active cortical dendrites modulate perception. *Science (New York, N.Y.)*, *354*(6319), 1587–1590. https://doi.org/10.1126/science.aah6066

Zolnik, T. A., Sha, F., Johenning, F. W., Schreiter, E. R., Looger, L. L., Larkum, M. E., & Sachdev, R. N. S. (2017). All-optical functional synaptic connectivity mapping in acute brain slices using the calcium integrator CaMPARI. *The Journal of Physiology*, *595*(5), 1465–1477. https://doi.org/10.1113/JP273116

2.1.2 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
818	Neuronal interactions during object learning	Yes	Database of chronically recorded calcium responses of identified subsets of inhibitory and excitatory neurons in the visual cortex during object learning

821	Connections to areas for object learning	Yes	Calcium imaging data of projections of relevant brain regions during object learning
2907	Synapse turnover in long-range projections	Yes	Data of bouton turnover in a pathway undergoing plasticity
819	Mouse cortical regions for object recognition learning	Yes	Wide field calcium imaging data of whole cortex measured in awake mice during object learning
846	Dendritic mechanisms of feedback	Yes	This component measures the effect of single cell stimulation and microstimulation on cortico-cortical circuit activation by imaging calcium signals in implanted microprisms with 2-photon imaging throughout a column.
895	Layer-specific fMRI to measure feedback	Yes	This component consists of high field fMRI data measuring feedback to non-feedforward stimulated layers of retinotopic-cortex while human participants view large image sets.

2.2 The multi-scale impact of cortical bistability during slow wave activity (SWA)

Work in the Paolucci, Gorostiza, Massimini, Mattia, Sanchez-Vives team focused on the investigation of cortical bistability and its impact on cortico-cortical interaction at multiple scales, as expressed during spontaneous and perturbed cortical slow wave activity (SWA) in humans and rodents. The team studied SWA expressed either during physiologic deep sleep, anaesthesia or induced by traumatic injuries and other pathological causes, and demonstrated the impact of cortical bistability on this multi-scale phenomenon using a combination of complementary experimental methods, novel theoretical models and analysis tools. Experimental techniques included ECoG, microECoG, hd-EEG, TMS, SPES and photo-stimulation. Theoretical models were developed at multi-scales. The team demonstrated the feasibility of high resolution fast simulations of SWA on computing platforms, including thousands of processing cores, invented (and evaluated the effect of) improved coding techniques in the simulation engine, related to the exchange of spiking messages and memory locality and fixed the requirements for future interconnects dedicated to cortical simulations. The addressed audience includes systems, clinical, molecular & theoretical computational neuroscientists, parallel/distributed computer scientists, as well as the HBP colleagues in Mouse Brain Organization, Human Brain Organization, Theoretical Neuroscience and HBP ICT Platforms.

According to the Project plans, the team reached its planned Milestones: i) First release of Slow Wave Activity Models and characterisation of hd-EEG scalp responses, and ii) Measurements of slow waves and opto pharmacologic modulation, and delivered the corresponding reports according to the schedule. Hereafter, we provide a synthesis of main results contributing to sections that broadly correspond to the activities of individual Tasks.

Slow-waves and complexity: from the micro-scale to the bedside.

Part of our research focused on the relationship between slow waves (i.e. bistable dynamics) and the emergence of complex cortical interactions, explored by perturbations and electrophysiological recordings at a multi-scale level. At the micro-scale, we employed an *in vitro* model (cortical slice) to test whether causal interactions can be enhanced by reducing sleep-like bistability with pharmacological manipulations (Figure 4: left). At the meso-scale, we performed electrophysiological measurements in anaesthetised rats to study bistable dynamics *in vivo* and we combined for the first time intracortical single pulse electrical stimulation (SPES) in humans undergoing pre-surgical evaluation, with simultaneous intracortical recordings and high-density electroencephalography during both wakefulness and sleep (Figure 4: centre) to link local bistable dynamics with global loss of deterministic cortico-cortical interactions. At the macro-scale, we

employed transcranial magnetic stimulation combined with EEG, in both healthy subjects and Unresponsive Wakefulness Syndrome (UWS) patients, to test whether a pathological, sleep-like form of neuronal bistability, may play a role in disrupting cortico-cortical communication and network complexity brain injured patients (Figure 4: right). Altogether, our results show that bistability and its effect on neural causal interactions can be studied at the multi-scale level and indicate a possible relationship between local neuronal dynamics, slow wave and complexity, drawing a first link between human data and experimental data and informing detailed, large scale simulations.

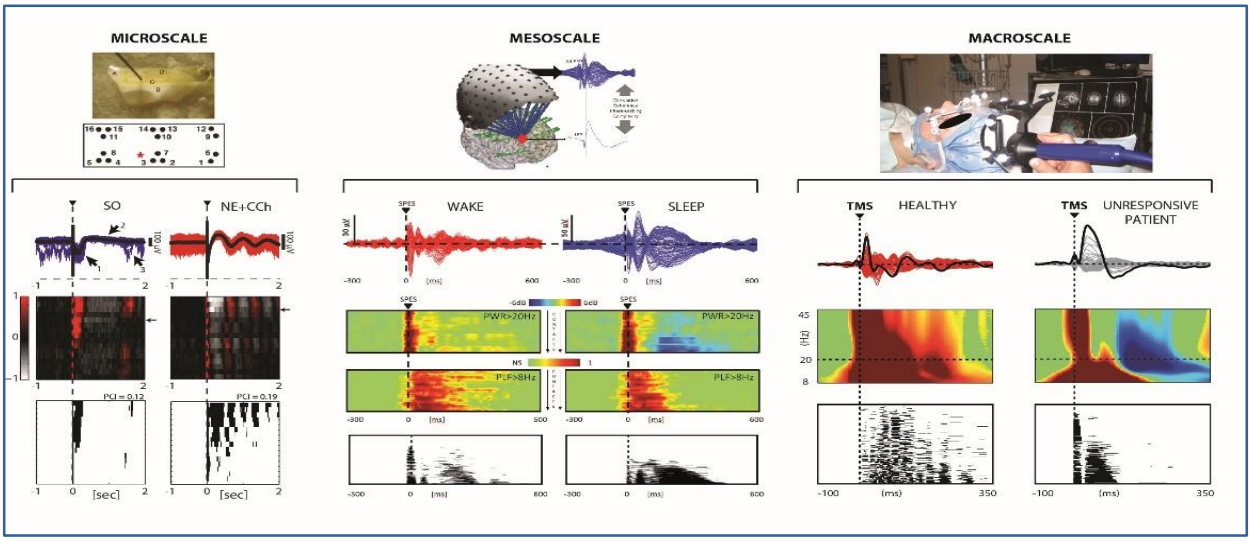


Figure 4: Bistability and complexity at multiscale, in sleep and in unresponsive wakefulness syndrome.

From left to right: Bistability and complexity in a cortical slice (D'Andola *et al.*, Cereb Cortex 2017), during sleep (Pigorini *et al. in preparation*), and for the unresponsive wakefulness syndrome (Rosanova, Fecchio *et al. submitted for publication*).

Investigation of cortical slow wave activity in rodents.

We proposed that slow oscillatory (SO) activity is the "default activity pattern" of the cortical network: a working framework to study cortical mechanisms and function, focusing on this emergent activity. As described in the previous section, we explored the role of cortical layers and of the thalamus in SO generation and propagation. Furthermore, in collaboration with the Theoretical Neuroscience Subproject, we modelled the influence of ephaptic transmission in columnar synchronisation during SO *in vitro* and *in silico*. We adapted the perturbational complexity index to an *in vitro* preparation to explore strategies to enhance cortical complexity and thus consciousness. We also tested DC electric fields to modulate cortical activity *in vitro,* and demonstrated that small fields have little impact on individual neurons, which gets amplified in the network, and generates a precise control of the emergent activity. We also developed neurotechnologies, such as a new system for cortex recording and stimulating with closed loop applications. Based on the link between SO, cortical function, and ensuing behaviour, we characterised SO in animal models of neurological disorders. We observed alterations in functional connectivity in the Fmr1KO mouse model of Fragile X syndrome, which could be associated with over-synchronization of the cortical network, and alterations in cortical activity, the development of which could be prevented, fully in some instances and partially in others, by genetic underexpression of the CB1 cannabinoid receptor. We also initiated a study on a mouse model of Williams Beuren syndrome (WBS). Our analyses suggest alterations in network functionality in anaesthetised WBS. We also recorded chronically implanted WBS mice during sleep-wake transitions, and during two behavioural tasks. Preliminary results suggest that low-frequency activity during non-REM sleep differs between WBS and WT mice, and that the performance differences in both tasks were correlated with alterations in this frequency domain. We devised a cell assembly model displaying SO. Modelling multiunit activity from simulated spiking activity allowed us to perform the same analysis used for experiments. We reproduced the modulation by DC fields, and reproduced and explained the experimental observations. With a similar approach,

we reproduced Fmr1KO mice observations, describing the dynamic network features in this hyperexcitable and hypersynchronised state and its implications on the network computations. Finally, we validated the IBEC designed photopharmacological tools, designed in our team, that allow modulation of slow oscillations in brain slices *in vitro* (see below).

Novel photostimulation techniques to remotely control brain waves.

It was demonstrated that muscarinic agonists can improve the frequency, and decrease duration and power of slow waves (delta frequencies). To modulate brain waves, we designed and prepared four novel light-regulated agonists of muscarinic receptors, and tested their efficacy in cells and brain slices under different light wavelengths. To obtain selective muscarinic agonists, we incorporated in the same structure: a) a potent nonselective orthosteric agonist, and b) a subtype-selective allosteric modulator, connected through a polymethylene linker, to provide the so-called dualsteric ligands. We also designed a set of potential photochromic muscarinic agonists by combining two or three of the following elements: 1) Iperoxo, the most potent orthosteric muscarinic agonist, 2) an azobenzene-based molecular photoswitch, and 3) an allosteric modulator of muscarinic receptors (e.g., W84, Naphmethonium, BQCA). We classified our compounds according to their favourable properties (photochromism, efficacy, selectivity). One of the compounds (PhtalAzoIper, PAI) fully satisfied the molecular and (photo)pharmacological requirements and was thus the first molecular tool to modulate slow wave activity in brain slices (Figure 5) and *in vivo*. Two manuscripts reporting our results are currently *in preparation*.

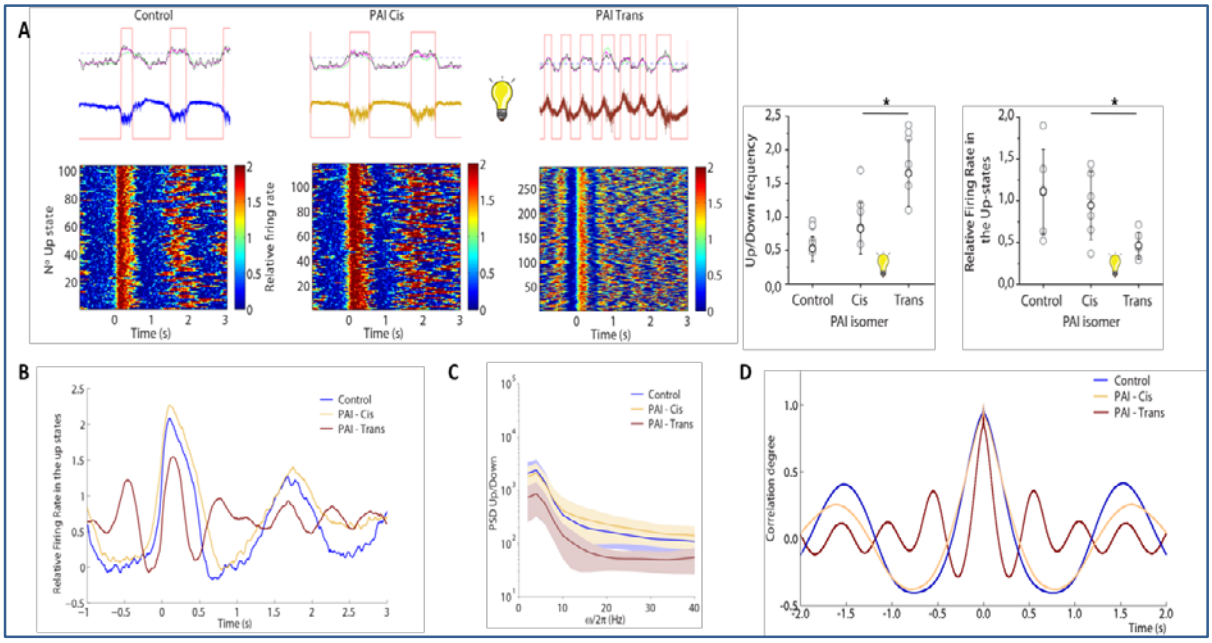


Figure 5: Muscarinic receptor activation increases slow oscillation frequency and reduces excitability.

Muscarinic receptor activation increases slow oscillation frequency and reduces excitability. A) Left, Representative LFP traces and raster plots of relative firing rate under control conditions (left), 200 nM of PAI Cis (middle) and 200nM Trans (right). Right, Up/Down frequency and relative firing rate during the Up states after PAI 200nM photoswitch. B) Average relative firing rate during Up states, C) Power spectrum density and D) Autocorrelograms illustrating spontaneous activity under the same conditions as in A.

Theory-driven analyses and multiscale modelling of slow-wave activity.

We bridged different experimentally-accessible spatial and temporal scales by developing effective models of cortical networks and theory-driven data analyses. As a key result, we characterised ongoing SWA in cortical slices recorded by our team and reconstructed wave activity from a 16-electrodes array (Figure 6), finding that a quantitative match between model and experiments could be obtained only if a specific balance between local and inter-modular connectivity is taken into account. The newly developed analysis tools are now successfully generalised to *in vivo* recordings of SWA from multi-electrode arrays (ECoG) in rodents. The laminar model of the cortex was also instrumental in i) designing and implementing the benchmark

to test and compare spiking network simulators (DPSNN and NEST), and ii) developing more ambitious models of SWA which incorporates other brain structures like the thalamus (in collaboration with Alain Destexhe). We extended also the aforementioned finding of a bistable nonlinear dynamics of layer 5 (L5) driven by layer 6 activity by analysing and modelling how L5 activity changes as anaesthesia fades out. Such transition can be described as a trajectory across an effective low-dimensional bifurcation diagram where the regularity of SWA reaches a maximum at an intermediate level of anaesthesia.

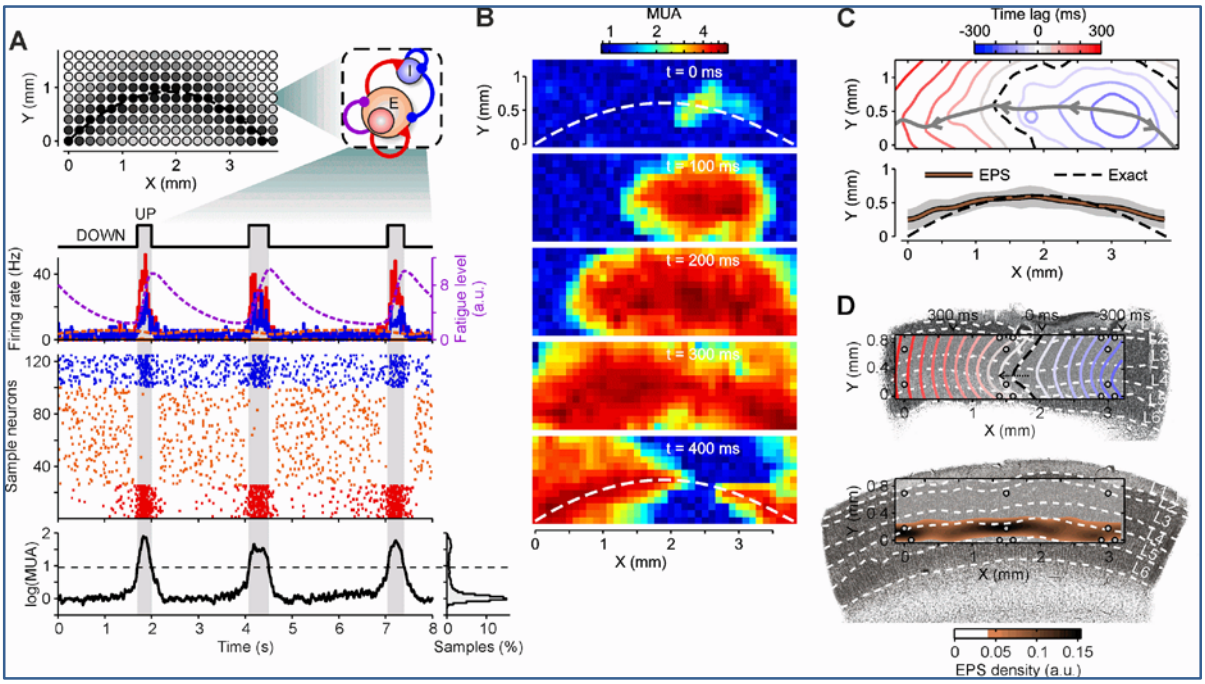


Figure 6: Large scale network of integrate and fire neurons modelling in vitro slow-wave activity.

Large-scale network of integrate-and-fire neurons modelling *in vitro* slow-wave activity (after (Capone *et al*. Cereb Cortex 2017)). A) multi-modular network of excitatory-inhibitory neuron networks (63000 IF neurons with 20 million of static synapses) with heterogeneous excitability, showing slow oscillations between Up and Down states. B) Propagating waves in simulations and C) analysis of their wave fronts matching designed structures. D) *In vitro* slow waves and the inferred match with the laminar structure of the cortex.

We progressed in the classification of patients with different levels of consciousness. As an alternative to the PCI, we are evaluating the hypothesis that spontaneous EEG recordings should reveal different 'self-susceptibilities' to be paralleled to TMS responsiveness. Extreme gradient boosting classifiers turned out to be very good on data segments not used in the training for a patient, although generalisation across patients is still poor.

High resolution multi-scale distributed simulation of Slow Wave Activity.

We studied higher efficiency custom interconnects and greener technologies for future exa-scale HPC cortical simulation platforms. We delivered a high-resolution (tens of billions synapses), fast (<1 ns per simulated synaptic event), scalable (up to 1024 hardware cores / MPI processes) spiking simulation model of cortical SWA (Figure 7) at biological densities (up to 45 thousand neurons/mm2 and thousands of synapses per neuron) with realistic long-range intra-areal interconnections.

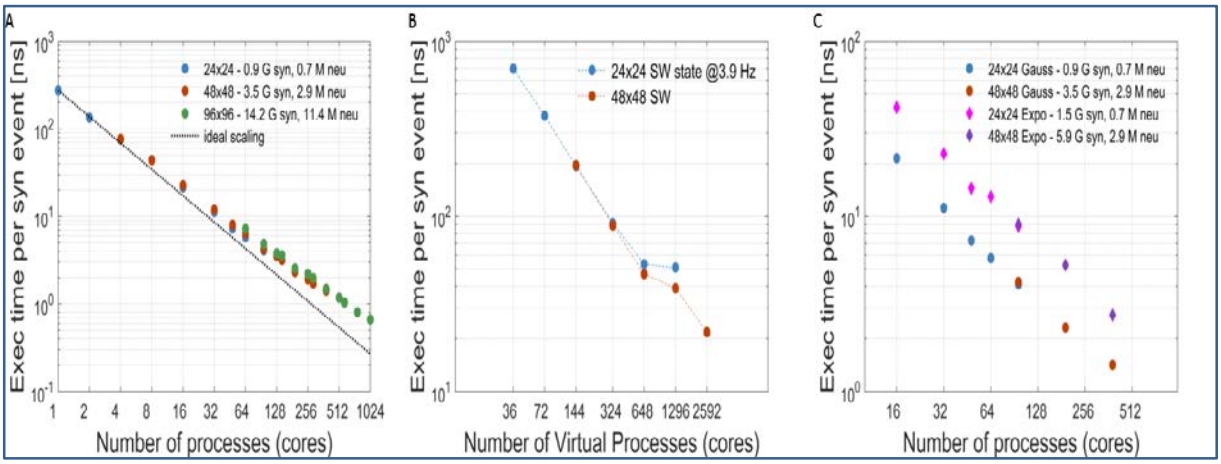


Figure 7: Scaling on distributed computing platforms of slow wave activity simulations.

A) Scaling on distributed computing platforms of Slow Waves Activity (SWA) for tree problem sizes, from 1 to 1024 MPI processes (DPSNN engine). Black line: ideal scaling. B) Scaling on NEST simulator (v 2.12.0), for two problem sizes, from 36 to 2592 processes. C) Impact of shorter range lateral connectivity (Gaussian decay with distance, circles) and longer range, biologically plausible exponential decay of lateral connectivity (diamonds) (run on DPSNN engine).

The model is used as a starting point for further activities contributing to the study of the interaction between SWA and plasticity (David LESTER) and is available in both DPSNN (Distributed Plastic Spiking Neural Network, INFN simulation engine) and NEST formats, thanks to a strict cooperation with the NEST development team (Hans PLESSER).

2.2.1 Achieved Impact

The team exploited several opportunities to address the general public about the importance of understanding physiological and pathological aspects of cortical slow wave activity: the 2016 European Researchers Night, the Open Day of the Florence HBP Summit, the HBP Italy event (March 2018, Pavia), a conference for a patients' association (FARPE, Valencia), a Marie Curie popularisation course in Brussels, publication of interviews in national economic newspapers (the Italian Sole 24 ore), several press-releases from the individual institutions of the team. Addressing young researchers, a keynote talk has been delivered at the 2016 HBP Young Researcher event in Budapest. Addressing European projects working on massive parallel computing, we discussed brain simulation requisites and collaborated with the teams of the ExaNeSt and EuroEXA projects. The team participated in the organisation of thematic workshops (EITN Paris) about slow wave dynamics and brain states and, to reinforce the link with the NEST development team, participated in the NEST user workshops and NEST conferences, and visited the Julich lab on several occasions. The scientific community at large has been reached through the publication of peer reviewed journal papers (Cerebral Cortex, Neuron, Nature Comm, J. Comp. Neuroscience, J. Comp. Neurol., Ann. Neur., Plos One, Br. J. Pharmacology, and peer reviewed conference papers (PDP 2018, PARCO 2017, DSD 2017) and related conference presentations. A PhD dissertation about the characterisation and optimisation of network traffic in cortical simulation was produced and will serve as bridge between the HBP community and the ExaScale computing community.

2.2.2 Highlighted publications

Biagioni, A. (PhD candidate), Paolucci, P. S. (tutor). (2018). Characterization and optimization of network traffic in cortical simulation. PhD thesis, Information and Communication Engineering Sapienza University of Rome. https://hdl.handle.net/11573/1082376

Capone, C., Rebollo, B., Muñoz, A., Illa, X., Del Giudice, P., Sanchez-Vives, M. V., & Mattia, M. (2017). Slow Waves in Cortical Slices: How Spontaneous Activity is Shaped by Laminar Structure. *Cerebral Cortex (New York, N.Y.: 1991)*, 1–17. https://doi.org/10.1093/cercor/bhx326

D'Andola, M., Rebollo, B., Casali, A. G., Weinert, J. F., Pigorini, A., Villa, R., … Sanchez-Vives, M. V. (2017). Bistability, Causality, and Complexity in Cortical Networks: An In Vitro Perturbational Study. *Cerebral Cortex (New York, N.Y.: 1991)*, 1–10. https://doi.org/10.1093/cercor/bhx122

Dasilva, M., Navarro-Guzman, A., Maiolo, L., Marrani, M., Ozaita, A., Sanchez-Vives, M. V.

(2018). Altered functional connectivity in a mouse model of Fragile X syndrome. *Advances in Cognitive Neurodynamics* (VI). Springer. (*in press*)

Pastorelli, E., Paolucci, P. S., Simula, F., Biagioni, A., Capuani, F., Cretaro, P., … Ammendola, R. (2018). Gaussian and exponential lateral connectivity on distributed spiking neural network simulation. (in press, PDP2018 proceedings, preprint on *ArXiv:1803.08833 [Cs, q-Bio]*. Retrieved from http://arxiv.org/abs/1803.08833

Rosanova, M., Fecchio, M., Casarotto, S., Sarasso, S., Casali, A. G., Pigorini, A., … Massimini, M. (2018). Sleep-like bistability, loss of causality and complexity in the brain of Unresponsive Wakefulness Syndrome patients. *BioRxiv*, 242644. https://doi.org/10.1101/242644

Sanchez-Vives, M. V., Massimini, M., & Mattia, M. (2017). Shaping the Default Activity Pattern of the Cortical Network. *Neuron*, *94*(5), 993–1001. https://doi.org/10.1016/j.neuron.2017.05.015

2.2.3 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
776	Electrical perturbations on slices during sleep-like pattern before and after drug application	Yes	- Providing data to deepen the mechanistic link between bistability and loss of complexity (D'Andola et al, CerbCortex 2017) - Providing insights for components 975
779	Intracortical SPES recording combined with hd-EEG and intracortical recording	Yes	- Providing data to characterise slow wave both at the meso- and macro-scale level (Pigorini et al, in preparation) - Providing data for Human Atlas (SP5) - Developing methods and providing insights for components 975
975	Investigating cortical bistability in vegetative patients with TMS-EEG recordings	Yes	- Providing data for observing pathological, sleep-like bistability in vegetative state patients (Rosanova, Fecchio et al. Bioarxiv 2018) - Providing data for large scale simulations (NEST)
648	Cortical recordings from anesthetized Fmr1KO mice	Yes	Provides data for tuning modelling of cortical function in disease (components 651 and 783)
778	Photostimulation of slow wave activity using light-regulated drugs	Yes	Stimulation of neurons with light flash based on light regulated active compounds targeted in specific receptors. It allows the spatio-temporal control of brain activity patterns.
782	Modelling and analysis of a cortical slice with spontaneous and perturbed slow-wave activity	Yes	- Model of a cortical slice expressing slow-wave activity matching *in vitro* experiments (Capone et al., Cereb Cortex 2017). - Analysis for the *in vitro* and *in vivo* slow-wave activity recorded from MEA. - Model used by components 740 and 651.
740	Multiscale cortico-thalamic model of the transition	Yes	- Mean-field and spiking neuron model of local cell assemblies describing brain state transition

	from slow-wave activity to wakefulness		(Tort-Colet, Capone, Mattia, Sanchez-Vives, in preparation).
1065	Co-design of interconnects simulators (report)	Yes	Characterisation and optimization of network traffic in cortical simulation, PhD thesis, February 2018, Information and Communication Engineering, Sapienza University of Rome, candidate: Andrea Biagioni (INFN), tutor Pier S. Paolucci (INFN)

2.3 Robotics, human fMRI, brain-based computational modelling and innovative technology for behaviour, electrophysiology in animals, optogenetics and data analysis

Here, we investigate brain mechanisms of multisensory integration and episodic memory. Episodic memory is the memory of our personal, conscious experiences, set within space and time. It defines who we are. The brain's ability to recall objects and experiences from multisensory information, such as vision, audition or touch sensation is key to understand human memory.

Hippocampal-neocortical interactions: Human 7 Tesla fMRI and MR-PET studies

We aimed to identify the circuit-level mechanisms of hippocampal-neocortical interactions during episodic reinstatement of multisensory experiences, object-scene associations and reward. First, we studied CA3 pattern-completion associated with episodic memories in relation to input and output activity of the entorhinal cortex (EC). Second, we examined 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 examined whether hippocampal-cortical mappings are preserved across input-output operations. Third, we studied 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.

The 7T fMRI pattern-completion in episodic memory study, in collaboration with the rodent electrophysiology components of SP3, has been completed. The results show how hippocampal-subfield activation is related to neocortical reinstatement of categorical information. During the last 6 months we prepared a manuscript focusing on the role of CA3 in establishing incidental associations during encoding. We created virtual reality 3D scenes with embedded virtual reality rendered 3D objects. We piloted a task in which the scenes are presented with 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. Before moving to 7T with this task, we decided to scan a group of 30 older adults with preclinical Alzheimer's Disease. These individuals have also provided CSF samples and we will therefore be able to relate deficits in pattern-completion and in activating CA3 to levels of tau and Aß42 pathology. As outlined in an earlier statement, the MR-PET component of this task has been delayed, because the nuclear medicine expert has left Magdeburg and the recruitment of a new person took a considerable amount of time. We now expect to start with this component in 4 months. In the meantime, we have focused on imaging the locus coeruleus, which, although being a noradrenergic structure, was recently shown to be responsible for releasing dopamine in the hippocampus. We published a paper showing that the integrity of the locus coeruleus in older adults indeed has an effect on hippocampus-dependent memory.

Progress on understanding relationship between grid and place cell networks

During the past 12 months, we been investigated how spatial cells in the hippocampus process environmental sensory information and self-motion using a recently developed 2D virtual reality system. We used virtual reality to dissociate visual environmental cues from those provided by self-motion, while recording place and grid cells in mice navigating virtual open arenas. Our results

showed that the two types of input had different influences on place and grid cell firing patterns, with place fields strongly reflecting (virtual) visual inputs and grid patterns reflecting a much greater influence of physical motion. These results suggest that place and grid cell firing patterns represent space in a different way, according to environmental information and physical self-motion, and are not necessarily mutually coherent.

Neural correlates of multisensory processing: Paradigm development and *in vivo* electrophysiological recordings

We conduct studies on multisensory integration and memory in sensory cortices and the temporal lobe in rodents, performing multi-feature detection and object recognition tasks, while recording and imaging population activity – at cellular resolution - across multiple cortico-hippocampal areas.

The development of a behavioural task for freely behaving rodents performing a multisensory object recognition task has been finalised (see Figure 8). This task forms the basis to answer questions regarding pattern completion mechanisms related to the retrieval of episodic memories, and is also modelled in robots. Furthermore, it links to biological deep learning based on the use of multisensory integration to recognise objects.

The first simultaneous ensemble and LFP recordings from the hippocampus, barrel cortex, visual cortex and perirhinal cortex were performed in a rat performing the above mentioned multisensory object recognition task (see Figure 9).

We finalised implementation of whisker tracking in complete darkness to closely monitor whisking behaviour under different modes of object sampling (see Figure 10).

The relation of two streams of sensory information (auditory and visual), is further investigated on the primary sensory level in head-fixed mice to gain more insights into laminar activity differences, LFPs and multisensory prediction errors. To this purpose, a 2-alternative forced-choice paradigm has been developed to teach mice a stimulus-detection task. This involved testing and construction of a novel training setup, which is operational since January 2018. Several animals are now undergoing training. Second, neurophysiological recordings were planned with a new setup (neurophysiological recordings with Open Ephys) and a new set of 64-channel silicon probes. This setup was constructed, and first pilot recordings indicate good recording quality. The setup is now prepared to record task-performing animals. Apart from setting up this novel Ephys component, we performed extensive 2-photon imaging on mouse V1 and a higher visual area (AL), offering novel insights in audiovisual integration in these areas, and differences in stimulus detection between these two areas. As a main result, AL showed a significantly higher detection sensitivity than area V1.

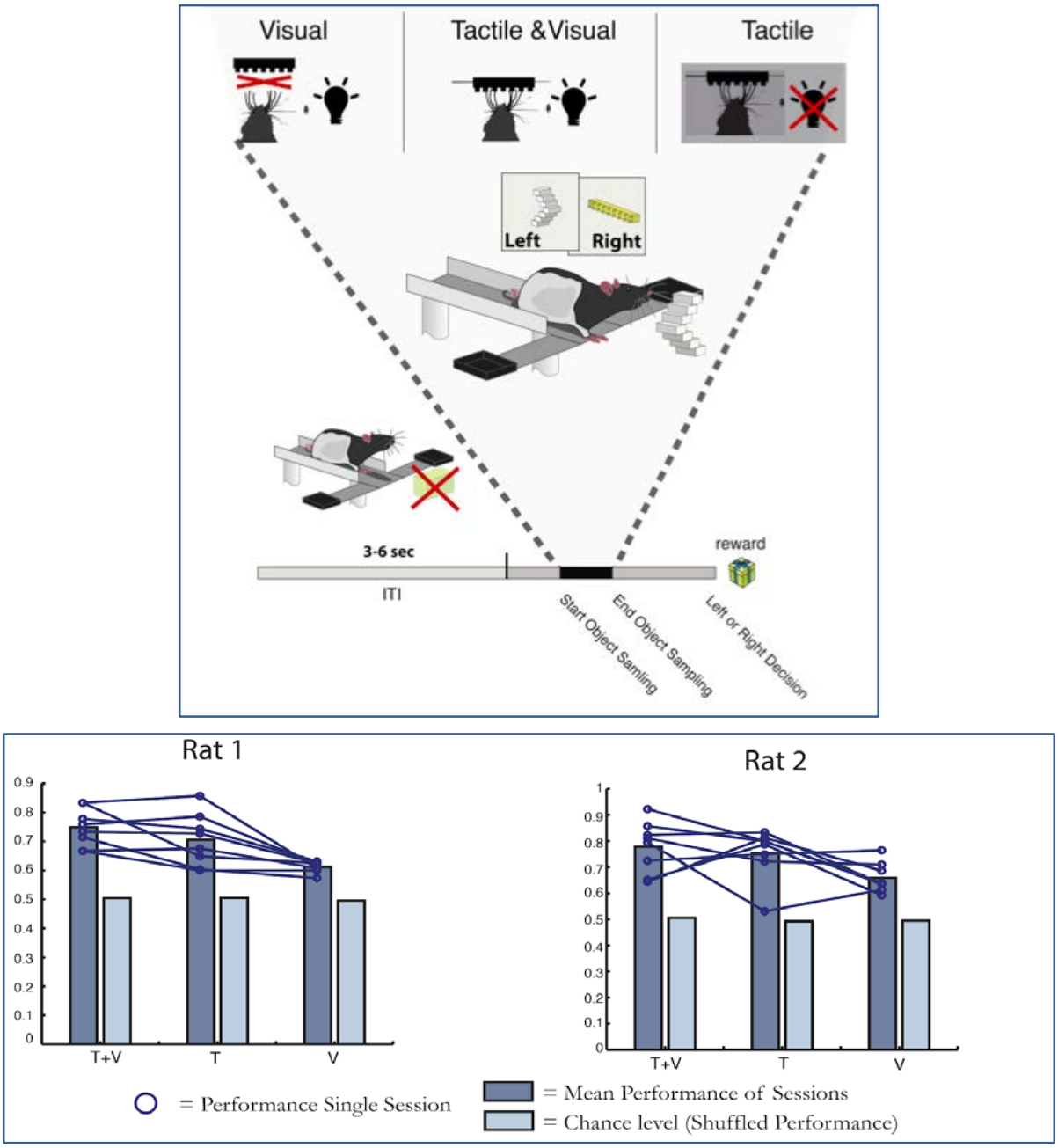


Figure 8: Rats can use different sensory modalities to discriminate between objects.

Rats can use different sensory modalities to discriminate between objects. Top: schematic of behavioural task developed for the rat. Bottom: example of behavioural performance of two rats. T = Tactile trials, V = visual trials, T+V = Visuo-tactile Trials.

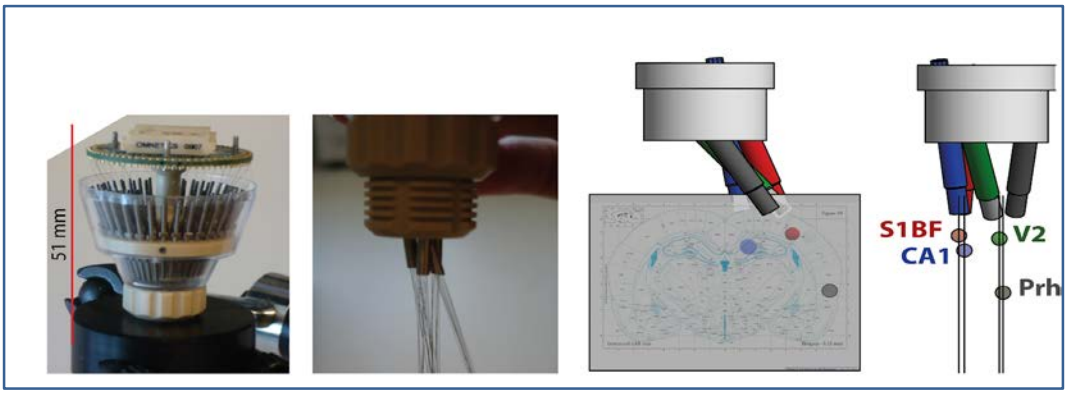


Figure 9: Illustration of employed quad-drive and targeted areas

Illustration of employed quad-drive and targeted areas: CA1 hippocampal region (CA1), Barrel Field (S1BF), Visual cortex (V2) and Perirhinal cortex (Prh).

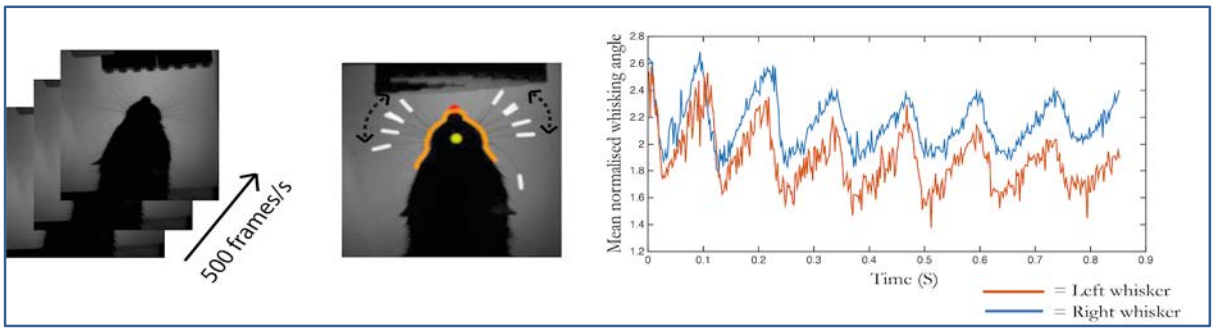


Figure 10: Schematic illustration of whisker tracking during object palpation in complete darkness

Schematic illustration of whisker tracking during object palpation. (Left) High-speed videos are acquired while rats sample objects. (Middle) Whisker and head-position are then tracked offline, resulting in behavioural readouts such as (right) mean whisking angle and whisking frequency.

Computational modelling of multisensory episodic memory

We are developing an episodic or event memory system modelled on the hippocampal system to create a sense of self for the iCub humanoid robot that has ecological, temporally-extended, interpersonal and narrative components set within a multi-layered model of mind and brain. Our hypothesis is that event memory can be usefully considered as an attractor network operating in a latent (hidden) variable space whose dimensions encode salient characteristics of the physical and social world in a highly compressed fashion. A single latent feature space can be used to represent memories across multiple sensory modalities providing sensory fusion. This can also be thought of as concept discovery—the identification of underlying invariance in patterns of multi-modal sensory flow. The model, which is implemented using "Gaussian process" learning models, can be analogised to a) compressed 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) pattern separation/completion and sequence generation via recurrent connections in CA3, d) decoding via CA1 and deep layers of EC, and e) reconstruction of remembered events by wider sensory areas (e.g. somatosensory, visual cortices). The current implementation, illustrated in Figure 11, left, demonstrates effective memory formation and retrieval of human faces, actions, voices and emotions. Due to its generative nature, and ability to interpolate, the system can also generate fantasy memories from parts of the latent variable space that have not been populated by real data. This leads to the possibility of imagined future events that have not yet been observed as in Figure 11, centre where the robot uses its own simulator to display an imagined future interaction. The ability of the system to reconstruct the sensory pattern associated with a recalled memory retrieved using a verbal cue, suggests that event memory can contribute to the grounding of linguistic symbols in sensorimotor experience.

Figure 11: Different parts of the same system. From the physical robot, to its simulation and finally to its memory model

Left: iCub operating in real-time to recognise actions and faces. The TV monitor behind the robot shows two latent variable spaces, the visual pre-processing of the camera scene, and the reconstruction of the remembered face based on the recovered memory. Centre: a screen-shot from the visual memory inspector which allows researchers to see iCub's simulation of itself and its perceptual world, here iCub represents a face and two objects on the circular table. Right: Extending the episodic memory model using probabilistic graphs.

Recent work has addressed combining Gaussian processes models with probabilistic graphs to create a broader computational structure that can further emulate the structure and function of the hippocampus. We have since then started the implementation of this approach by first considering its application in a dialogue agent. In this model, we define a list of responses the dialogue agent can have, together with a list of intents the user can have. This script has a non-linear flow with multiple topics of conversation possible ranging from the origin of iCub's hardware to politics. The defined responses and intents make up the nodes of our probabilistic graph and the learning task then is to interactively discover the edges and associated probabilities that will result in the required responses by the agent given an intent as illustrated in Figure 11 right).

Robotic systems: hardware implementation of multi-sensory episodic memory

Multi-sensory integration and spatial memory are both key components of the episodic memory system under study. We have taken a neurorobotics approach for this study to develop novel solutions to hard engineering problems. In this phase of the project, we commissioned a new robotic platform that incorporates an active array of artificial whiskers and a binocular vision system which we have called "WhiskEye" (see Figure 12: , left). This platform was used to gather preliminary visual-tactile data sets, based on a multi-sensory object discrimination study in rats undertaken by partner UvA. It also incorporates a functional cognitive architecture to direct attention and move through the environment which will be developed further in the next two years toward the complete mammalian cognitive architecture. Work has been proceeding to mimic the multisensory rodent task (see Figure 8) in the WhiskEye robotic emulation.

Figure 12: WhiskEye Robot (left) and MiRo Robot (right)

A model of spatial memory has been developed and demonstrated, using the HBP NeuroRobotics platform and the MiRo physical robot (see Figure 12: , right) that will be ported into the WhiskEye in the next phase. Finally, the RatSLAM spatial memory model has been extended toward a solution for 6D object recognition using an active array of artificial whiskers.

2.3.1 Achieved Impact

In general, we published articles in scientific journals, papers at leading conferences, and chapters in forthcoming books. We provided robot demonstrations at the HBP summit and other public engagement events.

- We have publication (Hammerer D, Callaghan MF, Hopkins A, Kosciessa J, Betts M, Cardenas-Blanco A, Kanowski M, Weiskopf N, Dayan P, Dolan RJ, Duzel E (2018) Locus coeruleus integrity in old age is selectively related to memories linked with salient negative events. Proc Natl Acad Sci U S A 115:2228-2233.)
- We have submitted a paper titled 'Spatial cell firing during virtual navigation of open arenas by head-restrained mice' to eLife, which it is currently under revision. Another paper, titled 'Differential influences of environment and self-motion on place and grid cell firing patterns', is currently under review by Science.
- We organised several workshops (HBP Fürberg in-depth modelling meeting, May 2017, organisers: Cyriel Pennartz and Wolfgang Maass). We also co-organised the Consciousness Symposium at SfN in November 2017, which included a talk by Pennartz. We hosted a booth and posters at the HBP innovation event in London, 2018 (general SP3 poster and a student poster covering work in Cognitive and Systems Neuroscience). We co-authored a cross-SP journal paper with Jan Bjaalie (SP5) in *European Psychiatry*. We organised a National Outreach Event in Amsterdam, which featured posters, talks, and exhibitions from our team.
- The iCub memory/language system was programmed to act in the role of an interviewer for the *BBC Radio 4 Today* programme, which aired on 30th December 2017 to an audience of 1M+ listeners. A multi-part exhibit, including brain-based robots and brain-inspired virtual reality systems, was demonstrated over 4 days in September 2017 at the New Scientist Live Exhibition at the Excel Centre London, the total audience of the Exhibition was around 30,000, of which, we estimate, around 6,000 interacted with our exhibit. Invited talks by Tony Prescott were given at IROS 2017 Human-In-The-Loop Workshop (audience: 200) and AAIC 17 Satellite Meeting (audience: 300).
- We had a MiRo robot demonstration of spatial memory at HBP summit in Glasgow and a WhiskEye robot demonstration of multi-sensory integration at HBP innovation event in London, 2018

2.3.2 Highlighted Publications

Arbab, T., Battaglia, F. P., Pennartz, C. M. A., & Bosman, C. A. (2018). Abnormal hippocampal theta and gamma hypersynchrony produces network and spike timing disturbances in the Fmr1-KO mouse model of Fragile X syndrome. Neurobiology of Disease, 114, 65–73. https://doi.org/10.1016/j.nbd.2018.02.011

Bassett, J. P., Wills, T. J., & Cacucci, F. (2018). Self-Organized Attractor Dynamics in the Developing Head Direction Circuit. *Current Biology*, *28*(4), 609–615.e3. https://doi.org/10.1016/j.cub.2018.01.010

Bjerke, I. E., Øvsthus, M., Papp, E. A., Yates, S. C., Silvestri, L., Fiorilli, J., Pennartz, C. M. A., Bjaalie, J. G. (2018). Data integration through brain atlasing: Human Brain Project tools and strategies. *European Psychiatry*. http://doi.org/10.1016/j.eurpsy.2018.02.004

Bos, J. J., Vinck, M., Mourik-Donga, L. A. van, Jackson, J. C., Witter, M. P., & Pennartz, C. M. A. (2017). Perirhinal firing patterns are sustained across large spatial segments of the task environment. *Nature Communications*, *8*, ncomms15602. https://doi.org/10.1038/ncomms15602

Martinez-Hernandez, U., & Prescott, T. J. (2017). Adaptive perception: Learning from sensory predictions to extract object shape with a biomimetic fingertip. In *2017 IEEE/RSJ International*

Conference on Intelligent Robots and Systems (IROS) (pp. 6735–6740). https://doi.org/10.1109/IROS.2017.8206590

Meijer, G. T., Montijn, J. S., Pennartz, C. M. A., & Lansink, C. S. (2017). Audio-visual modulation in mouse V1 depends on cross-modal stimulus configuration and congruency. *Journal of Neuroscience*, 0468-17. https://doi.org/10.1523/JNEUROSCI.0468-17.2017

Moulin-Frier, C., Fischer, T., Petit, M., Pointeau, G., Puigbo, J. Y., Pattacini, U., Low, S. C., Camilleri, D., Nguyen, P., Hoffmann, M., Chang, H. J., Zambelli, M., Mealier, A. L., Damianou, A., Metta, G., Prescott, T. J., Demiris, Y., Dominey, P. F., & Verschure, P. F. M. J. (2017). DAC-h3: A Proactive Robot Cognitive Architecture to Acquire and Express Knowledge About the World and the Self. *IEEE Transactions on Cognitive and Developmental Systems, PP* (99), 1-1. https://doi.org/10.1109/TCDS.2017.2754143

Pennartz, C. M. A. (2018). Consciousness, Representation, Action: The Importance of Being Goal-Directed. *Trends in Cognitive Sciences*, *22*(2), 137–153. https://doi.org/10.1016/j.tics.2017.10.006

Prescott, T. J., Mitchinson, B., & Conran, S. (2017, March 6). MiRo: An animal-like companion robot with a biomimetic brain-based control system [Proceedings Paper]. Retrieved March 28, 2018, from https://doi.org/10.1145/3029798.3036660

Salman, M., & Pearson, M. J. (2016). Advancing whisker based navigation through the implementation of Bio-Inspired whisking strategies. In *2016 IEEE International Conference on Robotics and Biomimetics (ROBIO)* (pp. 767–773). https://doi.org/10.1109/ROBIO.2016.7866416

Storm, J. F., Boly, M., Casali, A. G., Massimini, M., Olcese, U., Pennartz, C. M. A., & Wilke, M. (2017). Consciousness Regained: Disentangling Mechanisms, Brain Systems, and Behavioral Responses. *Journal of Neuroscience*, *37*(45), 10882–10893. https://doi.org/10.1523/JNEUROSCI.1838-17.2017

2.3.3 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
1140	Shrewbot++ robot platform	Yes	Visual-tactile mobile robot platform
2055	Functional topography of convergence zones for different sensory modalities	Yes	Functional topography of convergence zones for different sensory modalities (visual, auditory, tactile) with information about objects and scenes within perirhinal and entorhinal cortex.
2057	Pattern completion to multisensory episodic memory	Yes	New task for research on multisensory episodic memory in rodents has been developed. This was necessary to bridge the gap between rodent and human research.
2061	Multi-area ensemble mechanisms of object recognition in rodents	Yes	Silicon-probe recordings in freely behaving rodents to uncover how stimulus information presented through one sensory modality can result in memory retrieval of information in another modality
1681	Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1	Yes	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.

1307	iCub episodic memory system	Yes	Emulation of episodic memory for short human-robot interactions, including user-action-object recognition.

2.4 Methods and measures for understanding the mechanisms of consciousness

Here, we aim to shed light on the neuronal mechanisms of consciousness and to develop new methods for assessing consciousness. To succeed, we take advantage of experiments on human, animal and computer models, inspired by some of the most promising scientific theories of consciousness currently available, such as the integrated information theory and global workspace theory. Thus, our laboratories in Oslo, Milan, and Liege collaborate on the development and validation of theoretically driven methods and measures of consciousness vs. unconsciousness. We believe that our efforts can have significant scientific influence and clinical impact in diagnosis and management of brain-injured patients with consciousness disorders. Our research products will provide new knowledge to help clinicians make more informed decisions. Besides, our results can provide the basis of more reliable diagnostic methods and treatments.

As outlined below, our work has yielded significant advances with potential impact in the field of consciousness research, both practically and theoretically. Specifically, we performed validations of experimental protocols and measurements required for state-of-the-art experiments on human consciousness, compared these functional measurements with underlying structural data, laid the foundations for the interpretation of these novel measurements and their underpinnings at the neuronal level by employing animal models and detailed computer simulations. Overall, this constitutes a multimodal approach whereby measures of spontaneous EEG dynamics, brain responses to cortical perturbations, event related potentials (ERPs), and structural analysis are performed, combined and compared, from patients to experiments in healthy volunteers, rodent models, and *in silico* brain models.

Figure 13 shows an example of an EEG-based measure capable of objectively distinguishing between the awake and anaesthetised state in humans. This particular image includes a measure based on the directed information flow between EEG channels on the scalp, quantified by the directed transfer function (DTF). Panel A shows the timeline for an individual patient undergoing general anaesthesia. First, the patient is awake, then (marked by the first red arrow) the patient is rendered unresponsive by a bolus dose of propofol and judged to be unconscious by the anaesthesiologist. Much later (marked by the second red arrow), the patient re-emerges from the anaesthesia and is deemed to be conscious by the anaesthesiologist. Panel B shows the typical pattern of directed information outflow averaged across all awake patients, while panel C shows the typical directed information outflow of the patients while anaesthetised.

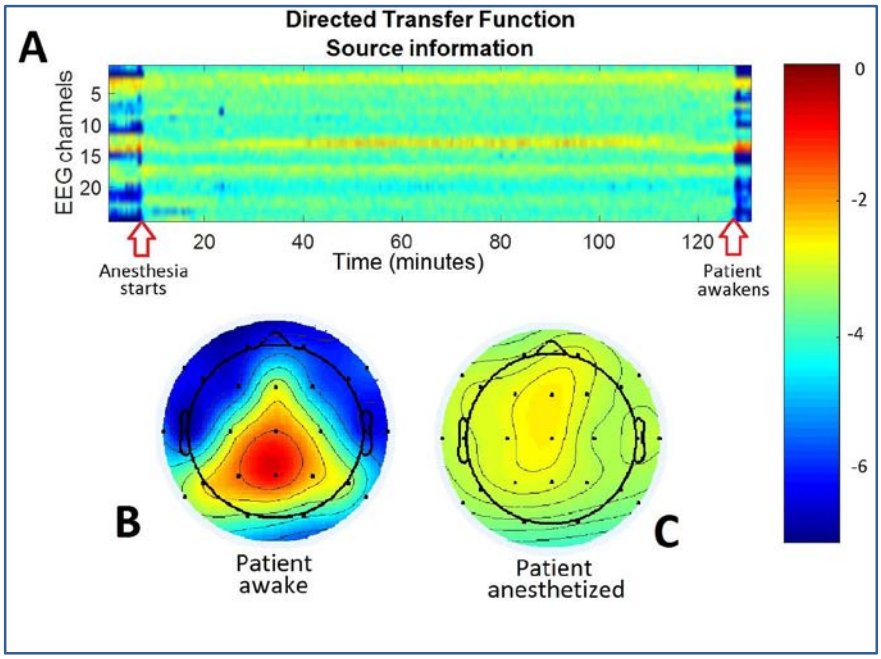


Figure 13: Distinguishing anaesthetized from awake state by EEG

Directed Transfer Function (DTF) changes between awake and anaesthetised condition in patients undergoing Propofol anaesthesia. The pattern of information flow (as quantified by DTF) changes abruptly when a patient is anesthetized (first red arrow), and then changes back to the pre-anaesthesia pattern upon awakening (second red arrow). In panel B and C, the spatial pattern of information flow on the scalp (seen from above, nose pointing up) when averaged across all patients

To complement the analysis of spontaneous dynamics, we performed an extensive exploration of the brain's capacity to integrate information employing a perturbational perspective. Through novel TMS/EEG measurements data on 40 new patients, we could pool together a large cohort of 81 subjects with different degrees of brain injury (including stroke patients, minimally conscious state (MCS), emergence from MCS and unresponsive wakefulness syndrome (UWS)). During the project, this patient cohort was analysed and stratified by means of the perturbational complexity index (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. Most importantly, this approach revealed three possible TMS-EEG patterns in clinically unresponsive patients (see Figure 14, panel A). 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 unconsciousness, iii) engage in a complex spatiotemporal dynamics similar to the one observed in conscious awake or dreaming subjects. Notably, this subgroup of UWS patients may retain a capacity for consciousness that is not expressed in behaviour.

In parallel, the results of our perturbational approach were analysed in a multimodal perspective using structural MRI (tractography, fractional anisotropy) and functional data (positron emission tomography (PET)). This led to a better understanding on the relationships between the complexity of electrical brain responses, anatomy and basic metabolic rates. Comparing TMS/EEG results with tractography showed that the relationship between directed functional connectivity and structural connections depends on the stimulation site and the frequency of the TMS-induced brain rhythms, thus highlighting the importance of taking into account the role played by different cortical EEG oscillations when investigating the mechanisms for integration and segregation of information in the human brain. Comparing PCI measurements with fractional anisotropy (FA) indicates that structure supports effective connectivity and complexity, even in brain-injured patients (see Figure 14, panel B). Moreover, increased structural damage decreases effective connectivity, which prevents the emergence of consciousness. Finally, comparing PCI and brain metabolism (using PET) showed robust correlations and complementarities, suggesting that jointly measuring the metabolic activity and the electrophysiological complexity of cortical circuits is a useful approach for the diagnosis and stratification of patients with consciousness disorders.

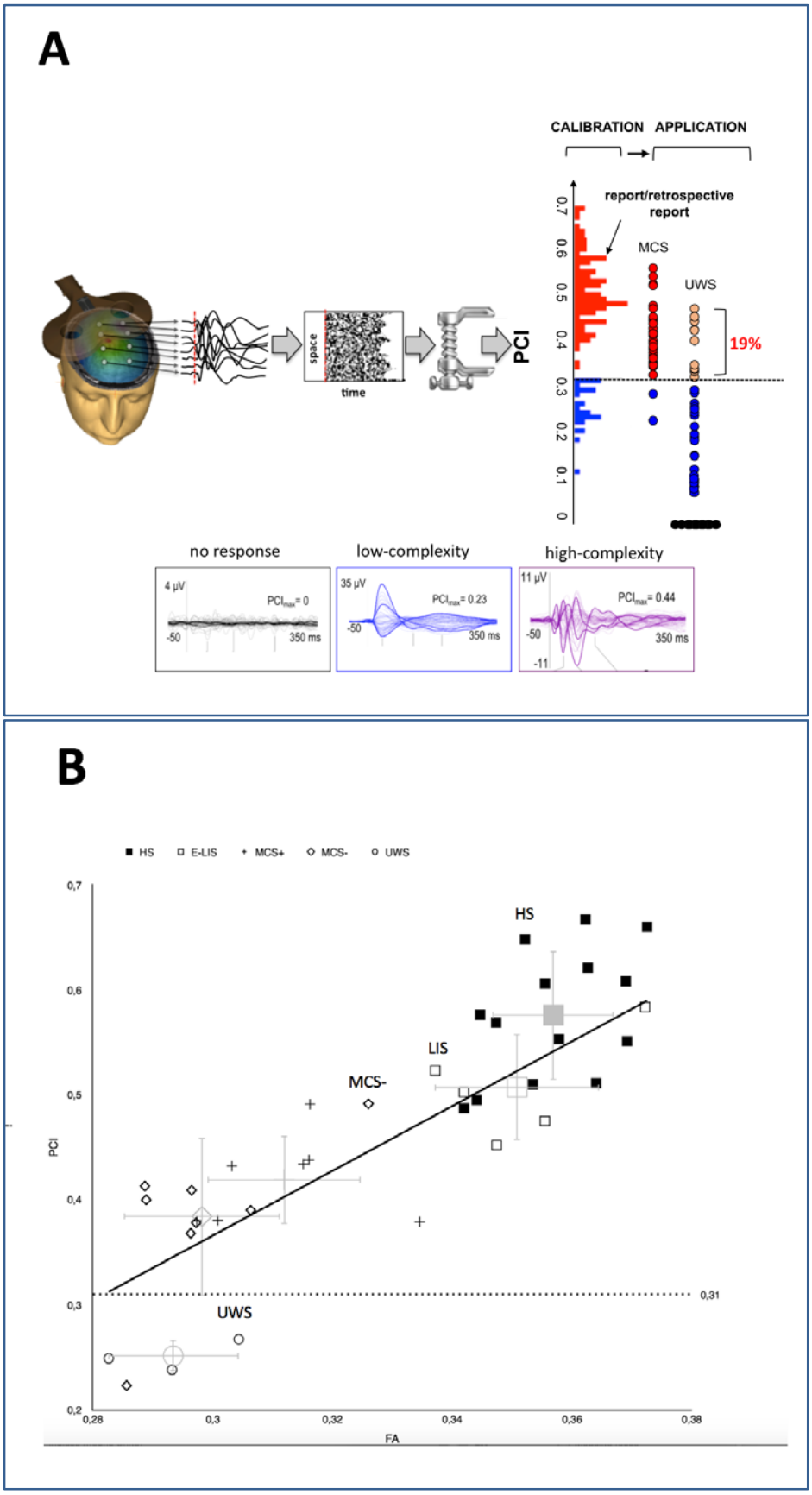


Figure 14: Brain complexity and structural connectivity in disorders of consciousness

(A) stratification of MCS and UWS patients by applying a PCI cut-off derived from benchmarking in healthy subjects. MCS patients are detected with high accuracy, whereas UWS are stratified in three categories (no response, low-complexity, and high-complexity). (B) correlation between PCI and fractional anisotropy values in healthy subjects (HS) and in patients with emergence of MCS and locked-in syndrome (E-LIS), MCS and UWS.

An overarching feature of our effort was to compare and integrate different measures. An example of this is highlighted in Figure 15. Two promising measures (i.e. the PCI and a synergy of 120 EEG-extracted markers using machine learning from a standardised oddball auditory stimulation paradigm (EEG-ERP)) were directly compared to separate conscious from unconscious states in 26 patients with severe brain injuries (i.e. UWS, MCS and emergence of MCS). In addition, measures inspired by theories of consciousness (PCI, an ERP based marker of active task engagement, and measures of complexity and connectivity in spontaneous EEG) have been compared within states of consciousness to test whether any of the measures are confounded with factors other than state and level of awareness. Specifically, two conditions with different degrees of cognitive loading were compared directly within the same subject.

Our results are published scientific articles on the developments, tests, and applications of measures of consciousness in novel situations.

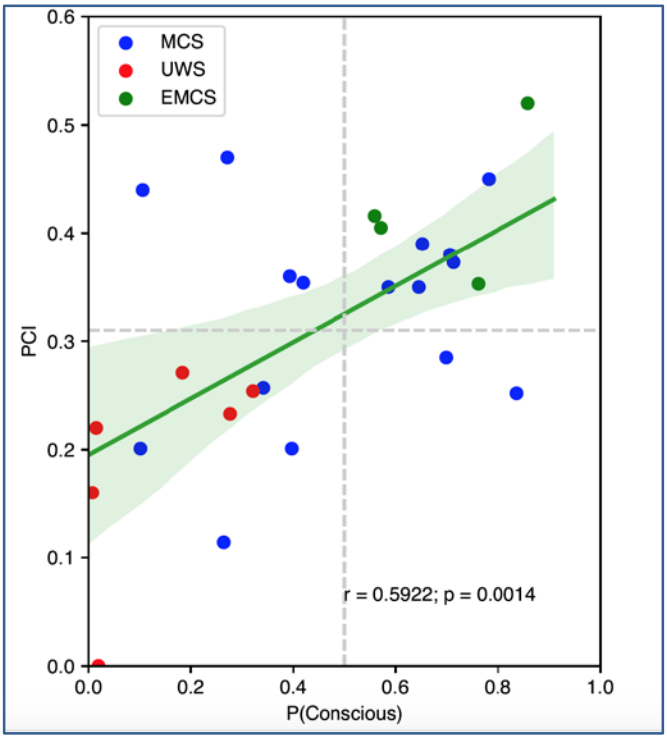


Figure 15: Perturbational complexity index (PCI) correlates with EEG markers in DOC patients

Perturbational complexity index (PCI) and the combination of EEG markers (that predict the individual probability of being (minimally) conscious using machine learning - P(conscious)) provided a consistent diagnosis for 77% of the severely brain-injured patients, and correlated positively.

In addition to studies of human subjects, we studied brain activity in a rodent model undergoing anaesthesia protocols comparable to those used in humans. This allowed us to more closely investigate the underlying neuronal mechanisms important for changes observed in humans during loss of consciousness. Specifically, methods for replicating the PCI in rodents have shown that the loss of complexity in the average global response to local stimulations is also apparent in rodents in the unresponsive, anaesthetised state (see Figure 16)

However, the rodent model allows for more close scrutiny of responses to single stimulations, and indicates that the story is more complicated than what we learned from human studies.

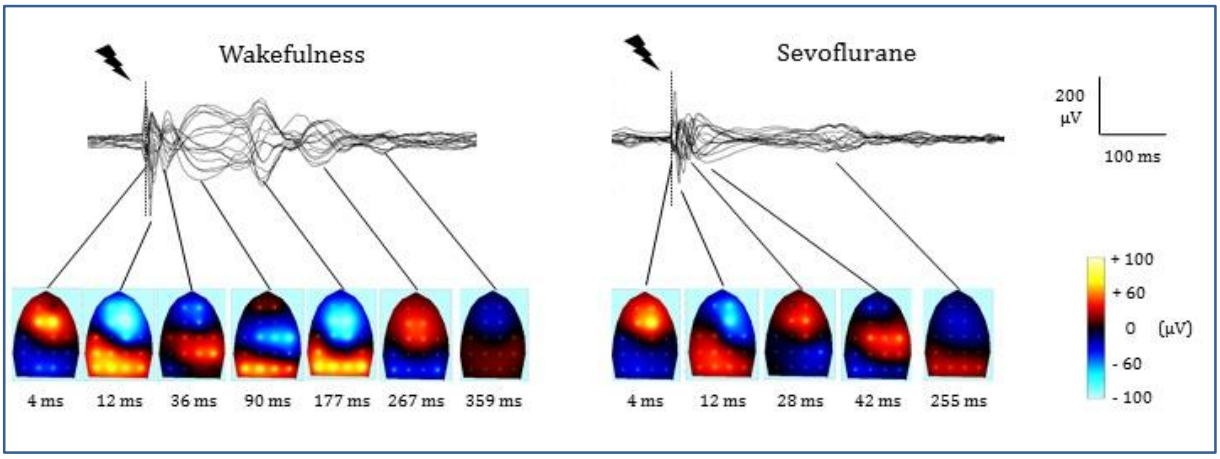


Figure 16: Different perturbed complexity in awake and anaesthetised state in rodents.

Spatiotemporal dynamics of cortical perturbation in rodents. Example of epidural EEG activity in response to electrical stimulation (dashed line) of the right secondary motor cortex, from the same rat during wakefulness (left) and during anaesthesia (sevoflurane, right). The electrophysiological traces in the upper panel represent the superimposition of ensemble averages of event-related potentials (ERPs) from each of the 16 recording electrodes, which are widely distributed over the cortical surface. The bottom panel shows the spatial distribution of the electrodes (white dots) and the colour-coded interpolation of the evoked potentials for single time points after the electrical stimulation. During wakefulness the evoked response is composed of long-lasting waveforms with multiple changes in polarity along time and across cerebral areas, while during anaesthesia the same stimulation produces a shorter response with fewer polarity changes. Similar to PCI-studies in humans, these differences in wave shape can be used to distinguish between conscious and unconscious states in animal models.

Computer simulations

The large-scale thalamocortical network model of Hill and Tononi has been translated into the neural simulator NEST and further developed from its original implementation with the support of Hans Plesser (SP7). At the current stage, the main results of the original paper can be reproduced (orientation selectivity of cells in the primary visual cortex; transition from wake to sleep). Although we could not achieve a perfect match with the results of Hill and Tononi, the model allows testing of predictions of the effects of cortical lesions and neuronal alterations on complexity and sensory transmission. The model is now prepared to be uploaded and shared with the public, in a form meant to make it relatively easy to expand or extend (for example by adding more cortical areas or layers, or by transitioning to new states of interest such as anaesthesia). The model should allow to test specific hypotheses generated in experiments which cannot (for ethical or practical reasons) be tested *in vivo*, and can in turn generate testable implications for *in vivo* experimental testing of mechanistic hypotheses and leading theories of consciousness.

2.4.1 Achieved Impact

We published peer-reviewed articles in international scientific journals and organised academic meetings, workshops, and symposia on consciousness research. We organised several workshops (HBP/EITN Paris workshop, 9-10 March, 2017, organisers and speakers from HBP, including WP3.4: Alain Destexhe, Kathinka Evers, Steven Laureys, Marcello Massimini, Cyriel Pennartz, Johan F. Storm). We co-organised the Consciousness Symposium at the annual Society of Neuroscience (SfN) meeting in Washington DC in November 2017, chaired by Johan F. Storm. It included talks by Marcello Massimini and Cyriel Pennartz, and resulted in a joint review article in Journal of Neuroscience (Storm, Boly, Casali, Massimini, Olcese, Pennartz, Wilke, 2017). We organised and contributed to several science outreach events in Liege and Oslo, including the European Coma Day, Forskningstorget (annual science fair in Oslo), and open/cross-disciplinary meetings at the University of Oslo and the Norwegian Academy of Science and Letters with talks by prominent consciousness researchers: Jean-Pierre Changeux, Rodolfo Llinas, Bjørn Merker, Cyriel Pennartz, and others. For the last 14 months, we have been organising and preparing the first large international HBP conference, on consciousness, to be held in Barcelona, June 21-22, 2018, chaired by JF Storm and organised by Alain Destexhe, Kathinka Evers, Marcello Massimini, Cyriel Pennartz, O Gosseries, JF Storm. The results from the PCI approach (Casarotto et al, Ann Neurol

2016) were highlighted in a cover article in Scientific American ("How to make a consciousness meter" November 2017), translated in several national editions. To share our PCI codes and data analysis pipeline we released a Jupyter notebook on the HBP platform ("A Theoretically Based Index of Consciousness", url: https://collab.humanbrainproject.eu/#/collab/5358/nav/41681) that illustrates the calculation of PCI on source EEG data (a wake/sleep example from the same subject is provided online). The collab has received 57 visits so far (Google Analytics, period: 1 Dec 2017 - 28 Feb 2018).

2.4.2 Highlighted Publications

Amico, E., Bodart, O., Rosanova, M., Gosseries, O., Heine, L., Van Mierlo, P., … Laureys, S. (2017). Tracking Dynamic Interactions Between Structural and Functional Connectivity: A TMS/EEG-dMRI Study. *Brain Connectivity*, *7*(2), 84–97. https://doi.org/10.1089/brain.2016.0462

Annen, J., Frasso, G., Crone, J. S., Heine, L., Di Perri, C., Martial, C., … Coma Science Group Collaborators. (2018). Regional brain volumetry and brain function in severely brain-injured patients. Annals of Neurology. https://doi.org/10.1002/ana.25214

Annen, J., Heine, L., Ziegler, E., Frasso, G., Bahri, M., Di Perri, C., … Laureys, S. (2016). Function-structure connectivity in patients with severe brain injury as measured by MRI-DWI and FDG-PET. Hum Brain Mapp. 2016 Nov;37(11):3707-3720. http://doi.org/10.1002/hbm.23269

Bodart, O., Amico, E., Gómez, F., Casali, A. G., Wannez, S., Heine, L., … Gosseries, O. (2018). Global structural integrity and effective connectivity in patients with disorders of consciousness. *Brain Stimulation*, *11*(2), 358–365. https://doi.org/10.1016/j.brs.2017.11.006

Bodart O, Gosseries O, Wannez S, Thibaut A, Annen J, Boly M, … Laureys S. Measures of metabolism and complexity in the brain of patients with disorders of consciousness. Neuroimage Clin. 2017 Feb 6; 14:354-362. http://doi.org/10.1016/j.nicl.2017.02.002

Casarotto, S., Comanducci, A., Rosanova, M., Sarasso, S., Fecchio, M., Napolitani, M., … Massimini, M. (2016). Stratification of unresponsive patients by an independently validated index of brain complexity. *Annals of Neurology*, *80*(5), 718–729. https://doi.org/10.1002/ana.24779

Chennu, S., Annen, J., Wannez, S., Thibaut, A., Chatelle, C., Cassol, H., …, Laureys, S. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. *Brain*. 2017 Aug 1;140(8):2120-2132. https://doi.org/10.1093/brain/awx163

Juel, B. E., Romundstad, L., Kolstad, F., Storm, J. F., & Larsson, P. G. (2018). Distinguishing Anesthetized from Awake State in Patients: A New Approach Using One Second Segments of Raw EEG. *Frontiers in Human Neuroscience*, *12*. https://doi.org/10.3389/fnhum.2018.00040

Lavazza, A., & Massimini, M. (2018). Cerebral organoids: ethical issues and consciousness assessment. *Journal of Medical Ethics*, medethics-2017-104555. https://doi.org/10.1136/medethics-2017-104555

Storm, J. F., Boly, M., Casali, A. G., Massimini, M., Olcese, U., Pennartz, C. M. A., & Wilke, M. (2017). Consciousness Regained: Disentangling Mechanisms, Brain Systems, and Behavioral Responses. *Journal of Neuroscience*, *37*(45), 10882–10893. https://doi.org/10.1523/JNEUROSCI.1838-17.2017

2.4.3 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
937	EEG in rodents	Yes	Spontaneous EEG data from rodents undergoing different types and levels of anaesthesia. Important for investigating mechanisms of consciousness and for testing measures and methods for such investigations.
941	Mechanistic analysis of ERP in rodents	Yes	Evoked EEG activity data from rodents undergoing different types of electrical stimulations (e.g. increasing current intensities) and in different states and conditions (e.g. wakefulness, anaesthesia). Important for mechanistic understanding of ERPs and ERP-based assessment in humans.
1062	PCI-like measure in rodents	Yes	Current evoked EEG activity data from rodents undergoing different types and levels of anaesthesia. Important for testing the currently most promising index of human consciousness (PCI), and developing the measure further to be applicable also in rodents.
1059	ERP in rodents	Yes	Reports regarding experiments on ERP/EEG in rodents (dissemination in scientific conferences and public events).
909	Large-scale modelling of TMS/EEG-PCI	Yes	A model (in NEST simulation software) for simulating large scale thalamocortical networks of spiking neurons in which potential mechanisms, measures and markers of human consciousness can be tested.
1063	TMS/EEG-PCI in wakefulness, sleep and anaesthesia	Yes	A model (in NEST simulation software) for simulating large scale thalamocortical networks of spiking neurons. The model can transition between wake-like and sleep-like states by tweaking relevant neuronal properties (ionic conductances and synaptic strength) in specific populations of cells.
780	TMS/EEG non-invasive perturbation recordings	Yes	Provides data to inform detailed computational models (components 1351, 909, 746) as well as mass models (component 1574).
1351	Simulation of the effects of brain lesion and cortical bistability on complexity	Yes	Provides a detailed computational model to test hypothesis on brain lesions and cortical bistability at the macroscale (component 780) and at the meso/macro scale (component 975).
717	Structure-function in healthy subjects	Yes	A report regarding experiments on brain structure-function interaction using TMS-EEG and MRI in healthy controls subjects (Amico et al, Brain Connect., 2017).
716	TMS-EEG data in DOC patients	Yes	TMS-EEG data in post-comatose patients. Important for testing the most promising index of human consciousness (PCI) and comparing it with other EEG measures.
715	EEG data in DOC patients	Yes	Resting state and auditory standardized oddball auditory stimulation paradigm EEG data in post-comatose patients. Important for developing a synergy of EEG-extracted markers using machine learning and comparing it with TMS-EEG data.
742	TMS-EEG data in sleep and anaesthesia	Yes	TMS-EEG data in healthy controls during sleep and undergoing general anaesthesia. Important for testing the PCI, and comparing it with other EEG measures and post-coma data.

719	Structure-function in DOC patients	Yes	Reports regarding experiments on brain structure-function interaction using TMS-EEG, MRI and PET in post-comatose patients (Bodart et al, Brain Stimulation, 2018; Bodart et al, Neuroimage Clin, 2017).
741	EEG data in sleep and anaesthesia	Yes	Resting state EEG data in healthy controls during sleep and general anaesthesia. Important for developing a synergy of EEG-extracted markers using machine learning and comparing it with TMS-EEG data and post-coma data.
942	The TMS/EEG-PCI and P3b response for assessment of consciousness	Yes	A report of progress towards testing and directly comparing two theoretically driven measures of consciousness.

2.5 Development of novel learning and plasticity models for visuomotor behaviours, predictive coding and brain state regulation in multi-layer systems

SP3 supports Co-Design Projects of HBP by contributing to studies on plasticity, modelling, and use of biological data with the goal of setting up modelling and computer simulation components in relation to data gathered in this Sub Project.

Eye movement simulation for NEST and the neurorobotics platform & Information theoretic models of layer 5 pyramidal cells

The neuronal differentiation between match and non-match stimuli is a challenge worthy of modelling in NEST simulation. Wibral has successfully ported context-sensitive neurons, as models of pyramidal cells, to NEST and Python to test novel information theoretic neuronal learning rules in large networks. Simulated neurons successfully implement different information theoretic learning rules, based on a novel partial information decomposition. Specifically, they successfully maximise unique information from driving inputs, the shared information of driving and contextual input, as well as the synergistic information between the two input classes. Optimisation goals can be chosen by a simple parameterisation of a generic learning goal. Testing of network models with these neurons for cortical disamplification of feedforward processing which contribute to masking and enhancing interactions will continue in the next period.

To provide neuroscientific data to model match and non-match stimuli, Muckli conducted an experiment utilising the Motion Induced Blindness illusion, in which early visual cortex activity is masked by top-down motion processes, so the feedforward information flow is interrupted and top-down projections replace the feedforward stream. However, when the Motion Induced Blindness ends, the feedforward signal breaks through again – described as prediction error. In a high-resolution human fMRI experiment, decoding of visible oriented targets is interrupted by the coherent motion field that causes the illusion. However, when the illusion is in effect (and the target is no longer perceived), decoding of orientation is possible in mid-layers of primary visual cortex (see Figure 17), which have been associated with stimulus-driven signals rather than top-down predictions.

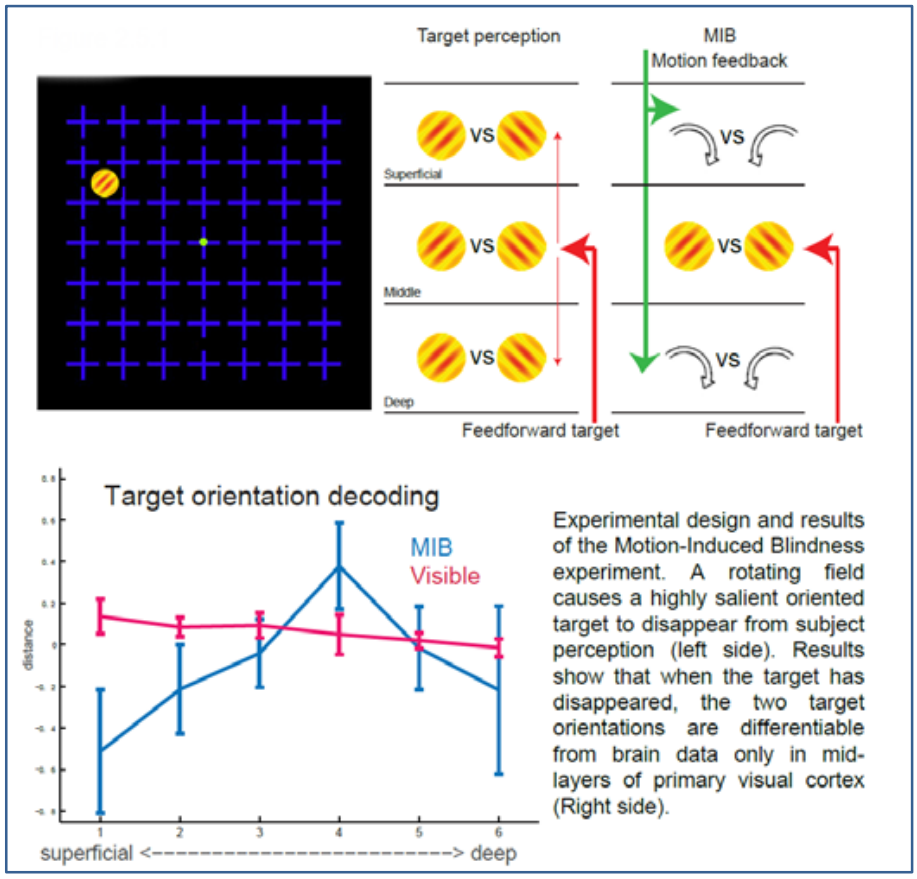


Figure 17: Motion Induced Blindness illusion reveals perceptual overwriting of feedforward stimulation in V1 cortical layers.

Motion induced Blindness at 7T reveals that orientation of non-visible stimuli can be decoded in mid layers of V1 (blue). Visible targets are best decoded in superficial layers (red). Data of 10 brain hemispheres.

The study of the interplay between slow waves and plasticity

Sleep is a physiological state in which the brain periodically expresses, at its early stage, a rhythmic activity at around 1 Hz. This is a rather stereotypical activity, a default activity pattern, which is invariantly expressed across animal species with widely different phylogenetic roots. Such invariance across evolution highlights the importance of sleep function, which in turn is manifold ranging from neocortical maintenance, energy conservation and memory consolidation. In particular, the latter implies an impact of sleep slow rhythms in shaping/rewiring the cortical network synaptic matrix. More specifically, synapses appear to be downscaled after a sleep cycle with exception of the largest 20%. Such global phenomena may in turn have a causal role in redistributing the spontaneous spiking activity expressed during the whole sleep period. Thus, understanding the impact of synaptic plasticity during sleep-like brain states is fundamental to understand its capability to contribute both to the self-consistency of this rhythm and to the impact on reinforcing memory engrams.

During the last two years, the teams of Paolucci and Mattia improved both the simulation engine and the cortical models by i) showing that large-scale simulations of SWA are possible when synaptic plasticity is incorporated; ii) identification of the conditions under which SWA is self-consistently expressed; and iii) showing that the simulations are `affordable' in terms of computational cost.

We started by refining a procedure, based on mean-field theory, to generate a cortical model with memories capable of sustaining SWA, matching experimental *in vitro* measures of the phenomenon. The rhythmic alternation between Up and Down local activity levels gives rise to travelling waves (SWA), when coupled to a near neighbourhood lateral connectivity. Together, this cortical network model and the simulation engine were improved to enable fast, scalable and efficient simulation of models expressing both SWA and irregular asynchronous activity. Tested model networks included up to tens of billions of synapses interconnecting up to tens of millions

of neurons simulated on platforms including up to thousands of hardware cores and software processes. Neurons have been arranged in spatial grids (composed of up to 96x96 cortical modules, grid step 400 μm). The modules have been interconnected assuming a connection probability decaying with the distance with a decay length **λ**= 240 μm compatible with biological values. For this activity on such large systems, a fast simulation engine like DPSNN (Distributed Plastic Spiking Neural Network simulator) was instrumental.

The preparation of the study of the interplay between SWA and memories requires plastic synapses. Therefore, we improved DPSNN by adding classic spike-timing-dependent plasticity (STDP) described in Gütig et al., J Neurosci, 2003. This STDP model was chosen as it is a flexible two-factor STDP and it is also implemented in NEST. We observed that the computational cost of this simple plastic model is not prohibitive for the DPSNN simulator. Simulation speed on one thousand cores is about 1ns per synaptic event for non-plastic models and preliminary measures show a decrease of about a factor 3 when plasticity is switched on. The simulations of the cortical model in SWA showed that, even in the presence of an evident effect of oscillations on synaptic weights (see Figure 18), the rhythmic multiscale activity patterns generated by the cortical systems with plastic synapses is stable for a relatively long transient period (see Figure 19).

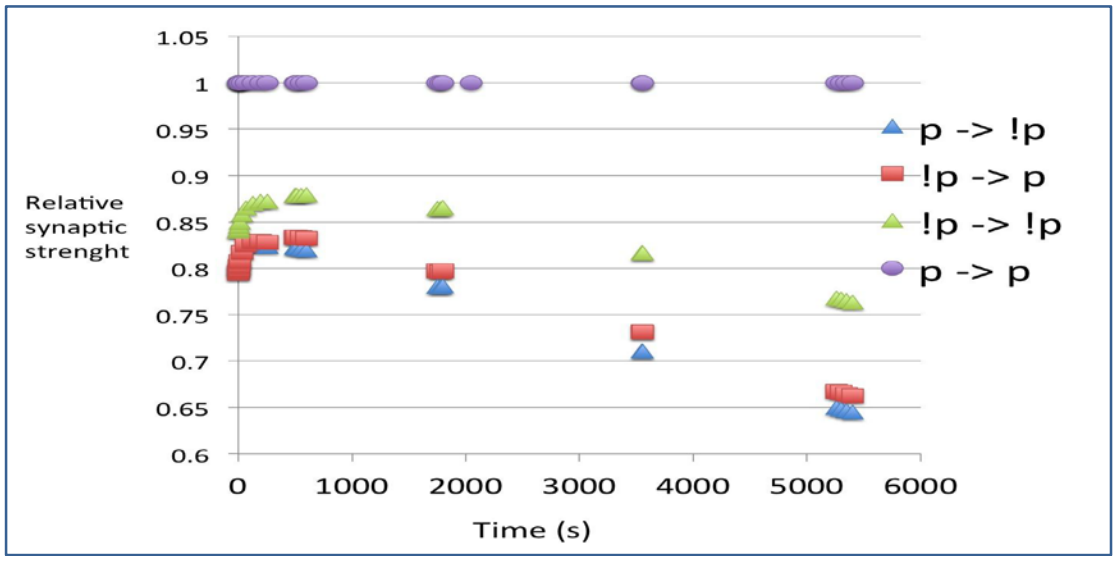


Figure 18 Time variation of relative synaptic strengths of a column undergoing slow oscillations.

Time variation of relative synaptic strengths of a cortical column undergoing oscillatory activity. Time variation of synapses connecting the population of neurons participating to the up-states (circles), neurons in a population not participating to up-states (green triangles), or two neurons where the presynaptic population participates to the up-state, while the postsynaptic does not (blue triangles), or vice-versa (red squares). All synapses strengths are normalized by the strength of the synapses connecting two neurons participating to the oscillation. In the caption, p stands for participating in the up-state, while not p (!p) for not participating.

The porting of the SWA model without plasticity from DPSNN to NEST was completed. In the last few months we tested the behaviour of NEST with the same STDP plasticity and prepared the the models in NEST format (SP6). Models and results will be shared with interested HBP partners using the HBP Collaboratory. In two years from now, the provision of NEST models is expected to enable the run on neuromorphic and neurorobotic HBP Platforms.

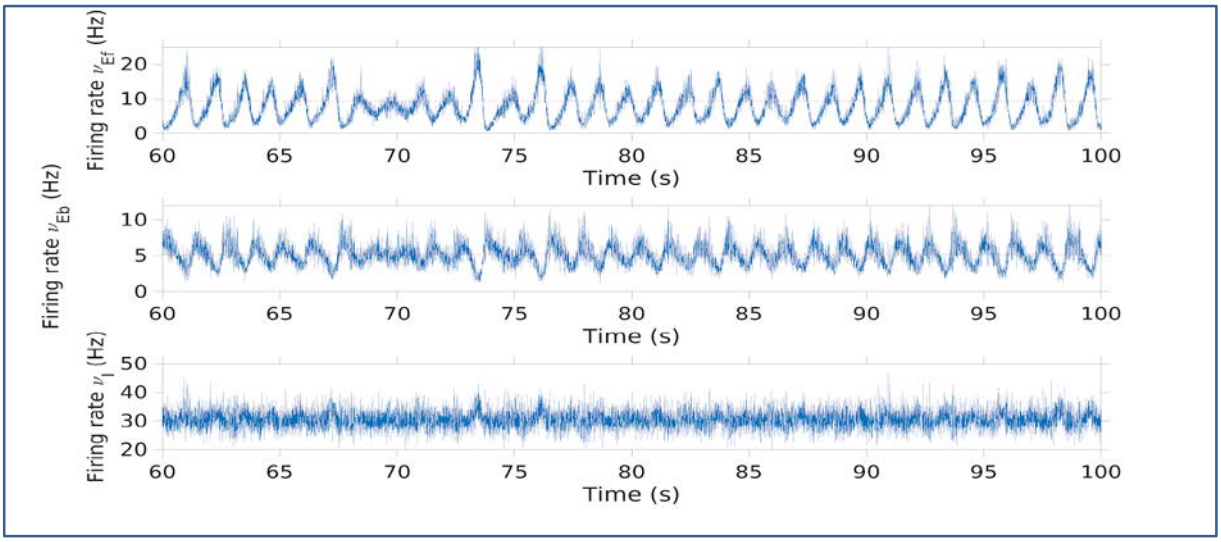


Figure 19: Time course of the slow-wave activity on a cortical module with plastic synapses.

Time variation of the firing rates of excitatory neurons participating to the slow-wave up-state activity (top panel), of excitatory neurons that do not participate in the slow-wave up-state (middle panel), and of inhibitory neurons (bottom panel). The Figure shows that the interaction between the causal variant of STDP and SWA caused a progressive decrease of the amplitude of the waves, but that slow-wave activity persists for a relatively long transient period.

The activity of this task was essential to prepare tools and models necessary to investigate the multiscale interplay between sleep and plasticity, which is a focus in the next two years. Key aspects of the future activity are: a) the evaluation of the stability properties of the SWA generated by a cortical network model incorporating plastic synapses and b) the study of the effect of SWA on the capability of recall memory engrams (distributed attractor states) stored in neocortex. Intuitively, we expect that the strong and coherent neuronal activation typical of SWA might strengthen (the relative weight of) synapses of functionally correlated neurons, while weakening the synapses connecting functionally uncorrelated neurons. To test this hypothesis, we must build a controlled simulation of a cortical module that i) expresses SWA, ii) incorporates synaptic plasticity, and iii) is a realistic representation of mammalian cortical networks. This is possible in collaboration with the Paolucci team, working on the production of mesoscale models, devised to bridge all brain scales when simulated on state-of-the art platforms with state-of-the art simulation engines.

Biologically Plausible Deep Generative Networks

Most computational models that focus on the aspect of biological plasticity only take into account the plasticity related constraints imposed by the brain, for example, development of learning rules that rely on locally available information. The architectural characteristics of neurons in the cortical sensory areas, like retinotopic arrangement of the receptive fields, must also be considered while developing these computational models. We trained a deep neural network in which the layers in the network are retinotopically mapped to the neurons in the layer below (see Figure 20).

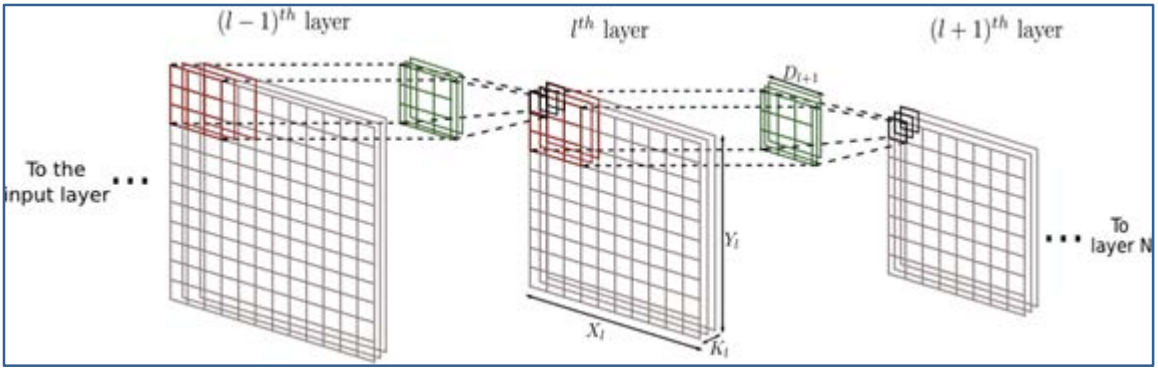


Figure 20: Architecture of a deep predictive coding network with retinotopical organisation of neurons

The network is trained as a generative model using real-world images as stimuli. The weights in the model are adapted such that they capture the structural regularities in the stimuli used to train the model. The trained model can be used to infer abstract representations for external stimuli presented to the network. These abstract representations carry information about the hidden causes that lead to generation of the stimuli in the external world. The lower layers in the model carry information about low-level features like orientations and deeper layers in the model carry information about higher-level features.

Currently, the model has been trained on a single modality i.e. visual input, but it can be generalised to train a model that can handle stimuli in multiple modalities. The model for multisensory input will be used to study the data recorded in animals.

Thalamocortical model simulating wakefulness, sleep, and state transitions

During the past 12 months we developed a large multilayer thalamocortical network model running with the neural simulation tool NEST. The model consists of tens of thousands conductance-based spiking neurons organised into distinct laminar cortical and thalamic regions. The model has the capability to transition between wake- and sleep-like activity patterns when the neuronal properties are appropriately adjusted (see Figure 21 below), and is designed to be easily expanded to include properties and regions relevant to the questions considered. Specifically, cycling through distinct states of consciousness (such as wakefulness and different sleep stages) seems to be important for learning. However, the exact roles of these states in learning is not well understood. The model is intended to provide a testbed to investigate the effect of particular learning rules on mechanisms and measures of integration and differentiation in thalamocortical networks, and the model can become useful to investigate how learning and plasticity interact with the sleep and wake states that mammalian brains naturally cycle through, in addition to being suitable for testing and generating predictions about consciousness in humans (which is the main purpose for the model).

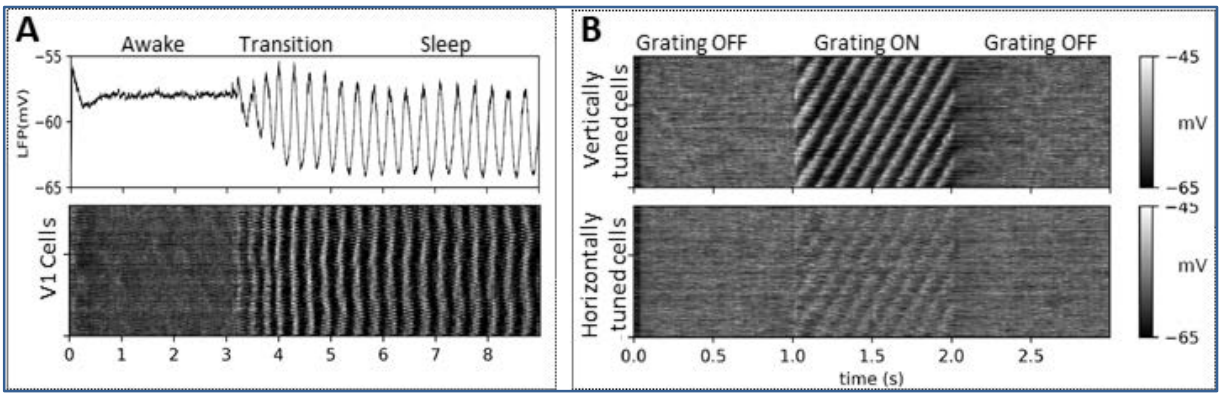


Figure 21: Initial results showing functionality of the thalamocortical model.

In A, a trace of the LFP (top) and a raster-like plot of membrane potential (bottom) of excitatory cells in V1 is shown as the relevant conductances slowly changed from wake-like to sleep-like values. In B, the activity in two cell populations in V1 (vertically and horizontally tuned cells in the top and bottom panels respectively) before, during, and after a moving vertical grating stimulus is fed into the primary thalamic nuclei in the model.

2.5.1 Achieved Impact

- Results were presented at the HBP Fürberg in-depth modelling meeting (2017), the Organization for Human Brain Mapping meeting (Vancouver, Canada, June 2017) and the Alpine Brain Imaging Meeting (Switzerland, 2018 - Best Poster Award for Motion Induced Blindness results). Wibral published papers in Entropy (Wibral, et al 2017, doi:10.3390/e19090494) and Brain & Cognition (Wibral et al. 2017, doi:10.1016/j.bandc.2015.09.004), that extend coding schemes for information theoretic predictive coding network neurons.

- NEST and DPSNN implementations of the SWA model were presented as posters:
  - Distributed large scale simulation of synchronous slow-wave / asynchronous awake-like cortical activity, Elena Pastorelli, Cristiano Capone, Francesco Simula, Paolo Del Giudice, Maurizio Mattia, Pier Stanislao Paolucci. Poster presented at: 2017 NEST Conference, 19-20 December 2017, Haus Overbach, Julich, Germany
  - Distributed large scale simulation of synchronous slow-wave / asynchronous awake-like cortical activity, Elena Pastorelli, Cristiano Capone, Francesco Simula, Paolo Del Giudice, Maurizio Mattia, Pier Stanislao Paolucci. Poster presented at: MSBDY 2017 (Brain Dynamics on Multiple Scales) Int. Workshop, 19-23 June 2017, Max Planck Inst. for the Physics of Complex Systems, Dresden, Germany
- Work in biologically plausible deep generative networks was published and presented as a poster: Predictive coding in deep neural networks. Shirin Dora, Sander M. Bohte and Cyriel M.A. Pennartz, Poster at the Workshop on in-depth learning, Fürberg (Austria), 2017
- The Hill and Tononi model development was presented as a poster at two independent conferences and formed the basis for two talks at HBP conferences (see below). In addition, the model is currently prepared for publishing on the HBP Collaboratory and Github to be available to the public. Finally, the model is tested for compatibility with the SpiNNaker system in Manchester.
  - Simulating deep sleep and awake states in a mammalian thalamocortical model. Nilsen, Andre Sevenius; Murphy, Ricardo; Juel, Bjørn Erik; Storm, Johan Frederik. Poster presented at: 2nd Nordic Neuroscience Meeting; 2017-06-07 - 2017-06-09
  - Implementation of the Hill-Tononi thalamocortical network model in the neural simulator NEST. Murphy, Ricardo; Nilsen, Andre Sevenius, Juel, Bjørn Erik, Storm, Johan Frederik. Poster presented at: Human Brain Project Summit; 2017-10-17 - 2017-10-20
  - The Hill-Tononi thalamocortical network model implemented in NEST. Nilsen, Andre Sevenius. Oral presentation at Human Brain Project Summit; 2017-10-17 - 2017-10-20
  - Thalamocortical model for studying the effects of neuromodulation on network properties.Juel, Bjørn Erik. Oral presentation at CDP5 workshop; 2018-01-24 - 2018-01-26.

2.5.2 Highlighted Publications

Dora, S., Pennartz, C. M. A., & Bohte, S. M. (2018). A Deep Predictive Coding Network for Learning Latent Representations. *BioRxiv*, 278218. https://doi.org/10.1101/278218

Pastorelli, E., Paolucci, P. S., Simula, F., Biagioni, A., Capuani, F., Cretaro, P., … Ammendola, R. (2018). Gaussian and exponential lateral connectivity on distributed spiking neural network simulation. *ArXiv:1803.08833.* Retrieved from http://arxiv.org/abs/1803.08833

Wibral, M., Finn, C., Wollstadt, P., Lizier, J. T., & Priesemann, V. (2017). Quantifying Information Modification in Developing Neural Networks via Partial Information Decomposition. *Entropy*, *19*(9), 494. https://doi.org/10.3390/e19090494

Wibral, M., Priesemann, V., Kay, J. W., Lizier, J. T., & Phillips, W. A. (2017). Partial information decomposition as a unified approach to the specification of neural goal functions. *Brain and Cognition*, *112*, 25–38. https://doi.org/10.1016/j.bandc.2015.09.004

2.5.3 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
743	Multi-scale software model of cortical structures expressing slow waves and the transition to other consciousness states (model)	Yes	Detailed model of layered thalamocortical model of conductance-based spiking neurons with the capability of transitioning between wake-like and sleep-like states, as well as responding properly to "retinal" input.
1037	Neuromodulation and plasticity mechanisms (model)	Yes	Development of simulation tools for studying the relation between neuromodulation and plasticity and connectivity, integration, differentiation, and cortico-thalamic arousal states.
1039	Analysis of neuromodulation and plasticity mechanisms (data)	Yes	Data from test cases of simulated networks cycling through arousal states.
909	Large-scale modelling of TMS/EEG-PCI (model)	Yes	Model development efforts in this component is tightly linked to, and prerequisites for, the components 1037 and 1039
1063	TMS/EEG-PCI in wakefulness, sleep and anaesthesia (model)	Yes	Model development efforts in this component is tightly linked to, and prerequisites for, the components 1037 and 1039
943	NEST/NRP eye movement simulation	Yes	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.
1035	Information Theoretic Network Model of Layer 5 Pyramidal Cells	Yes	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.

3. Component Details

Component details have been entered in the shared google doc: https://docs.google.com/spreadsheets/d/1gNRwfJx4aMNSwR9uWCXyOCheOGovDRI7vYWbnrHn-1U/edit#gid=0

4. Conclusion and Outlook

During the current period, we have substantially extended our understanding of the impact cortical feedback has on sensory processing. Experiments have shown that feedback is behaviourally relevant and necessary for perception, conveys predictive and contextual information, and improves processing of cluttered and noisy stimuli. These findings will be extended in the upcoming period by incorporating research questions concerning the temporal components of cortical predictions. Gaining knowledge about this topic will be particularly impactful when applying knowledge about the brain to real-world tasks, which are rarely static. Also, in order to maximise impact of addressing these questions, we continue to develop new collaborations with experts within HBP.

Furthermore, we tested the effects of bistability on cortical dynamics across scales (micro-, meso- and macro-scale), species (human, rodent, ferret slice) and models (pharmacological modulation, natural sleep and vegetative state). This comprehensive exploration, linking micro- to macro-scale, will 1) constrain theoretical models and simulations concerning the emergence of complex causal interactions in thalamo-cortical networks, 2) shed light on the basic neuronal mechanism underlying loss and recovery of complexity in both physiological and pathological brain states. We studied slow oscillations *in vitro* and *in vivo*, in healthy animals and in models of neurological disorders, anaesthetised and awake. We provided insights into the mechanisms underlying the generation and propagation of slow oscillations, and we identified key alterations in brain activity in animal models of neuropathology. We achieved the first light-regulated drug that allows manipulating brain waves with light. We learned important design lessons to further accelerate photostimulation tools during SGA2 and identified interesting questions to achieve a deeper understanding of the complex biochemical signalling underneath brain waves. Relying on the theoretical characterisation of slow-wave activity, we developed novel analysis tools leading to a more detailed representation of the phenomenon and a better understanding of the mechanisms underlying the multi-scale organisation of the cerebral cortex. With this knowledge, we developed new models of the cortical networks capable to match and predict experimental observations. We demonstrated the feasibility of SWA simulation of cortical areas at biological resolution (number of neurons / mm^2 and synapses/neuron) on computing platforms including thousands of processing cores, and developed efficient and scalable coding techniques (in particular concerning the exchange of spiking messages and memory locality) contributing to the definition of requirements for future interconnects of HBP systems dedicated to cortical simulations. Finally, we added synaptic plasticity to SWA simulations, and demonstrated the feasibility of plastic simulation at large scale on distributed computing platforms, opening the path to the exploration of the interaction between slow waves and encoded memories. There is growing evidence of the importance of SWA activity for the optimisation of the coding of memories acquired during wakefulness and for the recovery of optimal working points at the scale of the individual neuron and of neural networks. Deep sleep is a phenomenon common to all mammalian brains. Neuromorphic robotic platforms should model this. Our findings constitute a solid foundation to start the activity for the next two years, focusing on the detailed description of area-specific SWA characteristics, of the SWA-memory interaction and of the transition to higher complexity states.

Hippocampal-neocortical interactions in human 7 Tesla fMRI and MR-PET were studied. For our rodent studies, we developed a Virtual Reality system which has allowed dissection of visual and self-motion inputs to hippocampal spatial responses. We also developed behavioural training protocols and methodological procedures record population activity across multiple cortico-hippocampal areas in rats performing object recognition tasks, and gathered the first data. This serves as an important proof-of-principle and will be used to further fine-tune the experiments. Based on the first recording, a data-analysis pipeline will be constructed. We investigated first low-level steps of multisensory integration in the brain. The relevance of LFP-phase and spike relations provides a novel way of interpreting multisensory integration, and could provide insights in its relevance in other parts of the neural code, influencing neural models. We continue to develop a computational model of episodic memory modelled on the hippocampal system and to implement visual-tactile data based on the multisensory object discrimination study in rats into robotic systems.

We validated and tested a metric (brain complexity, PCI) that detects consciousness independently of sensory processing, executive functions and motor behaviour and we explored relevant dissociations in severe brain injury. By studying patients with focal injury we are gaining further insight on the effects of lesions on cortical complexity which will inform clinically-oriented computer simulations. Our efforts to measure consciousness in humans directly have an impact on the clinical treatment of consciousness disorders that will be deepened in the next years. Besides, the application of the same experimental approach in rodents opens the opportunity of testing hypotheses about the nature of consciousness generated from human studies in a more controlled model. At the same time, the optimisation of an *in silico* model of the brain is another experimental environment to test hypotheses in the near future. We believe that this will result in a virtuous circle, in which the insights from experiments in animals and computational models will inspire more accurate experiments in humans, increasing our understanding of mechanisms of consciousness that can be applied in clinic.

We investigated mismatch between feedforward and feedback signalling and took steps to develop information theoretic models of such mismatch using the NEST simulator. We showed that feedforward signals are observable in deep layers of cortex while perception is “overwritten” by top-down signals using high-resolution fMRI. These results develop a coherent picture of the targets of feedforward and feedback information to human early visual cortex. We also trained a deep neural network with retinotopic arrangement of receptive fields in a biologically plausible manner. The trained models use rate-based neurons and future work will focus on converting these models to a spike-based framework. Finally, we developed a large scale thalamocortical model, which was challenging and time consuming, but it resulted in a platform that can be used for testing theoretical predictions about network-level mechanisms related to arousal levels and states.