The Human Brain Project (HBP) FET Flagship Call for Expressions of Interest (CEoI) on "Systems and Cognitive Neuroscience"

Call publication date:	15 May 2015
Proposal Submission Deadline:	3 July 2015 at 17:00 CET
Total Budget of new SP (EU funding under HBP SGA1):	Projects selected will form a new Subproject 3 (Systems & Cognitive Neuroscience) in the SGA1 period. The HBP plans to allocate EUR 8.9 million EUR of SGA1 funding to the new SP3 (EUR 8 million for 4 research Proposals/Work Packages & EUR 0.9 million for Coordination).
More information	www.humanbrainproject.eu/web/public/call-eoi
Proposal submission	www.humanbrainproject.eu/web/public/call-eoi

- Proposals must be submitted by Groups of Partners consisting of 3-5 major research laboratories established in at least two different EU Member States or H2020 Associated Countries.
- This Call forms an integral part of the HBP's SGA1[1] funding proposal - it does not have its own standalone budget. Selected applicants will become part of the HBP's Subproject 3: Systems and Cognitive Neuroscience, and will form part of the HBP Consortium's application for SGA1 funding. Within the application, the planned budget for SP3 is EUR 8.9 million, although this may be modified by the Commission during negotiations after submission of the application. The requested funding for each EoI Proposal should not exceed EUR 2 million per Proposal.
- 4 Groups of Partners will be selected for funding. Upon selection, the Partners will all become full Members of the HBP Consortium.
- The project duration should be 2 years (1 April 2016 to 31 March 2018). Continuation of SP3's work beyond these two years (e.g. into SGA2) is envisaged.
- The selected Projects should contribute to the aims of the HBP, addressing a cognitive function in "Systems and Cognitive Neuroscience", and thereby link the existing HBP Subprojects (see https://www.humanbrainproject.eu/) by addressing ambitious cognitive and systems neuroscience questions. The Projects selected through this CEoI are expected to play an exemplary role within HBP: they would constitute the first examples of actual use of the HBP ICT Platforms and of their integration into the HBP Neuroscience Subprojects. Proposed activities should include highly innovative scientific knowledge, concepts and models that bring the field closer to the solution of a concrete and important problem in cognitive and systems neuroscience, in an interdisciplinary research approach.
- In particular, the research theme you propose should reflect as many of the following HBP crosscutting requirements as possible:
  - Have the capacity to bridge from basic anatomy & physiology to mapping and cognition, as well as theory and modelling;
  - Provide the capacity to interact with (use and/or feed) the HBP Platforms (at least 2 Platforms should be addressed) including specification of data and/or tools, which are accessible to the scientific community through the HBP Platforms;
  - Include two or more spatial and/or temporal scales;
  - Demonstrate the capacity to provide actual simulation models; include research work on disease models related to the cognitive function you will study; and
  - As far as possible, have potential for real-world applications (e.g. in software, atlas, robotics, neuromorphic computing, drug design, etc.).

[1] The HBP will submit its proposal for the first Specific Grant Agreement (SGA1) under Horizon 2020 , covering from April 2016 until March 2018,to the European Commission in Autumn 2015, including EUR 8.9 million for the Systems and Cognitive Neuroscience work covered by this EoI Call. EC approval is expected in early 2016.

Contents

1. The Human Brain Project at a glance

The Human Brain Project (HBP, https://www.humanbrainproject.eu/) is an ambitious 10 years long research initiative, and part of the EU flagship program (https://ec.europa.eu/digital-agenda/en/fet-flagships). HBP is developing innovative ICT platforms that will help neuroscientists integrating data and knowledge about the brain across all levels of its spatial and temporal organisation (from genes to behaviour, into detailed reconstructions and simulations) with the aim of better understanding the functioning of the human brain and its diseases.

2. Scope of the call

Through this Call for Expressions of Interest (CEoI), it is expected that **four project Groups of Partners** will be selected for EU funding under the HBP H2020 phase through this CEoI. Each proposal selected will form a separate Work Package. The four Work Packages selected via this call will form a new "Systems and Cognitive Neuroscience" Subproject (a new SP3). The Work Package leaders will elect their SP leader, who will coordinate the SP and represent it in the HBP governance.

Funding will be granted[2] for a runtime of two years (from 1 April 2016 to 31 March 2018). The partners of each selected Group of Partners will also be eligible for funding during the following phases of HBP (i.e., after April 2018, subject to continuation of EU funding). However, success in this CEoI should not be considered as a commitment by HBP (or the EU) to continue funding your work after the end of this 2-year period. The continuation of your funding will be subject to the same conditions as for all other HBP partners.

3. Expected scientific contributions and impact

Your research theme should *cut across* existing HBP Sub-Projects (see HBP structure plan for H2020, Annex 1) and address **ambitious systems and cognitive neuroscience questions**. Proposed activities should be based on the latest scientific knowledge, and include innovative concepts and models that bring the field closer to the solution of a concrete and important problem in **systems and cognitive neuroscience** in an interdisciplinary research approach. In addition to this, they should demonstrate their potential to shape the evolving HBP ICT platforms (SPs 5-10), thus showcasing the value that these platforms can add to the neuroscience community. They would constitute the first examples of actual use of the HBP ICT platforms and of their integration into the HBP neuroscientific Subprojects.

In particular, the research theme you will be proposing should reflect as many of the following HBP *crosscutting requirements* as possible:

- Bridge from basic anatomy & physiology to mapping, cognition as well as theory & modelling;
- Provide the capacity to interact with (use and/or feed) the HBP platforms (at least 2 platforms should be addressed) including specification of data and/or tools, which are accessible to the scientific community through the HBP platforms;

[2] See footnote 1 on page 1.

- Include two or more spatial and/or temporal scales;
- Demonstrate the capacity to provide actual simulation models;
- Include research work on disease models related to the cognitive function you will study;
- And to the extent possible, have potential for real-world applications (e.g. in software, atlas, robotics, neuromorphic computing, drug design).

You should provide a more detailed description of the planned implementation of your work for the first 2 years (1rst April 2016 – 31st March 2018) as well as its integration into the overall structure of HBP. But you should also give a brief outlook to the long term vision of the research theme (i.e., in a time frame of 7-10 years).

Under this CEoI you may propose any research theme as long as it is compatible with the requirements specified for this call. Examples of visionary research themes are provided in Annex 2. These examples have been prepared by HBP partners who are already involved in the present HBP ramp-up phase (October 2013 to March 2016). **These examples are indicative only**. Project Groups of Partners may decide to propose other inspiring research themes instead.

4. Groups of Partners, eligibility and funding

Your Group of Partners will include 3 to 5 partners from at least 2 countries. Only Groups of Partners consisting of high-level partners, research labs from academia or industry, have a chance of getting funded. Each partner must be eligible for EU funding under the H2020 rules[3]. Any organization / institution eligible for EU-funding can participate. This includes existing partners of the HBP project as well as institutions without a former involvement in HBP. Participation in more than one proposal is possible. All proposals are treated equally during the evaluation and are subject to the same evaluation criteria (see Annex 4).

The total EU-funding reserved for this call is EUR 8.9 million. It will be distributed according to the following scheme:

- EUR 2 million per Group of Partners maximum (for four Groups of Partners selected for funding through this call)
- EUR 0.9 million reserved for the coordination of the SP Work Package.

5. Proposal preparation and submission

A web platform for proposal submission will be available at www.humanbrainproject.eu/web/public/call-eoi. The platform provides the functionality to enter general proposal information and partner data. In addition, the actual proposal document needs to be uploaded to the platform. A combined document can then be downloaded for your reference. You can submit as many times as you like. The most recent

[3] The countries eligible to apply are all the EU Member States and the H2020 Associated Countries. For eligibility of other countries, see http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/international-cooperation_en.htm.

version will be considered for evaluation. The deadlines given in these guidelines are strict.

6. Proposal Evaluation

The proposals will be evaluated by independent recognised experts from the field of **systems and cognitive neuroscience,** as well as from the broader scientific community. They will be recruited from both inside and outside the current HBP Consortium. The names of the evaluators will be published after the evaluation is finished. Selected evaluators are not allowed to submit a proposal.

The evaluation will be performed in two steps. In the first step, external experts will review each proposal, looking at the scientific quality of the participating laboratories forming a Group of Partners, the scientific quality of the proposed project, the fit to the HBP, and ethical issues (Annex 3). This step will select a shortlist of up to 8 proposals.

In the second step, external reviewers and experts from different Subprojects within the HBP will examine the shortlisted proposals, looking primarily are their relevance to the proposed research to the HBP aims. The external and internal experts will jointly select four of the shortlisted proposals for admission to the HBP. Their decision will require formal endorsement by the HBP Board of Directors.

The evaluation criteria for this call are given in the evaluation template (Annex 4)

Annex 1: The HBP Structure under H2020

The HBP (https://www.humanbrainproject.eu/) is structured into 12 Subprojects: four Neuroscience Subprojects (SP1 to SP4), six ICT Platforms Subprojects (SP5 to SP10), and two Subprojects for Management (SP11) and Ethics & Society (SP12).

Subproject 1 (SP1): Mouse Brain Organization

The objective of SP1 is to generate neuroscientific concepts, knowledge, data sets and tools contributing to a better understanding of the multi-level and multi-scale organization of the mouse brain. Such results will be used to constrain and validate reconstructions and simulations of the mouse brain. Specifically, the Core Project will generate systematic, standardised structural data for key levels of biological organisation (the genome, the transcriptome, the proteome, cells, synapses, and connectomics) and targeted functional data, including supports these structural data. The Partnering Projects will generate complementary data sets documenting brain function and links from structure to cognition, other behaviours and systems neuroscience. SP1 will study differences between the mouse brain and those of other species and the human brain in particular. This will make it possible to use transformed versions of data for genes, transcripts, proteins, neuron morphologies, etc. to fill in gaps in our knowledge of the structural organisation of the human brain. For more information, see www.humanbrainproject.eu/strategic-mouse-brain-data.

Subproject 2 (SP2): Human Brain Organization

The objective of SP2 is to generate neuroscientific concepts, knowledge, data sets and tools contributing to a better understanding of the multi-level and multi-scale organization of the human brain. Such results will be used to constrain and validate a first reconstruction and simulation of the human brain. Human brain functional and structural segregation, its intersubject variability and genetic factors represent central elements of SP2, and contribute to the multimodal HBP-atlas, reaching from the molecular, cellular to the systemic level. SP2 will study differences between the human brain and those of other species and the mouse brain in particular. This will make it possible to use transformed versions of data for mouse genes, transcripts, proteins, neuron morphologies, etc. to fill in gaps in our knowledge of the structural organisation of the human brain. For more information, please see www.humanbrainproject.eu/strategic-human-brain-data.

Subproject 3 (SP3): Systems and Cognitive Neuroscience

The content of SP3 will be defined by the present Call for Expressions of Interest.

According to the HBP Mediation report (www.humanbrainproject.eu/-/the-hbp-mediation-report-delivered-today), the Subprojects of the HBP (and the constituent WPs) should be consolidated and integrated with a set of new crosscutting horizontal tasks to form a matrix-type project structure. These crosscutting activities should be organized in several Work Packages (WPs) to address challenging problems of systems and cognitive neuroscience which are led by PIs with a strong scientific background in the respective areas. These WPs should be aggregated to a new crosscutting Subproject **"Systems and cognitive Neuroscience: SCN"**. Both, the PI leading the crosscutting ("horizontal") WP and

the PI leading the "vertical" WP in the SPs defined in the FPA, need to take joint responsibility for the research in the crosscutting activity. The problems addressed by the crosscutting activities should be chosen in order to demonstrate the added value of the IT platforms and, if successful, to facilitate new and unprecedented insight in brain function and cognitive behaviour. The solution of these problems will likely require specific data that presently neither exist nor are likely to be collected by other international initiatives in the next 5 years.

Subproject 4 (SP4): Theoretical Neuroscience

The overall objective of SP4 is to establish solid theoretical foundations for modelling the brain across different levels of biological organization – see www.humanbrainproject.eu/theoretical-neuroscience. SP4 investigates models for key aspects or functions in conjunction with other SPs, such as for example simplified models of neurons, including non-linear dendritic computations, models of different brain signals, as well as models of synaptic plasticity, learning and memory. SP4 also investigates specific cognitive functions such as spatial navigation, attentional mechanisms and the genesis of different brain states by networks of simplified neurons. SP4 also investigates general computational principles at the level of synapses, dendrites, neurons or circuits, that can be implemented in neuromorphic circuits, neuro-robotics or in large-scale simulations. SP4 also operates the European Institute for Theoretical Neuroscience in Paris – see http://www.eitn.org/ .

SP4 is looking for tight interactions with experimentalists in SP3, in particular to constrain models from recordings at different levels or scales, such as intracellular studies, multi-electrode recordings or different imaging techniques. The SP4 partners are available to participate (non-funded) to cross-cutting proposals involving joint experimental and theoretical work.

Subproject 5 (SP5): Neuroinformatics Platform

The Neuroinformatics Platform is at the heart of the Human Brain Project – providing internet services to search and access neuroscience data, models and literature through multi-level brain atlases. The platform will also provide scientists with the tools to discover, analyse and predict data at all levels of the brain from genetic to cognitive and behavioural. The search engine is built around the HBP KnowledgeGraph, which tracks provenance for all data and models used in the project ensuring reproducibility and attribution for all contributions. Analysis of neuroscience data including feature extraction, cluster analysis, machine learning and data mining techniques support classification, data-driven ontologies and the prediction of missing data. SP5 is seeking proposals for co-design projects that would produce and curate high-value cognitive data sets, develop whole brain atlases of cognitive function and dysfunction, and provide multi-level analyses linking genes to cognition to support brain modelling and simulation. For more information please visit www.humanbrainproject.eu/web/public/eoi-neuroinformatics.

Subproject 6 (SP6): Brain Simulation Platform

The HBP Brain Simulation Platform provides tools and models to facilitate convergence between different modelling efforts, and to further our understanding of brain structure

and function across different levels of biological organization. The platform will allow community users to collaboratively develop and validate data-driven models of neurons and brain tissue in different areas (cortex, hippocampus, basal ganglia, cerebellum etc.), brain regions, and the whole brain; to upload and simulate models compatible with HBP-supported simulators and standards; to perform in silico stimulation and recording experiments; to simplify models; to link models to the Neurorobotics Platform for experiments in cognition and behaviour, and to compare results from different models. SP6 is soliciting contributions to a community effort to build data-driven models, and to use these models in novel *in silico* studies. Proposals that combine services from different HBP Platforms will be preferred. For more information, please visit www.humanbrainproject.eu/web/public/eoi-simulation.

Subproject 7 (SP7): High Performance Computing Platform

The goal of SP7 is to build, integrate and operate the hard and software components of the supercomputing, data and visualization infrastructure required to *(i)* run large-scale, data intensive, interactive multi-scale brain simulations up to the size of a full human brain, *(ii)* manage the large amounts of data used and produced by the simulations, and *(iii)* manage complex workflows comprising concurrent simulation, data analysis and visualization workloads. SP7 will co-design the HPC Platform in close interaction with the users and make it available to the wider neuroscience community. In the HBP's ramp-up phase, the HPC Platform will comprise existing supercomputing, data management and visualization capabilities at Forschungszentrum Jülich (Germany), the Swiss National Supercomputing Centre in Lugano (CSCS, Switzerland), Barcelona Supercomputing Centre (BSC, Spain), Cineca in Bologna (Italy), Karlsruhe Institute of Technology (KIT, Germany), RWTH Aachen University (Germany) and École Polytechnique Fédérale de Lausanne (EPFL). The goal of the next, operational phase is to provide a pre-exascale, data centric supercomputing capability of up to 50 PFlops and 20 PBytes of memory. The hard and software co-design of the HPC Platform together with the users will continue, including exploratory studies towards an integration of HPC with Neuromorphic Computing. For more information see https://www.humanbrainproject.eu/high-performance-computing-platform.

Subproject 8 (SP8): Medical informatics Platform

The aim of the Medical Informatics Platform is to provide researchers the ability to access and analyse large amounts of anonymised clinical data from hospital, research, and pharmaceutical clinical trial databases through an innovative data management system that we are building. The system integrates heterogeneous data formats seamlessly and federates data sources into a harmonized virtual database with a customized interface for navigation and data mining. The patterns discovered in the data ("biological signatures" which uniquely identify diseases) will generate new hypotheses about brain diseases for investigation and will lead to their novel classification, the latter based on biological, physiological and anatomical features in addition to the classical patterns of phenomenology expressed in symptoms, signs and syndromes. The data will also be available to answer public health and medical epidemiological questions proposed by the community of medical scientists and planners. In the long run our vision is that unlocking the wealth of information locked up in medical and research databases will provide a credible and rapid path to precision (or personalized) medical care. Our interaction with the computing and neuroscience components of the HBP will serve to test with lesion

models the functional and structural brain models and artifacts they produce. For more information see https://www.humanbrainproject.eu/medical-informatics-platform.

Subproject 9 (SP9): Neuromorphic Computing Platform

The objective of the NCP is to operate and further develop the world's first remotely accessible large-scale neuromorphic computing systems. It offers two complementary approaches to neuromorphic computing located at two sites in Manchester (UK) and Heidelberg (Germany). The Manchester site operates a system based on ARM cores linked by a high-bandwidth packet-based communication network. It offers high flexibility through programming and represents a simulation system running at real-time. The Heidelberg system is a physical model of biological networks featuring local analogue computation and binary, continuous time point-to-point communication. It operates in an accelerated mode providing access to biological timescales from milliseconds in a single experiment. The NCP provides a unified high-level software access to non-expert users from neuroscience, machine learning and industrial applications. Both approaches plan to develop next generation machines offering increased capabilities on the cellular and network modelling level with special emphasis on learning and development.

- What is the Platform and what can you do with it? Two unique implementations of large scale neuromorphic computing based on the many-core and physical model approaches
- How do you use the Platform? Access for non-experts is provided through a software based user interface requiring a knowledge of the neural network metalanguage PyNN
- How can cognitive and systems neuroscience contribute? Providing circuits based on spiking neurons performing cognitive computing tasks.

For more details, see https://www.humanbrainproject.eu/neuromorphic-computing-platform.

Subproject 10 (SP10): Neurorobotics Platform

The Neurorobotics Platform is an Internet-accessible simulation system that allows neuroscientists to validate cognitive and behavioral capabilities of brain models. To this end, users can plan, run and evaluate *in silico* behavioral and cognitive neuroscience experiments, in which brain models are connected to a virtual body which is then exposed to a virtual dynamic and sensory-rich environment. Scientists can then define experimental protocols and study behavioral or cognitive phenomena by running virtual experiments following these protocols. The platform will also provide detailed body-models, which are calibrated with real hardware acting in the real world. SP10 is looking for proposals from scientists who are interested in doing *in silico* cognitive and behavioral neuroscience experiments with the Neurorobotics Platform as part of a co-design project. These co-design projects will drive the development of the Neurorobotics Platform as well as other platforms from the user perspective by ensuring that all new features and capabilities are to the benefit of the platform users. For more information please visit www.humanbrainproject.eu/web/public/eoi-neurorobotics.

Subproject 11 (SP11): Management

The objectives of SP11 are to support HBP decision-making, operate the management structure and European Research Programme, ensure transparency and accountability toward funders and stakeholders, and maintain standards of quality and performance. SP11's primary responsibilities include coordination of the Project's scientific roadmap, in particular supervision of the Milestones and Deliverables for the set-up, testing and operation of the six ICT Platforms. For more information, see: www.humanbrainproject.eu/management.

Subproject 12 (SP12): Ethics and Society (SP12)

The overall objective of SP12 is to assist the HBP in engaging in Responsible Research and Innovation (RRI), and where indicated assist in promoting policies to ensure this (https://www.humanbrainproject.eu/ethics-and-society). SP12 monitors the project's research planning and results; analyses the social and philosophical implications of the work; involves researchers, decision-makers and the general public to deepen the conversation about future directions of research; and supports the robust management of ethical issues of the HBP as a whole. SP12's central aim is to identify potential ethical and social concerns at an early stage and to address them in an open and transparent manner, providing HBP scientists with opportunities to gauge public reaction to their work, and to hone their research objectives and processes accordingly, including to integrate standard operating procedures into their operations when indicated. SP12 will thus manage a major Ethics and Society Programme, which will explore the Project's social, ethical and philosophical implications, promote engagement with decision-makers and the general public, work to raise social and ethical awareness among Project participants; and which will ensure that the Project is governed in a way that ensures full compliance with relevant legal and ethical norms. For more information, see: www.humanbrainproject.eu/ethics-and-society.

Annex 2: Key Contacts: SP & WP leaders (PIs), SP Managers

SP1 Mouse Brain Organisation

SP leaders:

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SP Managers:

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SP2 Human Brain Organisation

SP leaders:

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SP3 Cognitive and Systems Neuroscience

SP leaders:

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SP4 Theoretical Neuroscience

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SP6 Brain Simulation Platform

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SP7 High Performance Computing Platform

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SP8 Medical Informatics Platform

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SP9 Neuromorphic Computing Platform

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SP10 Neurorobotics Platform

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SP11 Management

SP leader:

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SP12 Ethics and Society

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Annex 3: Examples of visionary research themes for HBP

Invariant multisensory object recognition

Understanding how the human brain achieves invariant representations of visual and auditory objects from (multi-)sensory stimulation is a fundamental question of neuroscience. While various biologically inspired models of invariant processing have been suggested, the detailed architecture of these models, especially object features in deep layers and the role of top-down connections, are hitherto not empirically validated. Proposals of this topic should create neural processing models of joint visual and auditory operations that process dynamic input from quasi-realistic stimuli (movies) and produce as output invariant representations describing the visual and auditory objects. Models should explain plasticity, e.g. how and at which level(s) new instances of objects (e.g. faces, voices) are learned. Comparative studies across species are critical to identify common processing modules and unique human properties in achieving invariant representations.

Perception action and embodiment – experiments and modelling

An overarching aim would be to study the neural mechanisms in cortex, basal ganglia and other forebrain structures that support the joint representation of action planning, execution, and perception, and its interaction with the multisensory representations of the body. The analyses may require both animal models and humans. Brain imaging with good spatial and temporal resolution could be critical, and using a battery of experimental tools to study these processes at the microcircuit and systems level. The experiments should form the bases for developing models of different aspects of these cognitive subsystems. The computational models should preferably include multiscale modelling at different levels from the microcircuit level to more abstract models. This work may also include clinically relevant applications, such as the use of multi-sensory stimulation in rehabilitation robotics.

The Neural bases of spatial navigation and episodic memory

Spatial navigation represents a complex function of the vertebrate brain. It requires the brain to remember a sequence of locations to find the way for instance in the morning from home to work. Central to this is processing in the entorhinal cortex and hippocampus. Several of the different cellular components of this control system have been identified like place cells, grid-cells, head direction cells and also others like speed cells and border cells. How these different components of the control system interact to form a memory of the path from A to B remains enigmatic. Much is also known about the neuronal underpinning in hippocampus, cell types, connectivity, transmitters, but this knowledge has not yet been translated into an understanding of the circuits generating navigation and as important the related episodic memory. To analyse these complex processes including the differential contribution of brain areas, multiscale modelling/simulation will be critical. Processes are of clinical importance in Alzheimer´s and epilepsy.

Functional interactions in different brain states – from wakefulness, sleep and anaesthesia to pathological states

This crosscutting project would link together different aspects related to brain activity (some of which are already present in HBP). Spontaneous and resting-state activity (including activity at different states of consciousness such as anaesthesia and sleep), would be collected from different species (from mouse to man), characterizing the different brain states and their associated network activity, at different scales from cellular (multi-electrode), to mesoscales (LFP/VSD) to macroscales (EEG/MEG/MRI), and explain the phenomena observed at higher scales by those obtained on lower scales. Experiments could also address how the spontaneous "ongoing" activity is necessary to explain sensory responses. They should also investigate pathologies associated to brain state, mostly epilepsy, but also sleep disorders or disorders associated to the perturbation of functional connectivity. The experimental data collected will be modelled in SP4, to identify not only the mechanisms, but also relate brain state with information processing or coding paradigms.

Pharmacological modulation of cortical circuits and cognition

Cognitive processes such as perception, decision-making, and action planning emerge from selective neuronal interactions afforded by the local and long-range connectivity of the cerebral cortex, and of the cerebral cortex with subcortical structures. Within this extensive network, complex functional interactions are shaped by transient fluctuations in global brain state on a shorter time scale (attention, motivation, reward), and by fluctuations on a longer time scale (learning/plasticity). This dynamic shaping of cortical circuits is, at least in part, mediated by the ascending modulatory systems of the brainstem (e.g., noradrenaline, dopamine, serotonine and acetylcholine). How these systems sculpt the cortical circuit interactions that give rise to specific cognitive acts is still largely unknown. Recent theoretical advances on this question have now put neuroscience in a position, from which explicit and specific hypotheses can be tested in a systematic and coordinated experimental effort. Projects along this line would cut across multiple levels of analysis, ranging from specific neurotransmitter molecules and receptors, to cortical microcircuits, to whole-brain networks, to cognition and behaviour, within a unified computational framework. They may lead to a better understanding of the impact of pharmacological agents and drugs on cognitive operations and their impairments.

Synapses: biology, theory and machines

This crosscutting project would address synapses as the overarching theme of investigation. Investigators would work on synapses and their role in the brain, as related to theory, computers and robotics. By bringing together the existing HBP groups presently working on synapses, with additional partners, a critical mass will be generated in areas spanning genetics, proteomics, physiology, cognition, theory, neuroinformatics, simulation, neuromorphic computing, robotics. There are many fundamental biological questions about the synapses that can be tackled (e.g. their role in representation of cognitive maps; plasticity and learning; is there a species conserved architecture of synapse diversity etc.). Synaptic biology is relevant to episodic memory, spatial navigation, human-specific biology, anaesthesia, perception etc. Because synapse biology is a major part of all neuroscience (genetics to behaviour) the neuroinformatics tools driven by this cross cutting proposal should have a wide usage in the community.

Probabilistic inference and decision making

How does the brain commit to a categorical choice in the face of uncertainty? A successful proposal on this topic could advance the state of the field along several directions: (i) Pinpointing the cerebral circuits and neural computations underlying probabilistic inference and decision-making; (ii) directly linking neuroimaging data in humans with microcircuit-level data obtained in non-human primates or other animal species performing analogous decision-making tasks. (iii) Unravelling how such circuits are shaped by neuromodulators across multiple scales, from specific neurotransmitter systems to cortical microcircuits, whole-brain networks ("circuits of circuits"), computational algorithms and overt behaviour; and (iv) translating those theoretical and neurobiological insights into biophysically detailed computer models of the underlying circuit interactions, suitable for implementation on the HBP Brain Simulation Platform or the Neuromorphic Computing Platform, and (v) investigating whether aspects of human brain diseases, such as schizophrenia, can be explained by disorders of probabilistic inference systems.

Human singularity

What makes the human brain unique in its representational and computational abilities? Candidates for the origins of human singularity include: emergence of language circuits; competence for symbols and recursion; social representations and theory of mind; or improved deep-learning algorithms. A cross-cutting HBP project could perform a systematic search for human-unique brain mechanisms within several disciplines, such as: comparative brain imaging using fMRI in humans and non-human primates; comparative electrophysiology; comparative genomics, transcriptomics, proteomics, cytoarchitectonic maps and receptor densities within targeted areas activated e.g. by language or by theory-of-mind; neurogenetic studies examining the synaptic, cellular and circuit effects of specific candidate genes of recent evolution in the human lineage; and theoretical modelling, leading to mathematical models for the cerebral representation of tree structures, linguistic structures, theory-of-mind inferences, or other intelligence tests thought to be uniquely feasible by humans.

Development & aging

Insights about brain development could provide key guidelines to set up priorities for the simulation or the robotics research programs. Building a primal sketch of a cognitive system before considering the mature one may be the winning strategy, especially when learning is taken into consideration. Such insights may be related for instance to the chronology of the maturation of the brain architectural areas or fiber pathways, but also of global cognitive systems involved in speaking, reading, etc. In addition, developmental models could help embedding realistic representations of inter-individual variability in the simulations. Such representations would be the door to simulate abnormal development leading for instance to psychiatric syndromes. In the same spirit, models of normal aging could provide key information for the simulation of abnormal aging leading to neurodegeneration.

Annex 4: Proposal Evaluation Criteria

1. Scientific excellence and impact • Credibility and soundness of the proposed research theme and degree of conformity to provided specifications (capacity to bridge from basic anatomy and physiology to cognition, multi-scale analysis and simulation capacity, disease models, etc.) • Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art (e.g. ground-breaking objectives of the long term vision of the proposal, novel concepts and approaches and their potential to become a seminar work, etc.) • Quality and effectiveness of the detailed 2 years research plan (including appropriateness of tasks and experiments, milestones, deliverables and indicators to monitor progress) • Enhancing innovation capacity and generation and integration of new knowledge • Ethical issues on the proposed research theme and research plan are reported under "Remarks", below.	**Score:** *(Threshold 8/10;* *Weight 30%)*
2. Relevance to the aims of the Human Brain Project Flagship • Contribution to HBP mouse-human neuroscience and to theory development • Contribution to the design and development of HBP platforms • Coordination with the other HBP Subprojects	**Score:** *(Threshold 8/10;* *Weight 30%)*
3. Quality of the Group of Partners and of the individual partners • Quality and relevant experience of the individual partners, and their contribution to the common goal • Quality of the Group of Partners as a whole (including complementarity, balance, involvement of key actors)	**Score:** *(Threshold 8/10;* *Weight 30%)*
4. Quality of resources • Appropriateness of allocation and justification of requested resources	**Score:** *(Threshold 6/10;* *Weight 10%)*
Remarks • Ethical implications and complying with applicable international, EU and national law	N/A
	Overall score: *(Threshold 8/10)*