Summary of the context and overall objectives of the project (For the final period, include the conclusions of the action)

What is consciousness? Can it be measured? While humankind has struggled with these questions for millennia, our project has focused on more modest but nonetheless ambitious and related goals. Inspired by recent developments in neuroscience and the potential role of fundamental mathematical concepts, we have studied, modelled, quantified, and attempted to alter observable aspects of consciousness. Our vision is that consciousness will someday be electromagnetically measured and altered, and that the associated needed insights will prove crucial to the development cognitive sciences.

Supported by computational neuroscience models, we aimed to create non-invasive consciousness-probing technologies integrating brain monitoring and stimulation with advanced techniques for data analysis. Based on the derived brain activity metrics, we have also explored intervention, i.e., the use of brain stimulation to alter consciousness. To achieve these goals, we have developed computer models of the brain and pursued parallel human studies – in sleep, anaesthesia, locked-in syndrome, disorders of consciousness, and in utero – supported by machine learning to disentangle the essential aspects of consciousness and establish links with artificial cognition research.

The project has also explored the ethical implications of such technologies and the prospects for clinical translation. Our work is part of a long-term paradigm-shift with profound social and clinical impact and provide key insights in fundamental neuroscience and artificial cognition research.

The objectives for the project were the following:

O1. Provide a scientific, theoretical framework of consciousness.

O2. Develop a physiologically validated computer model connecting electrical monitoring and stimulation of the brain with theoretical models of consciousness.

O3. Develop new methods for measuring consciousness.

O4. Develop technology to monitor and alter consciousness in research and medical applications.

O5. Validate and refine the methodology in different clinical scenarios.

O6. Study the societal and ethical implications of these technologies.

O7. Disseminate and exploit the project results via events, publications and products for tangible social impact.

Project results have demonstrated the central role that complexity plays on consciousness. From a theoretical point of view, complexity characterizes consciousness as the equilibrium between *integration* and *information*. Furthermore, the dimensions defining different consciousness states as described by Steven Laureys in 2005, which are based on wakefulness and awareness of subjects, have been systematically explored. In this context we realized that the wakefulness dimension is related to the thalamo-cortical connectivity,

whereas the awareness dimension corresponds to different degrees of cortico-cortical connectivity. Experimental work has clearly shown that consciousness state categories are not static ones, but that the consciousness states fluctuate depending on the wakefulness degree as a function of the balance between cortico-cortical and cortico-thalamic connectivity. The latter, in particular, appears to act as "consciousness switch".

From an experimental point of view Luminous has shown that complexity, as measured by an approximation based on the algorithm commonly used to compress data files or on particular spectral features, can be observed in brain signals both spontaneously elicited and after perturbation through non-invasive brain stimulation. This has allowed the implementation of several novel complexity-driven metrics, which have been successfully explored in in-silico simulations as well as in clinical relevant scenarios, i.e., during sleep, in foetal brain activity, anaesthesia, and disorders of consciousness.

By combining artificial intelligence methods, computer simulations of brain activity, and non-invasive brain stimulation, the LUMINOUS project consortium has developed new techniques to diagnose and treat diseases and disorders related with consciousness. The Luminous project has achieved different milestones in the field of neurophysiology and neurostimulation using non-invasive techniques especially relevant for sleep and disorders of consciousness, which pave new research paths for the treatment of related diseases.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far (For the final period please include an overview of the results and their exploitation and dissemination)

We provide here an overview of the project results achieved and their relation to the project objectives listed above.

1. The scientific framework developed along the Luminous project, based on ideas of information theory and complexity, is precise and general enough to make useful predictions and to develop empirical measures that can be successfully applied to different conditions in which consciousness is altered (sleep, anesthesia, coma, in utero). Crucially, it also provides a bridging principle that can extent both horizontally, linking different theories of consciousness, and vertically, linking multiple scales from global EEG dynamics to the microscale level of neuronal events.
2. Project research has delivered a novel theory of consciousness based on Algorithmic Information Complexity, providing a potential framework for the unification of different variants of information-driven theories of consciousness. Ongoing efforts aim to find common points between this and established theories.
3. We have developed COALIA, the first brain-scale computational model that links cellular-scale connectivity patterns with large-scale anatomic connectivity (brain connectome). The COALIA model can reproduce spontaneous EEG patterns, but also TMS-evoked EEG patterns, in different conditions of thalamo-cortical connectivity corresponding to different states of consciousness. COALIA has been exemplary used to simulate the effect of anesthetic drugs, and simulate the changes in EEG activity under propofol, which confirms the hypothesized mechanisms of action of propofol, and to simulate closed-loop NIBS protocols showing its usefulness to link theoretical and experimental works.
4. From the technological point of view, we have deployed a closed-loop experimental prototype, in which a brain stimulation protocol is launched automatically and in real

time according to an EEG feature that is being calculated online. We have used this prototype in a pilot study with MCS patients and obtained some promising initial results that show that stimulating MCS patients when they are in high vigilance levels may help improve signs of consciousness.

5. We have explored and validated a set of measures of consciousness that are conceptually related, complementary, and clinically useful. Among them the most promising ones are related with the complexity of spontaneous EEG signals. Its successful employment on data acquired in project related experimental work opens the door to facilitate the assessment of consciousness in clinical relevant scenarios.
6. We have managed to identify and classify successfully 150 conscious from unconscious subjects with 95% precision through the application of TMS-EEG. We have managed to create simple measures based on this data acquisition technique that result in the same precision with the potential of being used even at the patients' homes for monitoring their levels of consciousness.
7. We have observed an increase in the level of consciousness in 6 out of 17 MCS patients after a single session of frontoparietal tDCS network stimulation. Although the gained signs of consciousness were not sustained, this can be further explored with repeated tDCS sessions, since multisession tDCS is known to result in long-term improvements.
8. We have experimentally shown that foetuses are able to identify and distinguish complex sound sequences and that there is a learning process involved in foetuses very similar to the one in babies, children and adults.
9. We have created a system prototype to measure consciousness decrease during anaesthesia that will allow a more controlled dosage of the anaesthetic drug to avoid pain or cognitive impairments resulting from anaesthetic mis-dosing side effects.
10. For the first time we have have developed and successfully used with humans an experimental system to generate and sustain specific brain oscillations using a combination of tACS and rTMS. Such a system will find applications for memory enhancement as well as treatment of sleep disorders in the short-term.
11. We have managed to integrate tCS with fNIRS in a BCI system to be used for communication by complete Lock-In-Syndrome patients. In a case-study of this system we have shown in one patient an increase in the BCI performance with active tCS compared to sham.
12. Project results have been disseminated among the scientific community in form of over 50 journal papers, with over one hundred conference communications. Luminous work appeared in 30 media reports, which intended to disseminate advances among the general public. Approximately 50 public events were organized by consortium members among which it is worth mentioning numerous editions of the Coma Science Day, the Brain Awareness and Future Tech Weeks in Barcelona, and the final open lecture and research café at the University of Oxford.
13. The closed-loop brain stimulation prototype is already being used in an ambulatory test in Liege to treat Disorders of Consciousness patients. If successful, further exploitation of the technology will be transferred to Neuroelectrics.
14. Moreover, the system prototype for automated anaesthesia titration followed its innovation path through LUMINOUS support. The University of Oxford is actively developing this technology under further tech transfer "Development Pathway Funding Scheme" of the Medical Research Council for future exploitation.
15. Psychedelic drugs are increasingly taken into account by the pharmaceutical sector for the treatment of different diseases in mental health. Starlab expects to expand its customer segment target through the incorporation in its methodological portfolio consciousness metrics based on complexity, which have been developed within project works and are

showing good performance in the characterization of the effects such psychoactive substances. Indeed, Starlab is already providing a EEG-based Data Analysis Service for such a clinical trial, showing very early exploitation potential of our technology development.

Progress beyond the state of the art, expected results until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far)

Project work confirmed that outcomes will have a fundamental impact in neuroscience, providing key insights into consciousness, how to model, measure and alter it. Concretely:

- The interaction between theory, modelling, and experimental teams is showing extremely fruitful in defining physiology-based information-theory models of consciousness. The results can be verified through the relevant publications, among which is is worth pointing out the publication of “An algorithmic information theory of consciousness” and “Are there Islands of Awareness” papers. The first one proposes a new theoretical framework of consciousness based on Algorithmic Information Complexity. The second discusses the possibility of the presence of consciousness in isolation from the body and its environment.
- Important technological advances have been achieved by the development of 1) a computational brain model to be extensively used in consciousness studies in the future and 2) a closed-loop prototype for transcranial Electrical Stimulation. Successfully technology transfer to the clinical domain has been achieved by deploying the closed-loop system for University of Liege to conduct a study in which 12 patients are expected to be treated.
- We have implemented different machine learning solutions to provide Decision Support Systems in consciousness studies. A DSS for the prediction of the outcome of tDCS treatment on DOC has been developed together with diverse diagnosis DSSs for DOCs. We believe that the DSS for tDCS outcome prediction will become an important tool not only for tDCS DOC treatments, but in general for NIBS-based treatments, and clinical trials in drug-based treatments to further stratify the population to be treated and therefore optimize treatment time and cost.
- Starlab follows at this stage a Business Model based on the provision of Data Analysis Services. In this context Starlab has recently acquired a service to support a clinical trial related to the effects of tetrahidrocannabinol (THC), which constitutes the psychoactive substance in cannabis, and the treatment of associated addictions. Here it has been of paramount importance the technology advancement in Luminous, concretely in measurements of complexity based on LZW, which has been requested to be incorporated as endpoint in the study by our client.
- Clinical impact is based on experimental advances with respect to the State-of-the-Art. This have been most clearly achieved on the outstanding clinical applications to: 1) alter oscillatory brain activity in sleep through a combination of different types of Non-Invasive Brain Stimulation, 2) provide a more accurate diagnosis of Disorders of Consciousness (DOC) through numerous novel metrics, 3) enhance consciousness levels in DOC at individual level through the electrical stimulation of the consciousness network, and 4) automatically titrate anesthetics in real-time titration. Project developed techniques open as well a new window into the study of brain and consciousness in utero.

- One important part of the impact was the engagement of the general public in discussions on project goals and achievements. In this context the last year three events for the general public have been organized: Oxford Public Cafè, Liege Coma Day, and the Future Tech Week event at Starlab. Moreover, a survey has been conducted on the usage of NIBS for DOC treatment involving the general public.

Although Luminous has not provided an answer for the fundamental question of what consciousness is, or definitive technologies to measure and control it, we believe it has made important contributions to the field from many angles including theoretical, clinical, and technological ones. We are convinced that it will provide a firmer foothold for future research programs with our shared vision and mission.