Systems and Cognitive Neuroscience - Results for SGA2 Year 2: (D3.6.2 – SGA2)

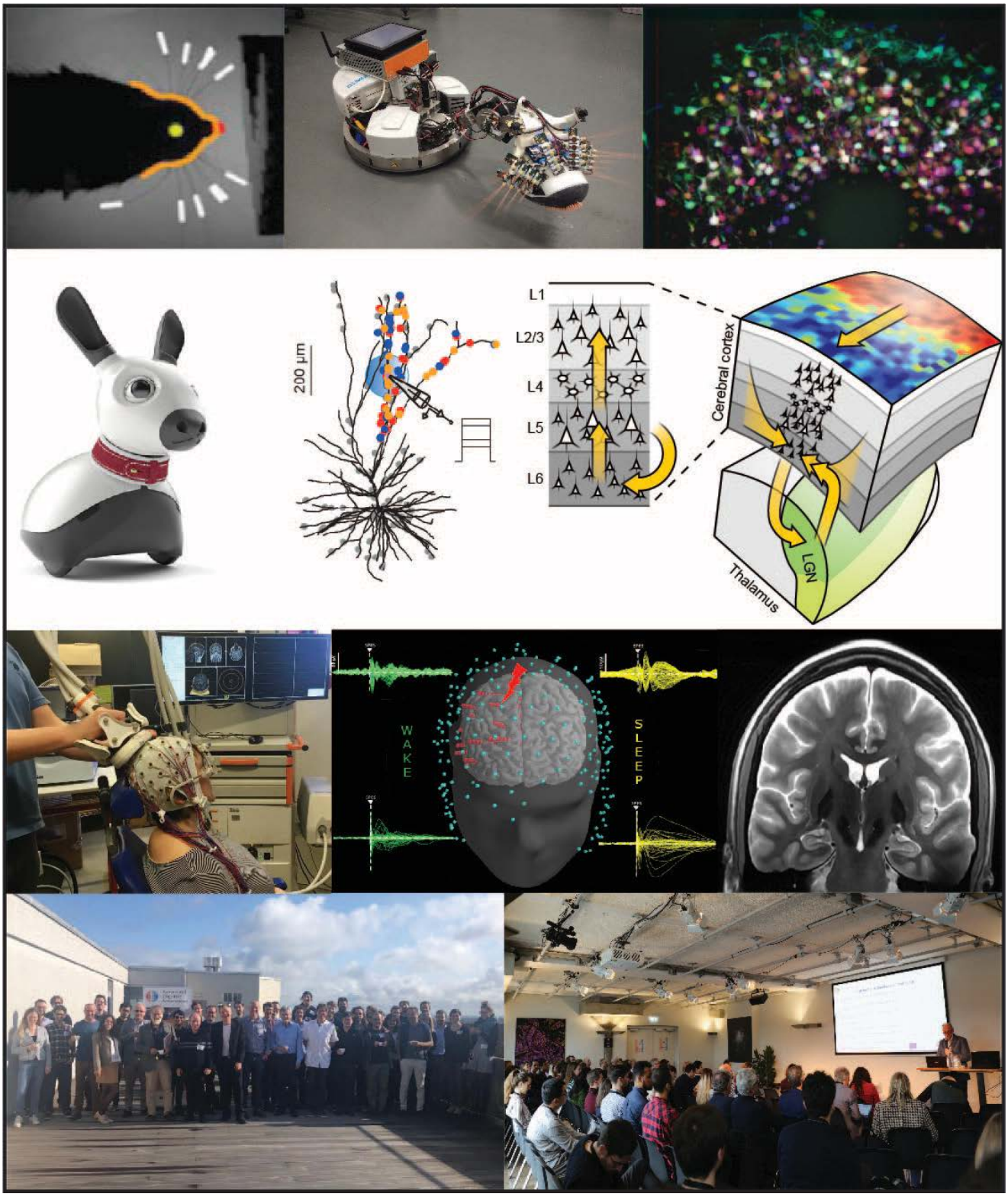

Figure 1: SP3 studies brain activity and cognitive functions from rodent to humans and robots

The Systems and Cognitive Neuroscience subproject (SP3) of the Human Brain Project asks: How does the brain produce cognitive phenomena such as memory and consciousness? Researchers simulate behavioural and cognitive processes and brain states, validate experimental protocols and acquire datasets. We study how cognitive functions and brain states can be measured and compared between animal, human and computational systems.

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Abstract:	This Compound Deliverable includes the achievements from SP3 Systems and Cognitive Neurosciences by M24 in SGA2.
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History of Changes made to this Deliverable (post Submission)

Date	Change Requested / Change Made / Other Action
23 Apr 2020	Deliverable submitted to EC
29 Jul 2020	Main changes requested: • P71: Before being published, at this is the main public deliverable of SP3, some editorial adjustment should be made, as the document makes a lot of references to Components, sometimes apparently bijectively corresponding to outputs, but sometimes it is much more obscure for the external reader what those are. • D3.6.2 should be editorially proofread before publication.
04 Aug 2020	Revised draft sent by SP/CDP to PCO. Main changes made, with indication where each change was made: • Change 1: removed all references to components from the document – as this is not so relevant for the external reader; • Change 2: updated the Table of Contents to match the removal of Component numbers; • Change 3: used full names in titles instead of abbreviations (e.g. SWA); • We have proofread the document.
31 Aug 2020	Revised version resubmitted to EC by PCO via SyGMa

1. Overview

SP3 delivered datasets, models and software to understand cognitive processes, such as sleep, memory and consciousness, from the microscopic level in rodents to human behaviour and robotics.

In two years, we have advanced modelling of bottom-up, lateral and top-down integration in recurrent convolutional and auto-encoding neural networks. Networks have been scaled up to real-world image classification tasks and are being used to explain and predict high-resolution human fMRI data, and electrophysiological, optogenetic and 2-photon calcium imaging rodent data.

In relation to sleep, we present experimental data, analysis tools, modulation techniques, theoretical models and simulations of deep sleep, coma and anaesthesia states, of the transition to wakefulness and of their complexity. The prototype of a multiscale, multi-methodology, modular workflow leveraging state-of-the-art information technology is a preview of how we plan to offer this body of knowledge to the public through EBRAINS.

Regarding perception, in order to understand how different unimodal (sensory) object features get integrated into coherent, multi-modal object representations, we acquired human brain imaging and rodent electrophysiological recordings, set up pipelines for data curation and analysis with the HBP platforms. We developed models of multisensory integration, spatial memory and navigation, and brain-inspired robots. A predictive coding model was integrated in a robot and shown to improve place recognition. These multi-level data are integrated into a theory for multisensory integration and neural compression, storage and reconstruction of memories.

We studied the basis for conscious, awake brain states and experience, such as perception and dreaming, as opposed to dreamless sleep, anaesthesia, or coma. Experimental data and computer models were collected, developed, and combined, in order to understand these processes across levels and species, from brain cells to behaviour and from rodents to humans. We have established ethical methods for measuring consciousness and improving the life of individuals with the associated pathologies and published a neurophilosophical framework for defining criteria of consciousness in animals, non-verbal humans and machines.

Finally, we have developed and integrated models of the motivational and action selection systems on the cognitive architecture of the robot MiRo. Such models were centred mainly around the dynamics and interaction of subcortical regions like the hypothalamus and the basal ganglia. These models will be made available via EBRAINS and the Neurorobotics Platform (NRP).

2. Introduction

Since April 2018, SP3 has contributed to provide rodent and human datasets, analysis tools, methods, and biologically plausible computational models of the brain to the neuroscience community, aiming to understand aspects of cognition in multiple scales in an integrated and collaborative manner with the HBP platforms and other SPs.

We studied cortical contextual processing of systems neuroscience at different levels (neuronal signalling, interactions between cortical layers, within cortical columns, between neighbouring areas, and between remote cortical areas). We have expanded the study of contextual processing beyond visuospatial and multi-sensory context to include temporal context. Key Result KR3.1 (deep neural network models for visual recognition with novel context-modulation units) was achieved through a collaborative effort of three institutions (UGLA, KNAW and UBER), each developing a sophisticated understanding of large-scale neural interactions and network models that integrate recurrent information processing in context-sensitive object recognition. This experimental work produced high-resolution human functional MRI data and electrophysiological, optogenetic and 2-photon calcium imaging rodent data to inform neural network models.

Furthermore, we investigated the cortical activity during sleep and the mechanisms that support the transition to higher complexity states and to wakefulness, with a specific focus on different states of consciousness. Key Result KR3.2 (sharing experimental data, simulation models and analysis tools relying on novel concepts and approaches to characterise high-resolution spontaneous and perturbed

multi-areal slow wave activity (SWA)) was achieved in a joint effort of five institutions (UMIL, IDIBAPS, IBEC, ISS and INFN). This laid the basis for the investigation of the cognitive functions of sleep and also contributed to the achievement of KR3.5. We provided HBP platforms with simultaneous scalp high-density electroencephalography (HD-EEG) and intracranial electroencephalography (Stereo-EEG) human datasets, rodent micro-electrocorticography (micro-ECOG), modulation methodologies and multiscale models of sleep, anaesthesia and excitability. Also, connectivity and parameters for simulation of whole cortical mouse hemisphere activity have been inferred from wide-field optical imaging data of SWA, provided by LENS. A collaboration of Work Packages in SP3 (WP3.2 and WP3.4) led to the integration of data, analysis pipelines and models into a prototype of EBRAINS multiscale, multi-methodology workflow.

For achieving Key Result KR3.3, we gained empirical insights in multisensory pattern completion in the brain, and compared firing rate responses from simulated neurons to firing patterns recorded from behaving rodents and humans. The role of episodic memories (conglomerates of information from multiple modalities) was investigated in both rodents and humans and in relation to information processed from different senses (e.g. auditory, visual) and domains (e.g. object-information, scene information). Also, we examined how unimodal cues are completed towards coherent multimodal memories at episodic retrieval in rodents and the environmental influence in self-motion and visual integration by taking advantage of a virtual environment. We successfully acquired behavioural data on multimodal integration and retrieval of episodic memories in humans and rodents which informed computational models of multisensory predictive coding (KR3.5). Together with the HBP Neuroinformatics Platform we built a use case for analysing synchrony amongst ensembles in cortex and hippocampus in the context of multisensory object recognition.

Consciousness research studies the brain's capability of conscious representations of the world and itself. For achieving Key Result KR3.4 (gather different measures of consciousness and their generalisation from different functional states and anaesthesia conditions in humans, animal models, computer simulations and neuromorphic circuits), four institutions (UIO, ULG, UMIL, UVA) collaborated to improve our understanding of neuronal mechanisms of consciousness. We have tested hypotheses in rodents and humans, and developed improved, theoretically driven methods for objective assessment of brain states and consciousness, for clinical and basic scientific purposes. Structural and functional brain imaging, scalp electroencephalography (EEG), combined with magnetic stimulation (TMS), were used in humans, and EEG, stimulation, and 2-photon imaging in animals, to record spontaneous brain activity, responses to cortical perturbations, and sensory evoked potentials, combined with computer simulations in brain network models. Moreover, we published a theoretical framework outlining criteria for consciousness in non-verbal humans, animals and machines.

Finally, to advance the Mammalbot architecture (a collaboration of Work Packages WP3.5 and WP3.3) in SGA2 we have focused on the motivational and action selection subsystems. We modelled the motivational system both at the dynamical and neuronal levels with a focus on the phenomenon of motivational conflict widely studied in the field of ethology. The neuronal models have focused on the interaction of the homoeostatic state representation by the hypothalamus and the dopaminergic reward system. Dopamine, in turn, works as the main interface with the subcortical action selection system; the basal ganglia. A complementary model was produced that implements cross-modal predictions and recall by way of multimodal predictive coding. This model was incorporated in the WhiskEye robot and shown to improve place recognition in a VR environment (with SP10). The major Outputs produced in this 2-year period of the Specific Grant Agreement 2 are presented in this document, organised per Key Result and their impact.

3. Key Result KR3.1

We will develop deep neural network models for visual recognition with novel context-modulation units. These units have separate integration sites for bottom-up driving input and for contextual input and will be informed by high-resolution human brain imaging and neuronal recordings (2-photon calcium and electrophysiology data from mouse somatosensory and visual cortices) relating to temporal expansion of context in neuronal computations.

3.1 Outputs

Key Result (KR3.1) is a combination of modelling and experiments, culminating in biologically plausible, contextual processing in deep recurrent neural networks at a scale capable of tackling modern image classification. This Key Result also delivers multi-level, cross-species data investigating contextual processing and temporal expansion in humans (high-resolution fMRI) and rodents (electrophysiological, optogenetic and 2-photon calcium imaging).

3.1.1 Overview of Outputs

3.1.1.1 List of Outputs contributing to this KR

- Output 1: Neural networks for flexible visual recognition and predictions
- Output 2: Human fMRI data for predictions in time and space
- Output 3: The role of feedback, inhibition and attention in learning
- Output 4: Apical amplification of human and rodent pyramidal neurons

3.1.1.2 How Outputs relate to each other and the Key Result

Outputs produced to accomplish this Key Result relate to biologically plausible neural network models, as well as functional human and rodent data for improving models. Output 1, which involves modelling, depends on Outputs 2, 3 and 4. Outputs 2, 3 and 4 investigate multi-level brain processes involving non-feedforward signals and stand-alone. Outputs are made available in the EBRAINS Knowledge Graph upon publication. Paradigms were developed between labs, providing complementary data informing neural network models.

3.1.2 Output 1: Neural networks for flexible visual recognition and predictions

Previously, we developed neural network models incorporating biologically inspired recurrent connections. We expanded models to process real-world images using bottom-up and lateral (BL) convolutional connections, endowing networks with robust performance dominance over state-of-the-art feedforward models. Network behaviour compares to human behaviour and learned lateral connectivity in early network layers compares to lateral connectivity in human early visual areas. We have submitted a manuscript (pre-print: P2284). We investigated similarities between human early visual cortex and a deep-learning neural network with encoder/decoder (autoencoder) architecture, trained to reconstruct occluded scenes. This network architecture has been compared to the brain's feedforward encoding of data and top-down decoding of data to generate scene predictions.

Table 1: KR3.1 Output 1 Links

Link to	URL
Model Repository (feedforward and recurrent neural network)	https://github.com/cjspoerer/rcnn-sat
Technical Documentation	https://www.biorxiv.org/content/10.1101/677237v3 (P2284)
User Documentation	https://github.com/cjspoerer/rcnn-sat/blob/master/README.md
Model Repository (NEST)	https://github.com/sepehrmn/nest-simulator/tree/bpid_kp_2017
Technical Documentation	https://doi.org/10.1016/j.bandc.2015.09.004 (P1092)
User Documentation	https://nest-simulator.readthedocs.io/en/latest/

Software Repository (NEST)	https://github.com/sepehrmn/nest-simulator/tree/bpid_kp_2017
Technical Documentation	https://www.biorxiv.org/content/10.1101/677237v3 (P2284)
User Documentation	https://github.com/cjspoerer/rcnn-sat/blob/master/README.md

3.1.3 Output 2: Human fMRI data for predictions in time and space

We investigated whether we can read out brain predictions about upcoming scenes. Subjects were exposed to a virtual reality apartment. We recorded fMRI during navigation through the partially occluded virtual apartment (to isolate top-down signal content). We could read out the identity of a future room from occluded brain areas while subjects were moving through the first room.

An important aspect of brain processing is where contextual information is transmitted from. We investigated functional connectivity using fMRI and occluded movies. We correlated cortical feedback activity in primary visual cortex with activity in higher areas during scene occlusion. We compared fMRI data from occluded early visual cortex with layers of an autoencoder network processing the same scenes (see Output 1). The network was more similar to brain activity than a classical supervised network, indicating that neural network models of vision should incorporate cortical feedback (P2107).

Table 2: KR3.1 Output 2 Links

Link to	URL
Data Repository	DOI: 10.25493/QX7C-WSR and 10.25493/82YA-0HU
Technical Documentation	
User Documentation	

3.1.4 Output 3: The role of feedback, inhibition and attention in learning

We developed an approach to image neuronal responses in dendritic tufts, the dendrite connecting the tuft to the cell body, and the cell body itself using *in vivo* two-photon microscopy of calcium signals in awake mice performing a visual task. We developed a software package for analysing calcium imaging data for subcellular structures. We adapted a visual occlusion paradigm from humans (in collaboration with Outputs 1 & 2) to mice to study feedforward and feedback processing in primary visual cortex (V1) in a multiscale, multi-species manner.

We developed behavioural tasks in which mice learn to respond to visual stimuli that are hypothesised to require feedback processing for identification. We found that higher cortical brain regions provide feedback to V1. Using two-photon microscopy and advanced methods to selectively manipulate neuronal activity, we found subsets of neurons that do not stimulate, but actually inhibit other visual neurons, playing crucial roles in integrating feedforward and feedback signals.

We examined how neural activity in monkey primary visual cortex changes during learning of complex shapes. Neural activity was higher at the border of the figure and weakly suppressed on the background prior to learning. After learning, shape backgrounds became strongly suppressed. If attention was directed away from the shape, the background was released from suppression. Results show that visual experience and attention both cause suppression of neural activity related to irrelevant stimuli in visual cortex, thus creating more accurate neural models of our environment (P2423).

Table 3: KR3.1 Output 3 Links

Link to	URL
Data Repository	https://kg.ebrains.eu/search/instances/Dataset/684eff17-358f-431d-849a-8b81332a1f19 (embargoed)
Technical Documentation	

User Documentation	and https://github.com/Leveltlab/SpectralSegmentation
Dataset Repository	https://kg.ebrains.eu/search/instances/Dataset/f5a6cbf3-7d74-4210-b8f1-236a9b44ea19
Technical Documentation	
User Documentation	

3.1.5 Output 4: Apical amplification of human and rodent pyramidal neurons

The apical amplification theory hypothesizes that depolarisation of the apical dendrites of neocortical pyramidal neurons can enhance response to the somatic inputs that specify a cell's selective sensitivity. To test this hypothesis, we developed paradigms and tested behavioural, recording and theoretical approaches. We described the XOR operation in human dendrites (P2281). We described how apical dendritic coupling with layer 5 pyramidal neurons relates to consciousness. We described a novel cortico-cortical pathway that links deep layer 6 with input to pyramidal neurons.

To test the effect of visual stimuli on visual and somatosensory responses 1) we are training mice to use visual cues (moving random dots) to guide behaviour, while we image from cortical soma and dendrites using prisms; 2) we are training head fixed mice to use both visual or tactile stimuli to detect novel objects; and 3) we are training mice in a two choice discrimination of images used in human fMRI (in collaboration with Outputs 1 & 2).

Table 4: KR3.1 Output 4 Links

Link to	URL
Data Repository	https://doi.org/10.12751/g-node.57a01e
Technical Documentation	and
User Documentation	https://www.jneurosci.org/content/early/2019/10/30/JNEUROSCI.1809-19.2019?versioned=true

3.2 Validation and Impact

3.2.1 Actual and Potential Use of Output(s)

Modern AI neural networks depend primarily on feedforward connections to transform data into meaningful task representations. Network models in Output 1 are robustly dominant due to added lateral or top-down connections. Therefore, these networks could have substantial impact on the AI community (P2284).

The autoencoder network described in Outputs 1 & 2 outperformed a classical supervised network in describing human cortical feedback activity, indicating that neural network models of vision will benefit from cortical feedback (P2107). Additionally, Output 3 describes how attention affects neuronal activity when the visual system processes objects. These results are valuable for artificial models incorporating attention.

Output 4 has described an expanded capability of human layer 2/3 pyramidal neurons, which were thought to share qualities with artificial neuronal networks and rodent neurons of the same class. This Output has shown that human neurons are uniquely capable of solving the XOR logic problem (P2281), making them more computationally sophisticated than previously thought. This discovery could inspire the AI community in designing computational units.

3.2.2 Publications

Publications produced during achievement of KR3.1 relate to neural network models (from Output 1) or human data (Output 2) and rodents (Outputs 3 & 4) to inform network models. Data come from experiments probing non-feedforward brain processes, signals often missing from models of visual recognition (P2284) and working memory (P2423). The importance of non-feedforward brain signals is discussed in P2107 and P2281.

- **P2284** (Output 1): Spoerer C.J., Kietzmann T.C., Kriegeskorte N. (2019): Recurrent networks can recycle neural resources to flexibly trade speed for accuracy in visual recognition. *BioRxiv*. doi: 10.1101/677237
- **P2107** (Output 2): Morgan A.T., Petro L.S., Muckli L. (2019): Scene Representations Conveyed by Cortical Feedback to Early Visual Cortex Can Be Described by Line Drawings. *J Neurosci*. 39:47, pp. 9410-9423. doi: 10.1523/JNEUROSCI.0852-19.2019.
- **P2423** (Output 3): van Vugt B., van Kerkoerle T., Vartak D., Roelfsema P.R. (2020) The contribution of AMPA and NMDA receptors to persistent firing in the dorsolateral prefrontal cortex in working memory. *J Neurosci*. 40:12, pp. 2458-2470. doi:10.1523/JNEUROSCI.2121-19.2020
- **P2281** (Output 4): Gidon A., Zolnik T.A., Fidzinski P., Bolduan F., Papoutsi A., Poirazi P., Holtkamp M., Vida I., Larkum M.E. (2019) Dendritic action potentials and computation in human layer 2/3 cortical neurons. *Science*. 367:6473, pp. 83-87. doi:10.1126/science.aax6239.

4. Key Result KR3.2

A collab including experimental data, simulation models and analysis tools relying on novel concepts and approaches to characterise high-resolution spontaneous and perturbed multi-areal slow wave activity expressed under different levels of activation at different scales (multiunit, LFP in rodents, intracranial and scalp recordings in humans).

4.1 Outputs

The Key Result (KR3.2) is a multiscale, multi-methodology, combination of experimental data (in rodents and humans), simulation models and modular analysis pipeline workflows applicable to both experimental data and simulation outputs regarding cortical slow wave activity expressed under deep-sleep and anaesthesia in physiologic and pathological conditions. It has been designed in strict cooperation with SP5 as an exemplar design of the EBRAINS conceived modular workflows.

4.1.1 Overview of Outputs

4.1.1.1 List of Outputs contributing to this KR

The following is a list of key Outputs produced during the period M1-M124 of SGA2 (April 2018 – March 2020):

- Output 1: Cortical multiscale data in mouse in different brain states and in models of cognitive deficits
- Output 2: Data curation and containers for simultaneous scalp HD-EEG and intracranial EEG recordings
- Output 3: Analysis pipeline for experimental (and simulated) SWA
- Output 4: Whole mouse cortical hemisphere simulation with connectivity inferred from experimental activity
- Output 5: Photo-modulation of SWA and brain state transitions with PAI

4.1.1.2 How Outputs relate to each other and the Key Result

"Cortical multiscale experimental data in mouse about different brain states under physiological and pathological conditions (Output 1)" and mesoscale and macroscale data in humans, "simultaneous scalp High-Density EEG (HD-EEG) and intracranial EEG recordings both in wake and sleep (Output 2)", both made available in the EBRAINS Knowledge Graph, are among the key inputs to the available prototype of "Analysis pipeline for experimental (and simulated) SWA (Output 3)", designed and developed in cooperation with SP5. This analysis pipeline is also: applied to simulation results 1) to characterise simulated SWA and 2) to infer from experimental SWA activity essential parameters, like functional connectivity, for the "simulation of SWA activity at the scale of a whole cortical hemisphere in mouse (Output 4)". The objective of taking control of the underlying molecular mechanisms is addressed by the "Output 5: Photo-modulation of SWA and brain state transitions with PAI", about the design and experimentation of a photoswitchable muscarinic neuromodulator.

4.1.2 Output 1: Cortical multiscale data in mouse in different brain states and in models of cognitive deficits

This Output is a product of T3.2.3 (IDIBAPS; P1996) and it is the basis for T3.2.1 (ISS) and T3.2.5 (INFN) models and analysis pipelines. It includes SWA data acquired with 32 electrodes ECoG data on both wild-type mice and two transgenic models of cognitive deficit that occur in children: Williams-Beuren syndrome (WBS) and fragile X syndrome (FXS). Several structural and functional brain alterations are characteristic of this syndrome, as well as disturbed sleep and sleeping patterns. This Output is key for the analysis pipelines described as Output 3.

Table 5: KR3.2 Output 1 Links

Link to	URL
Data/Model Repository	Propagation modes of slow waves: DOI: 10.25493/WKA8-Q4T Williams-Beuren Syndrome: DOI: 10.25493/DZWT-1T8 Fragile X Syndrome: DOI: 10.25493/ANF9-EG3
Technical Documentation	
User Documentation	

4.1.3 Output 2: Data curation and containers for simultaneous scalp high definition-EEG and intracranial EEG recordings

The group at the University of Milan (UMIL) produced two datasets of simultaneously recorded scalp HD-EEG and intracranial EEG (P2341). These datasets are now curated and findable in the KG and can be used to study how specific brain dynamics, such as slow waves, are generated during sleep and propagate from their sources (Pigorini *et al.*, [dataset]), employing ground-truth-based methodologies (Mikulan *et al*. [dataset, article under review]). Thus, they provide the first direct link between mesoscale and macroscale in humans.

Table 6: KR3.2 Output 2 Links

Link to	URL
Data Repository	Pigorini et al. DOI: 10.25493/30W7-0WK Mikulan et al. DOI: 10.25493/NXN2-05W
Technical Documentation	
User Documentation	
Data Repository	Pigorini et al. DOI: 10.25493/30W7-0WK Mikulan et al. DOI: 10.25493/NXN2-05W
Technical Documentation	
User Documentation	
Data Repository	Pigorini et al. DOI: 10.25493/30W7-0WK Mikulan et al. DOI: 10.25493/NXN2-05W
Technical Documentation	

User Documentation	

4.1.4 Output 3: Analysis pipeline for experimental (and simulated) Slow Wave Activity

SWAP (Slow Wave Analysis Pipeline) and SOAP (Slow Oscillation Analysis Pipeline) are products of the cooperation among INFN, ISS and IDIBAPS (Joint P2226), with the contribution of optical data acquired with GECI (Genetically Encoded Calcium Imaging) technique from CDP1 HBP partner LENS and the constant cooperation with SP5 on the suits for data analysis (Elephant, Neo and Snakemake; Julich-INM6) and for the data curation. SWAP and SOAP are provided to the public through the GitHub repositories listed in Table 7.

Table 7: KR3.2 Output 3 Links

Link to	URL
Software Repository	https://github.com/INM-6/wavescalephant (SOAP pipeline)
Technical Documentation	
User Documentation	
Software Repository	https://github.com/INM-6/wavescalephant (SWAP pipeline)
Technical Documentation	
User Documentation	

4.1.5 Output 4: Whole mouse cortical hemisphere simulation with connectivity inferred from experimental activity

In cooperation, INFN, ISS and IDIBAPS demonstrated the feasibility of large-scale spiking simulations of cortical SWA and asynchronous wake-like states at the scale of a cortical hemisphere, and at biological neural and synapses densities (Joint P2025). The functional connectivity and other parameters for simulation of SWA activity of a whole hemisphere of the wild type mouse have been inferred from calcium imaging GCaMP-6f recording (field of view: 4mmx5mm, pixel resolution: 50x50 µm2, temporal resolution: 40ms) provided by the SP1 partner LENS (Joint P1575). The data and simulation results are among those that can be analysed using the SWAP and SOAP analysis pipelines Outputs. The connectivity and other parameters that are essential to calibrate the simulations of cortical SWA are inferred using a likelihood maximisation technique that progressively increases the match between experimental data and the results of mean-field simulations.

Table 8: KR3.2 Output 4 Links

Link to	URL
Model Repository	https://kg.ebrains.eu/search/instances/Model/fa08c511f9b444922b0975f538b10abd (Mean-field model of SWA, whole mouse hemisphere), https://github.com/PierStanislaoPaolucci/2020WholeMouseCortHemisphMFsim and https://kg.ebrains.eu/search/instances/Model/cea3e597-2fbd-4022-bbfc-a64b9fa49d68 (Large-scale spiking model of SWA and AW), https://github.com/APE-group/201903LargeScaleSimScaling
Technical Documentation	
User Documentation	

4.1.6 Output 5: Photo-modulation of Slow Wave Activity and brain state transitions with PAI

The objective is the photo-modulation of SWA and transitions to higher complexity states taking control of the underlying molecular mechanism. Several light-regulated muscarinic ligands have been developed and characterised (agonists, antagonists). The most exhaustive characterisation has been

performed and published with the molecule named PAI (P1785). PAI (Phthalimide-Azobenzene-Iperoxo) is designed by introduction of an azobenzene photoswitch into the molecular structure of a muscarinic (M2 mAChR) agonist (phthalimide-iperoxo). Using the photoswitchable muscarinic neuromodulator PAI, synchronous slow wave activity was transformed into a higher frequency pattern in the cerebral cortex.

Table 9: KR3.2 Output 5 Links

Link to	URL
Data Repository	DOI: 10.25493/9V51-TJT
Technical Documentation	
User Documentation	
Data Repository	DOI: 10.25493/9V51-TJT
Technical Documentation	
User Documentation	

4.2 Validation and Impact

4.2.1 Actual and Potential Use of Output(s)

The interest in the topics addressed by KR3.2 is demonstrated by several facts. The special issue of Frontiers in System Neuroscience dedicated to the topic of brain states got in less than one year more than 240,000 views, and the joint papers P2226 (validating Output 3) and P2025 (validating Output 4) alone got more than 23,000 views. The workflow designed for the Use Case SGA2-SP3-UC002 (KR3.2 and KR3.4) under the guidance of INFN, in cooperation with SP5, has been adopted as an exemplar demonstration and prototype about how EBRAINS should design modular multiscale, multi-methodology, multi-species frameworks. The proposed KR3.2 pipeline has already been applied, outside the framework of KR3.2 original partners, also to wide-field calcium imaging data in rodents acquired by the SP1 partner LENS. KR3.2 Outputs got a strong interest also from SP4 partners, and at the HBP 2020 summit, a session dedicated to KR3.2 Outputs laid the basis for a joint live paper about multiscale, multi-species, multi-methodology investigation of brain states, their complexity and their transitions.

4.2.2 Publications

Publications produced during achievement of KR3.2 include rodent data (P1996 related to Output 1), human data (P2341, Output 2), analysis pipeline for data and simulations (P2226, Output 3), large scale simulations (P2025, Output 4) and optomanipulation (P1785, Output 5).

- P1996: “Altered Neocortical Dynamics in a Mouse Model of Williams–Beuren Syndrome”. Dasilva, M., et al. (2019). Molecular Neurobiology, 1-13. (Output 1, peer-review validation). DOI: 10.1007/s12035-019-01732-4
- P2341: “Simultaneous human intracerebral stimulation and HD-EEG: ground-truth for source localization methods”. Ezequiel Mikulan, et al. (2020) bioRXiv. (Output 2, currently under final stages of peer review). DOI: 10.1101/2020.02.14.948984
- P2226: “Analysis Pipeline for Extracting Features of Cortical Slow Oscillations”. De Bonis, et al. Frontiers in Systems Neuroscience, Vol. 13. (2019). (Peer-review validation of Output 3). DOI: 10.3389/fnsys.2019.00070
- P2025: “Scaling of a Large-Scale Simulation of Synchronous Slow Wave and Asynchronous Awake-Like Activity of a Cortical Model With Long-Range Interconnections”. Elena Pastorelli, et al. Frontiers in Systems Neuroscience, Vol. 13. (2019). (Peer review validation of Output 4). DOI: 10.3389/fnsys.2019.00033

- P1785: "Rationally designed azobenzene photoswitches for efficient two-photon neuronal excitation". Cabré, G., et al. Nature Communications, 10 (1): 907 (2019). (Peer review validation of the key methodology used in Output 5). DOI: 10.1038/s41467-019-08796-9

5. Key Result KR3.3

Acquisition of brain imaging and electrophysiological recording, models of multisensory integration and spatial memory and navigation, and brain-inspired robots (i.e. visual-tactile rodent-like robot and a humanoid robot).

5.1 Outputs

The collaborative effort of experimental, computational and theoretical scientists made it possible to achieve Key Result (KR3.3). This Key Result delivered brain imaging (rodent and human) and electrophysiological (rodent) datasets and models of multisensory (tactile/visual) interaction integrated with spatial memory and navigation in artificial and physical systems in robots. In a collaboration with SP5, we created a data pipeline to feed models which could be incorporated into robots (WhiskEye, MiRo).

5.1.1 Overview of Outputs

5.1.1.1 List of Outputs contributing to this KR

- Output 1: Multi-area electrophysiology along the rodent cortico-hippocampal hierarchy during multisensory object-discrimination
- Output 2: Systems-level functional data on multimodal integration of episodic memories in humans
- Output 3: Models of spatial/episodic memory dynamics for robotic system
- Output 4: Visual-tactile mobile robot "WhiskEye" for multi-modal, spike based spatial memory system
- Output 5: Rodent physiology: self-motion and visual integration
- Output 6 (Output 5 of KR3.5): Models of the motivational system and its integration with the action selection mechanisms in the Mammalbot architecture - This Output contributes to both KR3.3 and KR3.5.

5.1.1.2 How Outputs relate to each other and the Key Result

Output 1 and Output 2 allow interspecies comparisons of coherent episodic memory retrieval. The different approaches investigate this process on different time resolutions and anatomical scales. While the human FMRI (Output 2) investigates these processes on a layer-specific level in humans across a variety of brain regions, the rodent work (Output 1 and Output 5) complements this by disentangling cellular and population-level mechanisms related to precise temporal spike dynamics both in memory and sensory systems. This is of particular interest as mechanistic hypotheses regarding episodic memory mechanisms like pattern separation and pattern completion have rather been defined at the population-level and the translational evidence in humans has been sparse. To bridge that gap between micro-, meso- and macrolevel understanding of brain function we record data from the same brain regions (Medial Temporal Lobe) in humans and rodents and integrate our findings.

Strong interactions exist between Output 1 & 2 and Output 3, 4, and 6 as the empirical data inform the development of neurorobotic models. For successful episodic memory and multisensory

integration, the interplay of multiple brain structures and mechanisms is required. Empirical research in rodents and humans allows us to identify these at a functional level with various levels of specificity. In turn, neurorobotic models are used to test specific predictions flexibly by alternating model components. It is easier and more efficient to change parts of an existing model and test the effects than to perform empirical studies that require animal/human resources. Besides, robots are good models to test cognitive architectures, as they must process and act in their environment in real-time and as the sampling by artificial sensors is constrained by actual real-world sensory statistics (e.g. whisker kinematics).

5.1.2 Output 1: Multi-area electrophysiology along the rodent cortico-hippocampal hierarchy during multisensory object discrimination

We demonstrated that rats can be trained to reliably discriminate between different objects, based on visual and/or tactile input. We performed simultaneous multi-area ensemble (multi-cell) recordings in the visual and barrel cortices, as well as in perirhinal cortex and hippocampal CA1 region to understand how object-related memory content is retrieved and distributed across the cortico-hippocampal areas. Electrophysiology datasets are used to compare to predictive coding models. The next step is to compare firing rate responses from simulated neurons to firing patterns recorded from behaving rodents.

In a collaboration with SP5, we registered the data acquired from different subjects to the Waxholm reference rat atlas by reconstructing the full tetrode tracks. The coordinates of reconstructed tetrode tracks and recording locations, together with the metadata describing the experiment, were uploaded to the EBRAINS platform. The dataset contributes to the development of an analytical pipeline for the detection of moments on which cells synchronise their firing patterns (Use Case SGA2-SP3-UC003: https://wiki.ebrains.eu/bin/view/Collabs/sga2-sp3-uc003/). While specific analytical methods might work under specific circumstances, it is not given that all methods generalise for the variety of dynamics (non-stationarity of firing rates, etc), associated to different cell types and brain regions. The multi-area electrophysiology in this experiment is subjected to HBP's analytical pipelines which we develop together with SP5 (Neural Activity Resources).

Table 10: KR3.3 Output 1 Links

Link to	URL
Dataset repository	https://kg.ebrains.eu/search/instances/Dataset/963885a239e8d99e845ef0c1b38cdf01 (embargoed)
Technical Documentation	
User Documentation	

5.1.3 Output 2: Systems-level functional data on multimodal integration of episodic memories in humans

We acquired datasets to investigate multimodal integration and retrieval of episodic memories in humans. The first dataset allows to investigate pattern completion across domains (scene – object) in retrosplenial, hippocampal, entorhinal and perirhinal cortices. Functional data acquisition (3 Tesla) in a cohort of younger adults has been finished successfully. Data analysis started and results are interpreted in close collaboration with Output 1. The second dataset allows to investigate multisensory integration and pattern completion across domains (scene – object) and sensory inputs (auditory – visual) in the entorhinal-hippocampal circuitry as well as to identify the functional topography of convergence zones. We successfully transferred the behavioural task into a functional MRI paradigm for 7 Tesla imaging and finish data acquisition in younger healthy adults. Finally, we provide the first empirical data in humans on the involvement of hippocampal subfield CA3 in comprehensive recollection of multi-element events via pattern completion. These human data are compared to rodent data (Output 1) and used to inform models, robots and the Mammalbot

architecture. To enable comparison between different methodological modalities we share our data in the EBRAINS platform (Table 11).

Table 11: KR3.3 Output 2 Links

Link to	URL
Data Repository	https://kg.ebrains.eu/search/instances/Project/d1f6a09f-7b52-4b3d-9d18-4c88f62b0723
Technical Documentation	
User Documentation	
Data Repository	DOI: 10.25493/RSJX-G3U
Technical Documentation	
User Documentation	
Data Repository	https://kg.ebrains.eu/search/instances/Dataset/7269d1a2-c7ad-4745-972c-10dbf5a022b7
Technical Documentation	
User Documentation	

5.1.4 Output 3: Models of spatial/episodic memory dynamics for robotic systems

In a close collaboration of two partners (USFD and UWE) to develop multimodal spatial navigation capability for the WhiskEye robot, we have developed models of hippocampal "replay" that are being integrated into the animal-like robot MiRo. Hippocampal replay has been speculated to play important roles in mnemonic functioning, such as memory formation, retrieval and planning (P1710). By developing and augmenting these models for a spatial navigation task application in a robot, we hope to better understand how hippocampal replay contributes to memory capabilities when tested in realistic environments, whilst simultaneously contributing to bioinspired robotic mnemonic capabilities.

Table 12: KR3.3 Output 3 Links

Link to	URL
Model Repository	https://collab.humanbrainproject.eu/#/collab/79081/nav/535286
Technical Documentation	https://github.com/mattdoubleu/robot_replay-conceptual_proof
User Documentation	https://github.com/mattdoubleu/robot_replay-conceptual_proof
Model Repository	https://github.com/dcam0050/docker_starter
Technical Documentation	https://github.com/dcam0050/docker_starter
User Documentation	https://github.com/dcam0050/ssm
Report	P1710: https://royalsocietypublishing.org/doi/10.1098/rstb.2018.0025

5.1.5 Output 4: Visual-tactile mobile robot "WhiskEye" for multi-modal, spike based spatial memory system

The integrated visual-tactile mobile robot platform called WhiskEye, developed in the previous phase of the HBP, has been ported into the robot simulator adopted by the Neurorobotics Platform in the HBP. The cognitive architecture (Output 5 of KR3.5) that controls WhiskEye also connects to

the simulated platform and has been used to gather simulated data sets as WhiskEye explores its environment (Figure 2). These data have been used to develop a multi-modal spatial memory system that incorporates a predictive coding network for casting sensory information into a joint latent space suitable for place recognition and localisation (collaboration with UvA, KR3.5, and SP10). The grid cell model of the navigation system (termed pose cell network) is based on a continuous attractor network of spiking neurons and has been instantiated into the SpiNNaker neuromorphic computing system for real-time robotic experiments.

Visual tactile datasets that were captured from the simulated WhiskEye can be found in the EBRAINS repository for public access. These will be in the form of rosbags for ease of extraction and portability into the robotics community. The technical documentation and user guide for the NRP-based WhiskEye are available on GitHub via links on the HBP collaboratory (Table 13).

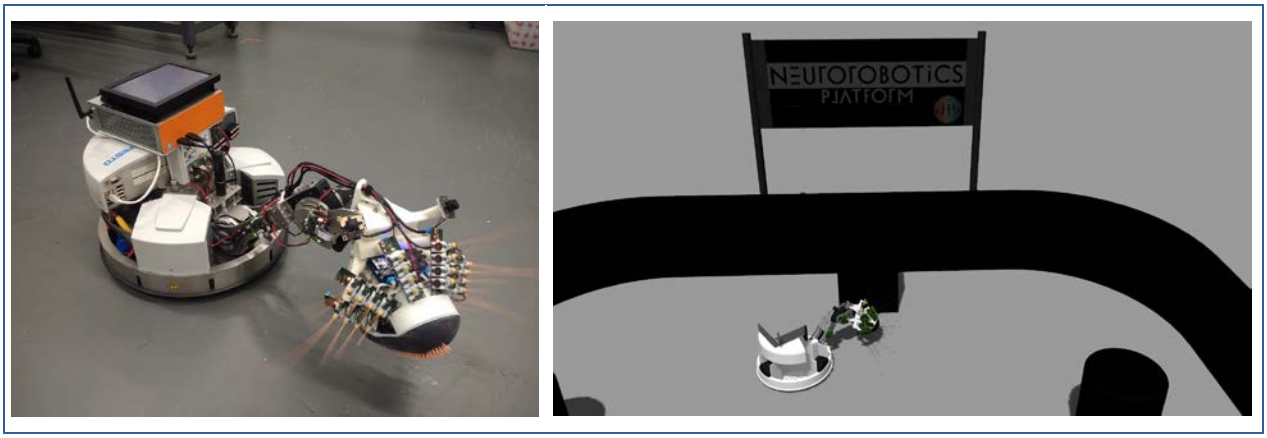

Figure 2: Physical WhiskEye platform in Bristol and the simulated platform available on the NeuroRobotics Platform

Table 13: KR3.3 Output 4 Links

Link to	URL
Data Repository	DOI: 10.25493/2ZBM-J1S
Technical documentation	https://collab.humanbrainproject.eu/#/collab/70961/nav/481270
User documentation	https://collab.humanbrainproject.eu/#/collab/70961/nav/481270
Software Repository	https://github.com/benef23/nrp_whiskeye_robot/blob/master/README.md
Technical documentation	https://collab.humanbrainproject.eu/#/collab/70960/nav/481265
User documentation	

5.1.6 Output 5: Rodent physiology: self-motion and visual integration

The relative influence of self-motion and environmental sensory inputs on the firing of place and grid cells within a given animal has not been quantified, it is not known whether the two cell types integrate these inputs separately or combine them to provide a single holistic representation. Virtual reality (VR) was used in our experiment to manipulate the relationship between physical self-motion signals and environmental visual information, so that we can compare their relative influences on the scales of the characteristic 2D spatial firing patterns of place and grid cells. Our results show that place cell firing patterns predominantly reflect visual inputs, while grid patterns reflect a much greater influence of physical motion. Thus, even when recorded simultaneously, place and grid cell firing patterns differentially reflect environmental information and physical self-motion, and need not be mutually coherent. This progress can help to elucidate the way we represent environmental location and potentially how we organise conceptual knowledge.

Table 14: KR3.3 Output 5 Links

Link to	URL
Data Repository	DOI:10.25493/R6ZZ-400
Technical documentation	
User documentation	https://osf.io/uk68w/

5.2 Validation and Impact

5.2.1 Actual and Potential Use of Output(s)

KR3.3 Outputs are an important contribution to the interdisciplinary and multimodal approach within the HBP. The acquired datasets are being used to test and validate analysis pipelines (SGA2-SP3-UC003) and atlas registration workflows from the Human Brain Project Infrastructure. One example is the reconstruction of tetrode tracks in 3D Waxholm reference atlas space (Output 1, in collaboration with SP5 - WP5.1, WP5.2 and WP5.4). The workflow demonstrated that precise recording locations could be extracted and that subtle differences in recording locations could intuitively be visualised across different experiments. A second example is the application and validation of the analytical pipelines "Time 2 Fire" (SGA2-SP3-UC003) to identify significant Unitary Events (events on which units synchronize their firing-rate, with WP5.7).

High resolution human fMRI datasets (Output 2) inform neurocomputational models and robotics. They allow a translation between microlevel results from animal studies to system-level approaches that need to be considered to successfully mirror brain function with neurorobotics. Moreover, a 7 Tesla fMRI dataset is supporting the development of specific co-registration algorithms that are important to register one type of brain image to another, contributing to KR3.1, in collaboration with Lars MUCKLI.

The models produced in close alignment with the datasets collected (Outputs 3 and 4) are available for public access and can be used for simulating multisensory integration and/or spatial and episodic memory dynamics in artificial and physical systems. Our data will provide insight into actual human brain function at the meso- and macrolevel. Accordingly, our findings on multisensory integration of episodic memories may be used by e.g. the Neurorobotics Platform for the verification of models.

The HBP research infrastructure integrates these interdisciplinary and multilevel data in various atlases and open resources. We herein contribute especially to the EBRAINS (e.g. Timo DICKSCHEID), the Virtual Brian (e.g. Petra RITTER) and inform the Neurorobotics Platform. The acquired datasets and results from ongoing analyses will additionally inform the Mammalbot approach and linked to data and models as we provide a larger, systems-level approach and can identify brain regions in an explorative manner that are important for multi-sensory integration of memories (see Output 5 of KR3.5).

5.2.2 Publications

The following publications show the circuit of multisensory processing (P1651) from a biological and computational approach (P1816, P1710 and P2221) and provide the first empirical evidence in humans for a specific involvement of hippocampal subfield CA3 in holistic recollection and cortical reinstatement of memories via pattern completion (P1960). For decades, such involvement has been suggested by animal research and computational models.

- P1651: Guido T. Meijer, Paul E.C. Mertens, Cyriel M.A. Pennartz, Umberto Olcese, Carien S. Lansink. The circuit architecture of cortical multisensory processing: Distinct functions jointly operating within a common anatomical network. Progress in Neurobiology (2019). 174(1-15). Output 1.

- P1960: Grande, X., Berron, D., Horner, A. J., Bisby, J. A., Düzel, E., & Burgess, N. (2019). Holistic recollection via pattern completion involves hippocampal subfield CA3. Journal of Neuroscience, 39(41), 8100-8111. Output 2.
- P1710: Prescott, T., Camilleri, D., Martinez-Hernandez, U., Damianou, A., Lawrence, N.D. (2019) Memory and Mental Time Travel in Humans and Social Robots. The Royal Society. DOI: 10.1098/rstb.2018.0025. Output 3.
- P2221: Keisuke Sehara, Viktor Bahr, Ben Mitchinson, Martin J. Pearson, Matthew E. Larkum, Robert N. S. Sachdev. Fast, flexible closed-loop feedback: Tracking movement in "real-millisecond-time" (2019). eNeuro - Society for Neuroscience. Output 4.
- P1816: Chen, G., Lu, Y., King, J. A., Cacucci, F. & Burgess, N. Differential influences of environment and self-motion on place and grid cell firing. Nat Commun10, 630 (2019). Output 5.

6. Key Result KR3.4

A collab to gather different measures of consciousness and their generalisation from different pathophysiological (e.g. brain injuries), physiological functional states and anaesthesia conditions in humans, animal models, computer simulations and neuromorphic circuits.

6.1 Outputs

Key Result (KR3.4) is a combination of modelling, software and experiments, that result into procedures to assess brain complexity measures in humans, in rats and *in silico* systems. This Key Result also delivers TMS/EEG data of human patients, *in-vivo* rat data and computer code for analysis and simulation. It also contributes, with data, models and algorithms, to a modular workflow of KR3.2.

6.1.1 Overview of Outputs

6.1.1.1 List of Outputs contributing to this KR

- Output 1: Test measures and mechanisms of consciousness in rats
- Output 2: Consciousness measures in healthy humans
- Output 3: Mechanisms of brain complexity and consciousness
- Output 4: Understanding the impact of lesions on brain complexity
- Output 5: Ethical, legal and social challenges
- Output 6: Multimodal integration of human structural and functional connectivity measures

6.1.1.2 How Outputs relate to each other and the Key Result

Outputs 1, 2, 3 and 6 quite directly relate to Key Result KR3.4 as they produce data that can be used to calculate promising measures of consciousness for animals (Output 1), humans (Outputs 2 and 6), and thalamocortical models (Output 3) in different states. In this way, the proposed measures can be tested in normal, pathological, and simulated physiological states related to changes in consciousness. In brief, measures based on notions of complexity, connectivity, and information integration seem to behave most consistently with consciousness states and in accordance with intuitive relations to consciousness across states and model systems.

6.1.2 Output 1 - Test measures and mechanisms of consciousness in rats

The Perturbational Complexity Index (PCI) measures the complexity of the electroencephalographic response to local stimulation (e.g. electric) of the cortex and it has been proposed as reliable measure of consciousness in humans. We adapted the PCI method in rats *in vivo* and tested it by comparing wakefulness to anaesthetised states. We tested clinically relevant anaesthetics, like propofol and sevoflurane, but also ketamine, which is known to produce "dream-like" experiences in humans with behavioural unresponsiveness. Cortical complexity dropped from wakefulness to general anaesthesia induced by propofol and sevoflurane. By contrast, ketamine anaesthesia induced an intermediate level of complexity. We then investigated possible mechanisms underlying the break-down of PCI and found evidence for a possible role of neuronal bistability in the reduction of complexity and functional connectivity. We also compared PCI results with other proposed measures of consciousness based on spontaneous EEG activity (e.g. Lempel-Ziv Complexity, Coalition Entropy, Phi-star and Phi-geo). Lempel-Ziv Complexity (in range 25-45 Hz) correlated the best with PCI and allowed a better discrimination of brain states. We also developed and provided a protocol for disconnecting brain hemispheres in rats. The method describes the custom tools and the procedure for a sagittal cut of corpus callosum that minimises cortical damage. All the collected data and Matlab/Python codes for analysis will be available in the HBP Knowledge Graph soon after revision and shared with the community.

Table 15: KR3.4 Output 1 Links

Link to	URL
Data Repository	https://doi.org/10.25493/S0DM-BK5 and https://doi.org/10.25493/5ZJY-PHB
Technical Documentation	
User Documentation	
Data Repository	https://doi.org/10.25493/8CQN-Y8S
Technical Documentation	
User Documentation	
Data Repository	https://doi.org/10.25493/QZVT-MYM
Technical Documentation	
User Documentation	

6.1.3 Output 2 - Consciousness measures in healthy humans

In order to test, compare, and further develop measures of consciousness in healthy humans, we applied some of the most promising measures from electrophysiological recording (e.g. based on complexity and connectivity) in control and novel clinical conditions. Results appear to be in accordance with predictions from the integrated information theory of consciousness and previously published results, except for uni-hemispheric anaesthesia which did not show a clear drop in complexity in the anaesthetised hemisphere. In addition, a comprehensive review of various electrophysiological measures of consciousness has been performed which shows among other that measures of complexity perform consistently in classification of conscious states. Sharing of results and data, as well as analysis and collection of new data from novel conditions are in progress. An early version of a package of measures of consciousness is available online (KR3.4) and will be expanded and added to the HBP Knowledge Graph.

Table 16: KR3.4 Output 2 Links

Link to	URL
Data Repository	https://kg.ebrains.eu/search/instances/Project/62e1a139-c331-45a1-a1d6-e9c222d3c52d?group=public
Technical Documentation	
User Documentation	

6.1.4 Output 3 - Mechanisms of brain complexity and consciousness

Using our multi-area Hill-Tononi thalamo-cortical network model (see Output 4 in KR3.5) we are investigating the cellular and network mechanisms underlying brain states associated with consciousness and unconsciousness. Similar to [1] and [2], transition from a wake-like state to a sleep-like state is affected by increasing the AMPA, persistent sodium, potassium leak and sodium/calcium-activated potassium conductance. At the cell level, alternating depolarised UP and hyperpolarized DOWN states are evident in sleep, and these give rise to slow oscillations in the LFP as observed experimentally. Also consistent with observation [3], a measure of LFP complexity and two measures of LFP variability were found to decrease during simulated sleep. Similarly, the state-transition perturbational complexity index was higher in wake than sleep, as reported in [4], while the spectral exponent was less negative in wake than sleep, as in [5]. A paper reporting these results is in preparation. Code and parameter values necessary to reproduce key figures in this paper will be uploaded to the public database ModelDB.

References: [1] Hill & Tononi, 2004. J. Neurophysiology 93: 1671-1698. [2] Esser, Hill & Tononi, 2009. J. Neurophysiology 102: 2096-2111. [3] Schartner et al, 2017, doi: 10.1093/nc/niw022. [4] Comolatti et al., 2019. Brain Stimulation 5: 1280-1289 . [5] Colombo et al., 2019. NeuroImage 189: 631-644.

Table 17: KR3.4 Output 3 Links

Link to	URL
Model Repository	https://kg.ebrains.eu/search/instances/Model/c996a8fed0868b82e8e7d9b003ca38e6
Technical Documentation	https://github.com/ricardomurphy/Multiarea-Hill-Tononi-thalamocortical-network-model
User Documentation	https://github.com/ricardomurphy/Multiarea-Hill-Tononi-thalamocortical-network-model

6.1.5 Output 4 - Understanding the impact of lesions on brain complexity

We have revisited the pipeline underlying the computation of the Perturbational Complexity Index (PCI) previously introduced as a neurophysiological TMS/EEG marker of the potentiality for consciousness in severely brain-injured patients The pipeline, which also contributes to the Use Case SGA2-SP3-UC002 (https://github.com/thierrynieus/PerturbationalComplexityIndex), is coded in Python, includes an updated version of the original PCI Lempel-Ziv algorithm (PCI_LZ [1]) and can alternatively be run at the sensor level (P1719). The overall work confirms that the classification of brain-injured patients based on PCI is in line with previous studies.

We conducted TMS/EEG studies on patients with severely injured brains and with cortical strokes. In the former study, we observed a loss of complex EEG responses as the cortical circuits fell into silence (OFF-period) upon receiving a TMS input (P1516). In another study we assessed the impact of focal cortical lesions on brain complexity. In a group of patients, we found that complexity is reduced locally in the perilesional area as compared to the contra-lateral intact area.

PCI was also generalised to whole-brain simulations and to cerebellar brain slices. In the simulations we demonstrated that PCI is higher in the ‘wake’-like state with respect to ‘sleep’ and ‘anaesthesia’-like states. In the cerebellar slice experiments, we adapted the original definition of PCI to account for the different signal sources and analysed PCI for different mossy fibre inputs.

[1] Casali, A. G. et al. 2013, doi:10.1126/scitranslmed.3006294.

Table 18: KR3.4 Output 4 Links

Link to	URL
Data Repository	https://doi.org/10.25493/WBJX-2M0

Technical Documentation	https://github.com/iTCf/lesions_and_complexity
User Documentation	
Software Repository	https://doi.org/10.25493/5TNA-R5P
Technical Documentation	
User Documentation	
Software Repository	https://github.com/thierrynieus/PerturbationalComplexityIndex
Technical Documentation	
User Documentation	

6.1.6 Output 5 - Ethical, legal and social challenges

This Output tackles the ethical, legal and social implication of working on consciousness disorders. We have developed questionnaires for clinicians and caregivers to debrief opinions and impressions of using brain stimulation in mediating human consciousness. We also created questionnaires for patients' relatives and professional caregivers about end-of-life decision making for patients with disorders of consciousness, which aims to improve the understanding of decisions on the (dis)continuation of life-sustaining treatment in this population. Data are still being analysed. Last, we are organising an international Ethical Symposium for scientists, caregivers, patients and families but for practical reasons, it will be held during SGA3. We also developed a theoretical framework for assessing consciousness in animals, machines and non-verbal humans (P2013).

Table 19: KR3.4 Output 5 Links

Link to	URL
Report	P2013: DOI: 10.3389/fnsys.2019.00025

6.1.7 Output 6 - Multimodal integration of human structural and functional connectivity measures

We acquired multimodal datasets using electroencephalography (EEG) combined (or not) with transcranial magnetic stimulation (TMS), and magnetic resonance imaging (MRI) in physiological, pathological, and pharmacological modifications of consciousness. These data are shared through the HBP Knowledge Graph, and resulted in several publications (P2324, P2211, P2116, P1944, P1941). We also directed our efforts toward sharing our patients' data and models through the Medical Informatics Platform (MIP).

Table 20: KR3.4 Output 6 Links

Link to	URL
Data Repository	https://doi.org/10.25493/G8E3-DQE
Technical Documentation	
User Documentation	

6.2 Validation and Impact

6.2.1 Actual and Potential Use of Output(s)

A preliminary release of a Python package for computing promising measures of consciousness from spontaneous activities is available online, useful for analysis of brain activity recordings. The Python module to compute the different versions of the perturbational complexity index is being used in ongoing studies and in published works.

Datasets from electrophysiological and structural imaging recordings from humans and rats in different conditions that have been used for testing measures and theories of consciousness are currently being shared through the EBRAINS platform following curation (Output 1 & 6). Code for an expanded, multi-area, thalamocortical network model can be used to investigate cellular and network mechanisms thought to be associated with consciousness in humans. The surgical protocol for disconnecting brain hemispheres in rats (Output 1) will be published in the Knowledge Graph and it could be useful to study "split-brain syndrome" and to investigate the impact that alterations of network connectivity might have on cortical dynamics.

6.2.2 Publications

P2333 is a review paper relevant for all Outputs (1 to 6), addressing the problem of islands of awareness that have important implications for debates about the nature of consciousness. P1718 is a doctoral thesis produced on electrophysiological markers of consciousness, work which started in SGA1 and was finalised in SGA2, finding several markers to distinguish consciousness states in patients and healthy volunteers. P2370 is relevant for Output 1 and describes methods and results for reproducing Perturbational Complexity Index in rats *in vivo*. P1516 shows that loss of brain complexity after severe injuries is due to a pathological tendency of cortical circuits to fall into silence (OFF-period) upon receiving an input, a behaviour typically observed during sleep (Output 4). P2013 brings a framework for measuring consciousness in both biological and artificial systems (Output 5). P2324 confirms that the dataset of Output 6 has been efficiently acquired, and the results of this publication show that local short-range communication of brain regions in α-band is stronger in patients with disorders of consciousness compared to healthy states, which suggests that information is segregated in local regions in these patients.

- P2333: Bayne, T., Seth, A. K., and Massimini, M. (2020). Are There Islands of Awareness? Trends in Neurosciences 43, 6–16. doi:10.1016/j.tins.2019.11.003. Whole WP.
- P1718: Juel, B. E. (2019). Electrophysiological Markers of Consciousness: Measures of connectivity, complexity, and signal diversity in EEG for distinguishing between conscious and unconscious brain states. http://urn.nb.no/URN:NBN:no-71069. Output 2.
- P1516 Rosanova, M., Fecchio, M., Casarotto, S., Sarasso, S., Casali, A. G., Pigorini, A., et al. (2018). Sleep-like cortical OFF-periods disrupt causality and complexity in the brain of unresponsive wakefulness syndrome patients. Nature Communications 9. doi:10.1038/s41467-018-06871-1. Output 4.
- P2013: Pennartz, C., Farisco, M. Evers, K. (2019) Indicators and Criteria of Consciousness in Animals and Intelligent Machines: An Inside-Out Approach. DOI: 10.3389/fnsys.2019.00025 Output 5.
- P2324: Mortaheb S, Annen J, Chatelle C, Cassol H, Martens G, Thibaut A, Gosseries O, Laureys S. A Graph Signal Processing Approach to Study High Density EEG Signals in Patients with Disorders of Consciousness. Conf Proc IEEE Eng Med Biol Soc. 2019 Jul;2019:4549-4553. Output 6.
- P2370: Arena A., Comolatti R., Thon S., Casali A.G., Storm J.F. (2020). General anaesthesia disrupts complex cortical dynamics in response to intracranial electrical stimulation in rats. BioRxiv. https://doi.org/10.1101/2020.02.25.964056. Output 1.

7. Key Result KR3.5

Computational modelling of multisensory deep predictive coding with potential use in AI and robotics.

7.1 Outputs

Key Result KR3.5 aims to deliver comprehensive and neurobiologically plausible cognitive architectures for biomimetic agents. It also delivers seven different modelling components that target different phenomena in the brain such as encoding and retrieval of memory during sleep, object recognition, conscious and unconscious states, multisensory integration for place recognition, and motivation and action selection using large-scale cortical neural network models. These models are integrated into a single architecture for biomimetic robots.

7.1.1 Overview of Outputs

7.1.1.1 List of Outputs contributing to this KR

- Output 1: Deep-sleep induced normalisation and association of memories improving awake classification
- Output 2: Deep Predictive Coding Network accounts for response properties of visual neurons
- Output 3: Multisensory integration for place recognition in robots
- Output 4: Multiarea Hill-Tononi thalamocortical network model
- Output 5: Motivational and action selection subsystems of the Mammalbot architecture

7.1.1.2 How Outputs relate to each other and the Key Result

The focus of this Work Package has been to improve our understanding of multisensory information processing in the brain by means of biologically plausible computational models and illustrate applications of these models in real world AI and robotics problems. Deep predictive coding models developed (Output 2) provide a means to study multisensory integration in lower as well as higher cortical areas. Further, their application for place recognition in robotics (Outputs 3) has demonstrated the performance improvement that can be achieved by these models in comparison to traditional approaches. Expanding these models by incorporating observations from studies on sleep (Output 1) will further help in improving the performance of these models on AI and robotics problems. These enhanced models contribute as components of the cognitive Mammalbot architecture (Output 5) that brings together motivational and action selection subsystems present in the brain.

Furthermore, Output 1 of KR3.3 (Electrophysiology) provides empirical evidence to restrain and inform KR3.5 (deep network for predictive coding), thereby making it more biologically plausible. While the biological plausibility of models can improve our fundamental understanding of sensory processing and memory processes by the brain, a second aim is to test the applicability of these models in real-world situations, the robots must deal with comparing their performance to other existing models.

7.1.2 Output 1: Deep-sleep induced normalisation and association of memories improving awake classification

While disconnected from external input and from the duties associated with wakefulness, animal brains are free to optimise internal representations, create novel association and plans and recover

optimal working points for reduced energetic costs of activity. Future generations of bio-inspired artificial intelligence will benefit from the introduction of mechanisms inspired from those observed in brains during sleep.

Human brains spend about one-third of their life-time sleeping and sleep is present in every animal species that has been studied. This happens notwithstanding two negative facts: the danger caused by sleep, that diminishes the capability to defend against predators and other threats, and the reduction of time available for activities targeting immediate reward. Sleep must therefore serve essential functions. In June 2019, we published the paper P2024 demonstrating that sleep-like slow oscillations improve visual classification in a thalamo-cortical spiking model through synaptic homeostasis and memory association. The corresponding NEST model has been released through the EBRAINS Knowledge Graph. A network of spiking AdEx neurons is trained (STDP plasticity) to encode, retrieve and classify images of handwritten digits. Then, sleep-like oscillations are induced. A differential homeostatic process is observed. Slow oscillations induce both an unsupervised enhancement of connections among groups of neurons associated to instances of the same class (digit) and a simultaneous down-regulation of stronger synapses created by the training. This is reflected in a hierarchical organisation of post-sleep internal representations. This promotes higher performances in post-sleep retrieval and classification tasks and creates hierarchies of categories in integrated representations.

Table 21: KR3.5 Output 1 Links

Link to	URL
Model Repository	https://kg.ebrains.eu/search/instances/Model/97670076281ccbdc38ea2c2d76a64e64, https://github.com/PierStanislaoPaolucci/2019thalCort-SNN-SO-AW-mem
Technical Documentation	
User Documentation	

7.1.3 Output 2: Deep Predictive Coding Network accounts for response properties of visual cortical neurons

We have developed a method for training deep neural networks using a neurobiological principle of predictive coding. These networks employed a network architecture which was developed to reproduce the idea of increasing receptive field sizes across the cortical hierarchy. We analysed trained models to study neuronal properties like sparseness, selectivity, image selectivity, etc. Our results indicate that many response properties of cortical neurons are reproduced by these deep networks without being explicitly imposed on the network. For instance, the networks exhibit an increase in average selectivity across successive layers in the model which has also been reported in experimental data. Additionally, we also identified a possible reason for inconsistent results reported on sparseness in experimental literature.

We have modelled multi-compartment Layer 5 context-sensitive neurons and Layer 2/3 additive neurons using information theoretic learning rules. These neurons have been implemented in large networks for simulations. Such networks are capable of completing AI-style tasks and are compared to cortical architectures. These neuron models have been delivered to NEST for integration into the package. Validation of these models is being completed by the NEST development team. Additionally, we have implemented non-feedforward connections in deep learning frameworks to tackle object recognition tasks (see KR3.1, Output 1).

Table 22: KR3.5 Output 2 Links

Link to	URL
Model Repository	https://gitlab.com/shirindora/msi_pc/
Technical Documentation	
User Documentation	
Model Repository	https://github.com/sepehrmn/nest-simulator/tree/bpid_kp_2017, https://nest-simulator.readthedocs.io/en/latest/
Technical Documentation	

User Documentation	
Model Repository	https://github.com/sepehrmn/nest-simulator/tree/bpid_kp_2017
Technical Documentation	https://www.biorxiv.org/content/10.1101/677237v3
User Documentation	https://github.com/cjspoerer/rcnn-sat/blob/master/README.md

7.1.4 Output 3: Multisensory integration for place recognition in robots

We report on the development of a model for integrating multisensory information in a predictive coding network. Building on that work (see Output 2), we used the model for a practical application in robotics. More specifically, the representations inferred from a deep neural network trained using predictive coding on visual and tactile sensory inputs were used for the problem of place recognition in navigating robots. The results obtained from the model clearly show that the representations obtained from the model outperform the traditional models used for this problem. This work was done using simulation of the WhiskEye robot in Gazebo with SP10 and work on application of the model in the actual platform (WhiskEye) is being carried out in collaboration with Martin PEARSON at University of West England.

Table 23: KR3.5 Output 3 Links

Link to	URL
Model Repository	https://collab.humanbrainproject.eu/#/collab/70961/nav/481270 and https://github.com/aalto-intelligent-robotics/ViTa-SLAM
Technical Documentation	
User Documentation	

7.1.5 Output 4: Multiarea Hill-Tononi thalamocortical network model

The cellular and network mechanisms underlying brain states and conditions permitting or suppressing conscious experience remain elusive. Computational models of neuronal networks can help interpret experiments and generate testable predictions. With these considerations in mind, we have implemented in the neural simulator NEST a 'toy brain' comprising left and right hemispheres, each with three cortical areas and associated thalamic nuclei. Each neuronal layer comprises hybrid conductance-based/integrate-and-fire neurons based on [1]. Intrahemispheric connectivities are based on [2], with modifications to synaptic weights to enhance the propagation of the response to trans-cranial magnetic (TMS) stimulation. Interhemispheric connectivities are based on [3]-[6]. For comparison with ECoG and EEG data, the principal output of the model is the local field potential (LFP) estimated as a weighted sum of synaptic current magnitudes [7]. The implementation allows modification of network parameters via text files or python functions. Parameters for wake and sleep are provided. As observed experimentally, cells exhibit irregular asynchronous activity in the wake state, but synchronised UP and DOWN states with associated slow LFP oscillations during sleep. The model also reproduces results obtained with various candidate measures of consciousness. These results are described in more detail under Output 3, KR3.4.

References: [1] J. Neurophysiology 93: 1671-1698. [2] J. Neurophysiology 102: 2096-2111. [3] J. Comparative Neurology 168: 313-343. [4] Ann. Rev. Neuroscience 27: 419-451. [5] Nature Neuroscience 10: 663-668. [6] Nature Neuroscience 18: 170-181. [7] Plos Computational Biology 11: e1004584.

Table 24: KR3.5 Output 4 Links

Link to	URL
Model Repository	https://github.com/ricardomurphy/Multiarea-Hill-Tononi-thalamocortical-network-model
Technical Documentation	

User Documentation	https://kg.ebrains.eu/search/instances/Model/c996a8fed0868b82e8e7d9b003ca38e6

7.1.6 Output 5: Motivational and action selection subsytems of the Mammalbot architecture

By means of our implementation and integration of the hypothalamus and basal ganglia models, we showed that it is possible to satisfy multiple, conflicting internal drives with a modification of attentional salience in response to sensory inputs and simulated homeostasis. Such conflicts are modelled using principles of dynamical systems that drive the internal processing of the homeostatic parameters in the robot.

We developed and studied a neuronal model of the interaction of the main regions involved in motivated behaviour in mammals. In particular, our current version of the model includes: a homeostatic representation mechanism based upon the structure of the dorsomedial hypothalamus (Hammel mechanism); a model of the lateral hypothalamus and the modulation of the ventral tegmental area's dopaminergic neurons; and a feedback loop through the nucleus accumbens that generates different patterns of dopaminergic output as a result of the internal state.

The resulting cognitive architecture, as implemented for the robot MiRo is shown in Figure 3. The general framework is expected to be compatible with other robotic platforms like WhiskEye, which, having a bespoke control system adapted to its hardware, shares the same biomimetic principles. Indeed, the tool chain used in Mammalbot is expected to abstract away hardware-specific aspects and allow seamless integration on specific robots.

The biomimetic component of the architecture is focused on the motivational and action selection subsystems, along with the spatial attention module. We are collaborating closely with UWE to integrate multimodal spatial navigation capabilities based upon models of the hippocampus. Basic learning strategies have been implemented as a result of the modulation of learning rules in the corticostriatal synapses by the emergent dopamine signal from our model. Finally, we are studying the potential integration of depth perception and predictive coding models into the Mammalbot.

We have additionally developed a graphical user interface (GUI) compatible with the MiRo platform that displays both static and dynamic information about the model's internal state, so that observers may better understand the processes driving the robot's motivated behaviour.

Table 25: KR3.5 Output 5 Links

Link to	URL
Model Repository	https://github.com/ABRG-Models/MammalBot
Technical documentation	https://collab.humanbrainproject.eu/#/collab/45330/nav/311439
User documentation	https://github.com/ABRG-Models/MammalBot

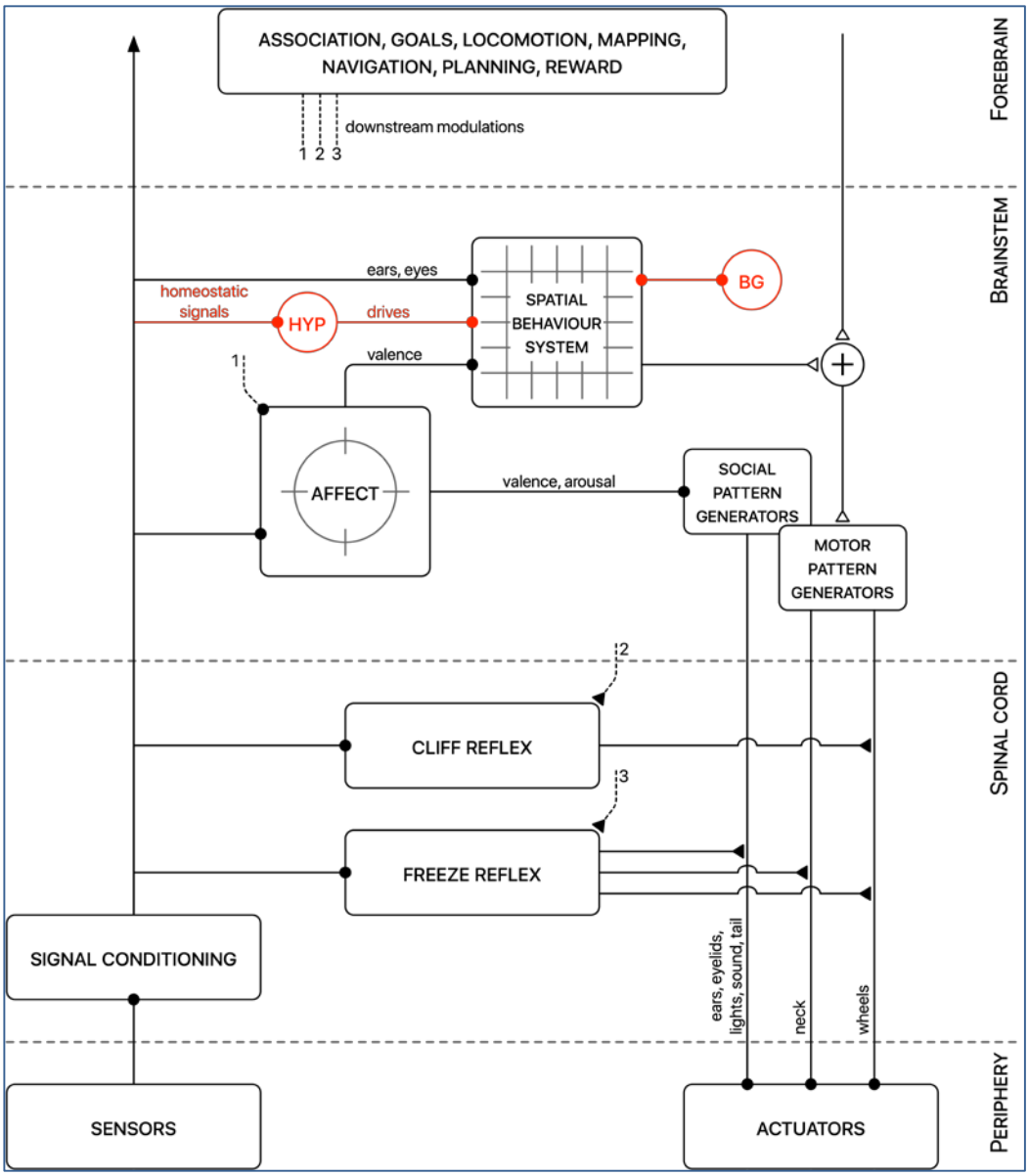

Figure 3: MiRo's current implementation of the Mammalbot architecture

7.2 Validation and Impact

7.2.1 Actual and Potential Use of Output(s)

The "Sleep-memory interaction in a thalamo-cortical spiking model" has been released through GitHub (https://github.com/PierStanislaoPaolucci/2019thalCort-SNN-SO-AW-mem) and EBRAINS KG (https://kg.ebrains.eu/search/?facet_type[0]=Model&q=paolucci#Model/97670076281ccbdc38ea2c2d76a64e64). It is a contribution of WP3.5 to the CDP5 (Plasticity). The combination of this simplified model with the final SGA2 results of WP3.2 (large scale spiking simulations of Slow Wave and Asynchronous activity) lay the basis for the planned SGA3 study on the interaction between brain states and memories in large scale networks. Furthermore, it is conceivable that recurrent multi-areal multi-level networks employed in future Bio-inspired Artificial Intelligent systems will need to enter in specific brain-states to normalise, optimise and associate their internal representations. The multi-area Hill-Tononi thalamocortical network model is currently being used within WP3.4 (UiO and Milan) to simulate brain states underlying consciousness and unconsciousness. The model is now publicly available and may be of interest to other researchers investigating the neurobiological basis of consciousness. A multi-sensory extension of the deep predictive coding model (Output 2) was

developed and implemented in a biomimetic navigating robot both in physical world (Output 3) and a virtual platform (AALTO, SP10).

7.2.2 Publications

Publications produced during achievement of KR3.5 relate to how sleep-like slow oscillations improve visual classification in a thalamo-cortical spiking model (Output 1; P2024), deep predictive coding model of the visual hierarchy (Output 2; P2345) and its multi-sensory extension and implementation in a navigating biomimetic robot (Output 3; P2129), and methods used in designing and implementing the cognitive architecture of motivation and action selection in a biomimetic robot (Output 5; P2340, P2344).

- P2024: C. Capone et al. (2019) "Sleep-like slow oscillations improve visual classification through synaptic homeostasis and memory association in a thalamo-cortical model" Scientific Reports, Vol. 9, No. 1. DOI: 10.1038/s41598-019-45525-0
- P2129: O. Struckmeier, K. Tiwari, S. Dora, M. J. Pearson, S. M. Bohte, C.M.A. Pennartz, V. Kyrki. 2019. MuPNet: Multi-modal Predictive Coding Network for Place Recognition by Unsupervised Learning of Joint Visuo-Tactile Latent Representations. arXiv:1909.07201v1 [cs.RO].
- P2340: Ling, F., Jimenez-Rodriguez, A., & Prescott, T. J. (2019, December). Obstacle Avoidance Using Stereo Vision and Deep Reinforcement Learning in an Animal-like Robot. In 2019 IEEE International Conference on Robotics and Biomimetics (ROBIO) (pp. 71-76). IEEE.
- P2344: Edmondson, L. R., Rodriguez, A. J., & Saal, H. P. (2019). Nonlinear scaling of resource allocation in sensory bottlenecks. In Advances in Neural Information Processing Systems (pp. 7543-7552).
- P2345: S. Dora, S.M. Bohte, C.M.A. Pennartz. 2020. Deep predictive coding accounts for emergence of complex neural response properties along the visual cortical hierarchy. bioRxiv doi: 10.1101/2020.02.07.937292.

8. Conclusion and Outlook

SP3 has developed models that integrate recurrent information processing in context-sensitive object recognition. These brain-inspired network architectures are able to outperform equivalent networks utilising simpler cortical architectures. Models have been inspired by data investigating cortical contextual processing at multiple levels of systems neuroscience. These data include high-resolution human fMRI data, rodent electrophysiology, rodent optogenetic and 2-photon calcium imaging data, as well as human sub-neuronal electrophysiology data for investigating the information processing properties of human neurons. Studies have substantially expanded our understanding of the processing capabilities of dendrites, single neurons and cortical areas. Experimental data obtained as part of KR3.1 have been collected to inform neural network models and are being made available upon publication for use in devising computational and cortical architectural design hypotheses.

We have also created the foundations needed to offer to the community a multiscale, multi-methodology, multi-species corpus of knowledge about brain-states and their transitions. In particular, in KR3.2 we focused on cortical slow wave activity expressed under deep-sleep and anaesthesia in physiologic and pathological conditions, and transitions to higher complexity states. We combined experimental data (in rodents and humans), simulation models and modular analysis pipeline workflows applicable to both experimental data and simulation outputs. Also, achieving KR3.2 laid the basis for the investigation of the cognitive functions of sleep (interplay between deep-sleep and memories) conducted in WP3.5, leading to KR3.5. Another important contribution has been the design, in cooperation with SP5, in the framework of Use Case SGA2-SP3-UC002, of a prototype of the analysis workflows that will be adopted in EBRAINS during SGA3.

The architecture of our brain allows us to rapidly and efficiently construct a representation of the outside world based on different streams of sensory information. The acquisition of human and

rodent recordings used as the biological ground for modelling multisensory integration and spatial memory in artificial and physical (robotic) systems (KR3.3) contributed to the development of a visual-tactile robot (WhiskEye), and offered models of important aspects of cognition (memory and perception) run on the HBP platforms. We have succeeded in delivering the majority of the data planned and this was sufficient to achieving the project goals. The data are being used to define the computational predictive coding models of object representation and memory, which in turn have been used to drive robot behaviour. In parallel, we have worked with SP5 on mapping our unique 4-area ensemble recordings on the Waxholm space and on the prototype pipeline Time2Fire (SGA2-SP3-UC003) to analyse spike synchrony. The outlook is to expand these successful collaborations in SGA3 (SGA3 WP2 and WP3 interactions) and construct multi-area spiking models performing object recognition.

The work done for achieving KR3.4, "ConsciousBrain" consisted mainly of developing methods and measures for tracking conscious states. In order to accomplish this, we have explored mechanisms of conscious and unconscious states such as bi-stability, information integration, structural and functional connectivity. Through broad application of methods and analysis in rodents, models, and humans, we have broadened the basis for empirical investigations into consciousness and also released tools and data for the broader scientific community. These results have increased our understanding of underlying brain mechanisms and dynamics in patients with disorders of consciousness, and offer promising future pathways to help such patients. In addition, with validation and extension of tools to rodents and models, future mechanistic investigations can be performed to better understand how contents and states of consciousness are generated and modulated. Finally, we developed a theoretical framework for assessing consciousness in animals, AIs and non-verbal humans.

Through the motivational and action selection mechanisms we developed, we demonstrated the possibility of a successful integration of such subsystems in a biomimetic robotic platform in order to generate diverse behaviours that satisfy internal needs. Additionally, by means of simulations, we were able to advance our understanding of how the dopaminergic reward system serves as an interface between the internal state and the motor system. All this, along with the tools developed to visualise and integrate the different models at the technical level, has shown to be critical in the understanding of the generation of complex exploratory and goal-oriented behaviours. As part of our future work we will focus on the development of a framework that allows a seamless integration of such architecture in a robotic platform. Additionally, thanks to the progress done to date, we are in a position of better understanding the interaction between the underlying brain regions, in order to test hypothesis and generate predictions about a wide range of phenomena grounded on motivation and motivational conflict.