

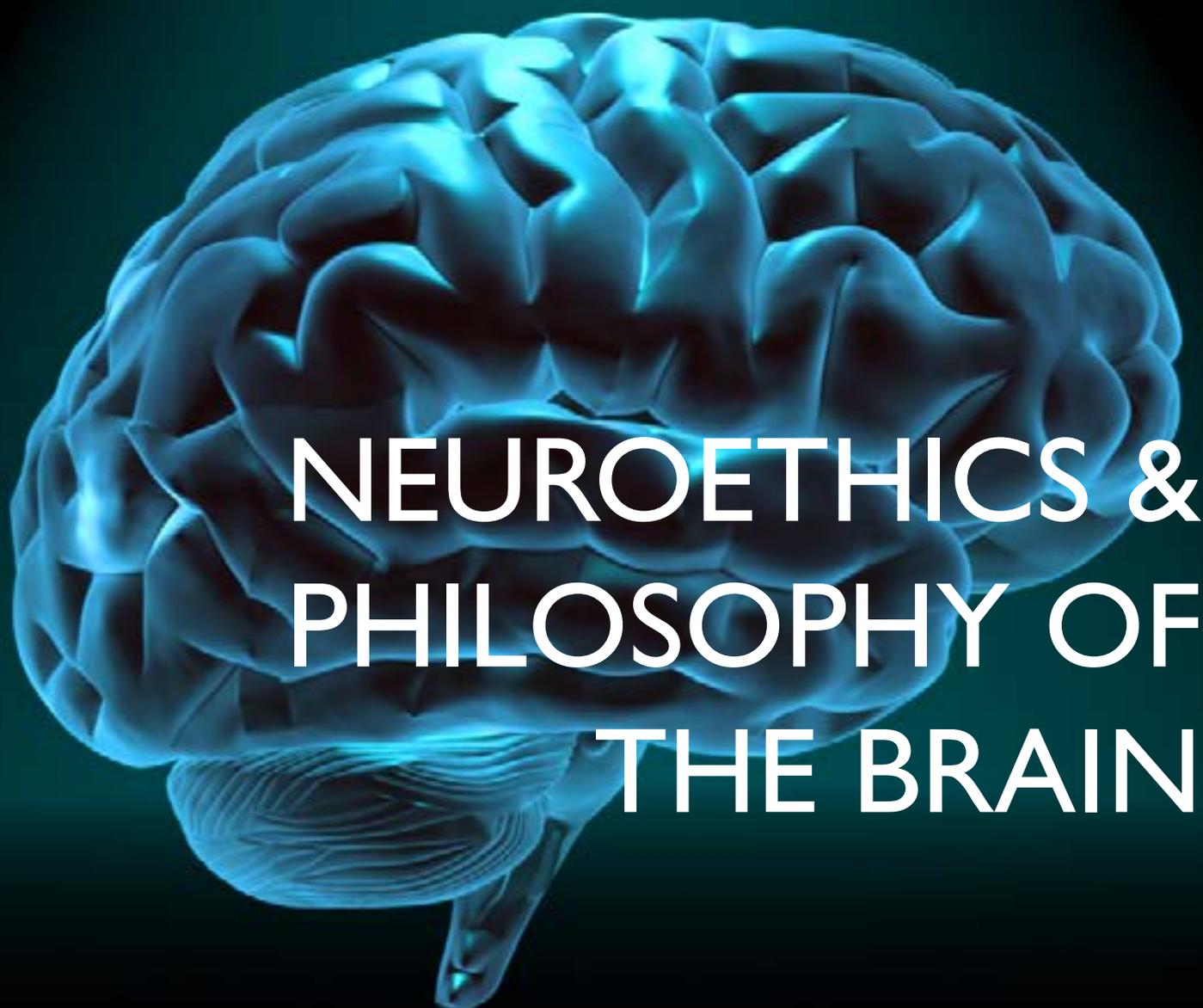


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Human Brain Project

Approaching future issues



NEUROETHICS & PHILOSOPHY OF THE BRAIN

Centre for Research Ethics & Bioethics

A collection of books and articles

Fourth edition

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NEUROETHICS & PHILOSOPHY OF THE BRAIN

Understanding the human mind and brain is one of the greatest challenges facing science in the 21st century. Neuroscience, philosophy, psychology and psychiatry all offer different models for understanding how the mind and the brain work, explanations that often come with particular sets of philosophical, ethical and social issues.

In order to address these issues, we need research in neuroethics and neurophilosophy. This research can be divided into fundamental neuroethics/neurophilosophy ('neuroscience of ethics'), and applied neuroethics/neurophilosophy ('ethics of neuroscience'). The former is primary to the latter, in that adequate applied research must be based on solid theory.

In our research we use a conceptual approach to neuroethics and neurophilosophy, focusing primarily on fundamental research questions, notably concerning consciousness, human identity, and the self. We are developing a theoretical framework for neuroethics within which practical issues can fruitfully be analysed. We are developing a theoretical framework for neuroethics to make analysis of practical issues fruitful. We examine the concepts that neuroscience uses and the impact that neuroscientific language and categories has on ethics and society

We investigate applications of neuroscience and ethical assessments of neuroscientific research. Current PhD projects look at how we can use neuroimaging and other methods to understand [how the mind works in people who can't use their behaviour to communicate](#) and [what it is like to be unconscious](#). We are also part of the European Community (FET) Flagship [Human Brain Project](#) where we look at the ethical and social questions that are raised when we model the human brain, e.g. through the method of simulation.

The CRB neuroethics research team is an international, multi-disciplinary group. Our backgrounds allow us to approach these issues from theoretical, philosophical, social, bio-political and clinical perspectives. We collaborate closely with neuroscientists to understand the ethical and philosophical questions that neuroscience brings.

We have long standing collaborations with [Collège de France](#) and the [Pasteur Institute](#) in Paris, the Centro de Investigaciones Filosóficas ([CIF](#)) and the Institute of Cognitive Neurology ([INECO](#)) in Buenos Aires. We also work with [Universidad Central de Chile](#) the [Coma Research Group](#) in Liege, the [Canada Research Chair of Mind, Brain Imaging and Neuroethics](#) in Ottawa, the Neuroethics Group of the [Pellegrino Center for Clinical Bioethics](#) of the Georgetown University in Washington DC, the [Bioethics Unit](#) of the Italian National Institute of Health in Rome, the [KTH](#) Royal Institute of Technology in Stockholm and the [Karolinska University Hospital](#) in Stockholm.

Uppsala, October 2017



Kathinka Evers,
Centre for Research Ethics & Bioethics (CRB), Uppsala University

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PEER REVIEWED ARTICLES

Cahn-Fuller K, Shook J, Giordano J, Moral mentation: What neurocognitive studies of psychopathy may really offer the internalism/externalism debate, J Cognition and Neuroethics, forthcoming.

Abstract: There is ongoing debate in moral philosophy and psychology about whether moral judgments necessarily motivate an agent's actions (what is known as internalism), or if moral judgments do not inherently motivate an agent to perform moral actions (what is known as externalism). Investigations focusing upon brain structures and functions that are involved in moral cognition (and which constitute an aspect of the discipline of neuroethics) have been leveraged in attempt to resolve this debate.. In this way, neuroethics – as the neuroscientific studies of moral thought and actions - is important to informing both philosophical notions of morality, as well as the practices of forensic psychiatry and the legal system, which increasingly look to empirical data about psychopathy to understand and mitigate criminal behavior. However, brain science is unlikely to provide definitive answers to the conceptual questions that drive the current internalism/externalism debate. Thus, moving forward, it will be necessary to carefully define the questions that neuroscience is employed to address and answer, and equally vital to ensure that empirical findings are not distorted to support preconceived theoretical assumptions. In this way, neuroscientific investigations – and neuroethics - can be employed in a conciliatory way. Not only to balance views of processes operative in moral cognition, but to bring together the sciences and humanities to both address questions about human morality, and iteratively raise ethical, legal and social questions about what research findings actually mean, and what medicine – and societies – will effect through the use of such information and meanings.

Farisco M, Salles A, Evers K, Neuroethics: A Conceptual Approach, Cambridge Quarterly of Healthcare Ethics, forthcoming.

Abstract: In this paper, we start by identifying three main neuroethical approaches: neurobioethics, empirical neuroethics, and conceptual neuroethics. We focus on conceptual approaches which generally emphasize the need to develop and use a methodological *modus operandi* for fruitfully linking scientific (i.e., neuroscience) and philosophical (i.e., ethics) interpretations. We explain and assess the value of conceptual neuroethics approaches and explain and defend one such approach that we believe is particularly fruitful to address the various issues raised by neuroscience: fundamental neuroethics.

Shook JR, Giordano J, Ethics transplants? Addressing the risks and benefits of guiding international biomedicine, AJOB-Neuroscience, forthcoming.

Abstract: In this paper, we address the planned body-head transplant (B-H-T) proposed by Canavero, to occur in China later this year. We speak to a current report by Canavero and /Ren, and to a rebuttal by Wolpe, and we argue that research plans such as those exemplified by Canavero's B-H-T experiment look more like opportunism at present. All the same, the controversial issues regarding intra- and cross-cultural ethical norms and conduct do create a timely opportunity to develop a broader and deeper conception of a globally relevant neuroethics. We strongly urge that neuroethics embrace this intercultural vantage point. We assert that neuroethics need not – and should not – dictate social priorities or impose a regulatory code based on a single country's lessons learned from hard experience. Nuanced neuroethical evaluations can develop practical guidelines by asking contextual questions first and delivering recommendations second. This approach would not retard progress; it would be a positive resource to enable the highest-quality professional conduct and scientific credibility. Neuroethical consultations should be cooperative, deliberative, future-oriented, and multi-national as any neuroscientific project. Neuroethical engagement should avoid inflexible absolutism as well as relativism, appreciating instead a consensus view of what constitutes good science and sound medical practice. There is no need to transplant western ethics or law into non-western countries, or vice versa. Neuroethics as an international enterprise should guide

innovative brain science with sensitivity to both the exigencies of particular cultures and the contingencies of inter-cultural engagement.

Akram F, Giordano J, [Research domain criteria as psychiatric nosology: Conceptual, practical and neuroethical implications](#), *Camb Q Health Care Ethics- Clin Neuroethics*, 2017; 26(4): 592-601.

Abstract: Diagnostic classification systems in psychiatry have continued to rely on clinical phenomenology despite limitations inherent to that approach. In view of these limitations and recent progress in neuroscience, the National Institute of Mental Health (NIMH) has initiated the Research Domain Criteria (RDoC) project in order to develop a more neuroscientifically-based system of characterizing and classifying psychiatric disorders. The RDoC initiative aims to transform psychiatry into an integrative science of psychopathology in which mental illnesses will be defined as involving putative dysfunctions in neural nodes and networks. However, conceptual, methodological and Neuroethical and social issues inherent to and/or derived from the use of RDoC need to be addressed before any attempt at implementing use in clinical psychiatry. This essay describes current progress in RDoC, defines key technical, neuroethical and social issues generated by RDoC adoption and use, and posits key questions that must be addressed and resolved if RDoC are to be employed for psychiatric diagnoses and therapeutics. Specifically, we posit that objectivization of complex mental phenomena may raise ethical questions about autonomy, the value of subjective experience, what constitutes normality, a disorder, and what represents a treatment, enablement and/or enhancement. Ethical issues may also arise from the (mis)use of biomarkers and phenotypes in predicting and treating mental disorders, and what such definitions, predictions and interventions portend for concepts and views of sickness, criminality, professional competency and social functioning. Given these issues, we offer that a preparatory neuroethical framework is required to define and guide the ways in which RDoC- oriented research can – and arguably should - be utilized in clinical psychiatry, and perhaps more broadly, in the social sphere.

Raynor S, Giordano J. [Treating Alzheimer's dementia with CT-induced low dose ionizing radiation: Problematic, yet potential for more precise inquiry](#), *Dose Response*, 2017; 15(3): 1-4.

Abstract: This commentary evaluates a recent single-case study by Cuttler et al that posits that a series of computerized tomographic (CT) scans ameliorated symptoms and signs of advanced Alzheimer's dementia in an elderly female patient. The report proposes that CT scanning delivered low-dose ionizing radiation (LDIR) that activated adaptive mechanisms in the brain to induce the effects observed and reported. However, the report evidenced methodologic problems that threaten the validity and value of its approach, stated results, and conclusions. We provide discussion of these issues, with view and intent toward developing more precise investigations of the potential mechanisms and utility of LDIR in treating Alzheimer's dementia and possibly other neurodegenerative disorders.

Herrera-Ferra K, Giordano J, [Recurrent violent behavior: Revised classification and implications for global psychiatry](#), *Front Psychiatry*, 2017; 8 (151): 1-4.

Abstract: In this paper, we propose that instantiating recurrent violent behavior (RVB) as a psychiatric classifier may leverage medical and psychosocial interventions in order to improve both mental health care and public safety needs, as consistent with Article 25 of the UN Declaration of Human Rights., and the WHO Mental Health Action Plan. We acknowledge that instituting RVB as a psychiatric classifier does not necessarily guarantee proper –if any- medical assessment or care, especially in developing and non-developed countries. We address distinctions between developed and non-developed countries mental health services, and seek to align our proposed use of RVB as a psychiatric classifier to be in accordance with the Global Mental Health Initiative. We address technical, as well as neuroethico-legal and social issues that such a proposal may foster, and posit approaches toward their address and possible resolution.

Evers K, Changeux JP, [Proactive epigenesis and ethical innovation: A neuronal hypothesis for the genesis of ethical rules. Response by the authors](#), *EMBO reports*, 2017; 18(8): 1272.

Abstract: In her commentary to our article on proactive epigenesis, Arleen Salles constructively criticizes aspects of our approach that, she suggests, merit further analyses and justification. We welcome her contributions that we consider both pertinent and useful to the development and application of our ideas. In particular, as Salles argues, core concepts should be more clearly defined, and normative claims must be justified.

Salles A, [Proactive Epigenesis and Ethics](#). *EMBO reports*, 2017; 18(8): 1271.

Abstract: A recent article by Kathinka Evers and Jean Pierre Changeux offers a new approach to the issue of moral change. They propose proactive epigenesis as a tool to communicate and establish social and ethical norms in education and upbringing so as to build better societies. In this short commentary I explain their view and then identify and explain some of the normative issues raised by their proposal. In particular, I focus on some moral claims they make that raise deep questions about justification and frameworks and thus require further discussion. Based on my analysis, I propose that the authors themselves further develop their views and elaborate on the specifically moral issues raised by their proposal and hope that their joint work on this issue inspires empirical and theoretical research from disciplines such as moral philosophy, pedagogy, and social science to further examine proactive epigenesis and the possibilities it opens for addressing moral improvement.

Racine E, Dubljevic V, Jox R, Baertschi B, Christensen J, Farisco M, Jotterand F, Kahane G, Muller S, [Can Neuroscience Contribute to Practical Ethics? A Critical Review and Discussion of the Methodological and Translational Challenges of the Neuroscience of Ethics](#), *Bioethics*, 2017; 31(5): 328-337.

Abstract: Neuroethics is an interdisciplinary field that arose in response to novel ethical challenges posed by advances in neuroscience. Historically, neuroethics has provided an opportunity to synergize different disciplines, notably proposing a two-way dialogue between an 'ethics of neuroscience' and a 'neuroscience of ethics'. However, questions surface as to whether a 'neuroscience of ethics' is a useful and unified branch of research and whether it can actually inform or lead to theoretical insights and transferable practical knowledge to help resolve ethical questions. In this article, we examine why the neuroscience of ethics is a promising area of research and summarize what we have learned so far regarding its most promising goals and contributions. We then review some of the key methodological challenges which may have hindered the use of results generated thus far by the neuroscience of ethics. Strategies are suggested to address these challenges and improve the quality of research and increase neuroscience's usefulness for applied ethics and society at large. Finally, we reflect on potential outcomes of a neuroscience of ethics and discuss the different strategies that could be used to support knowledge transfer to help different stakeholders integrate knowledge from the neuroscience of ethics.

Farisco M, Evers K, Salles A, [The Computational Shift in Neuroscience: A Multifaceted Neuroethical Analysis](#), *AJOB Neuroscience*, 2017; 8(1):W4-W5

Abstract: Lately it has been argued that a paradigm shift in neuroscience is necessary, a turn from a hypothesis-led approach grounded on empirical observation, to a data-led simulation modeling grounded on the computational analysis and manipulation of big data repositories. This novel approach is known as "predictive biology." It is notably exemplified by the European Human Brain Project, which aims at overcoming the existing limitations and fragmentation of contemporary neurosciences by digitalizing the massive empirical data available and developing highly sophisticated tools, such as computer models and simulations, to achieve an integrated knowledge of the brain. The development of predictive computational neuroscience is usually justified for both epistemological (i.e., the intrinsic limitation of the empirical methodology) and practical (i.e., the need for new therapeutic and clinical applications) reasons. We think that the proposed computational shift raises the need for a specific neuroethical reflection.

Palchik G, Chen C, Giordano J, [Monkey business? Development, influence and ethics of potentially dual-use brain science on the world stage](#), *Neuroethics*, 2017; 10: 1-4

Abstract: At the recent annual meeting of the International Neuroethics Society, Dr. Mu-Ming Poo, of the China Brain Science Project, provided an overview of the proposed future directions and goals of neuroscientific research in China. Through concentrated efforts of the Institute of Neuroscience of the Chinese Academy of Science (CAS), China is rapidly developing increasingly greater scientific and technological capability – and global prominence – in brain research. Poo emphasized the strong translational focus of such research in light of recognized epidemiological trends in neurological disorders. What effect might this have on a broader, international scale? This raises concerns about tacit capabilities, and to yoking NHP studies and findings to military agendas under programs of dual- or direct-use. Such endeavors are not unique to China, as many countries, including the United States, engage in brain research that is applicable to, and employed for national security. In this paper, we posit that it is important to examine methods, (explicit, implicit, and possible) uses, and consequences that can be incurred from brain science. Therefore, if neuroethical address and analyses are to authentically inform international guidelines and policies that direct the sound conduct and use of brain science, then veracity, veridicality, and clarity in the discourses and activities of neuroscience *and* neuroethics will be ever more essential- regardless of where they occur.

Lipina S, Evers K, [Neuroscience of Childhood Poverty: Evidence of Impacts and Mechanisms as Vehicles of Dialog With Ethics](#), *Frontiers in Psychology*, 2017; 8: 61.

Abstract: Several studies have identified associations between poverty and development of self-regulation during childhood, which is broadly defined as those skills involved in cognitive, emotional, and stress self-regulation. These skills are influenced by different individual and contextual factors at multiple levels of analysis (i.e., individual, family, social, and cultural). Available evidence suggests that the influences of those biological, psychosocial, and sociocultural factors on emotional and cognitive development can vary according to the type, number, accumulation of risks, and co-occurrence of adverse circumstances that are related to poverty, the time in which these factors exert their influences, and the individual susceptibility to them. Complementary, during the past three decades, several experimental interventions that were aimed at optimizing development of self-regulation of children who live in poverty have been designed, implemented, and evaluated. Their results suggest that it is possible to optimize different aspects of cognitive performance and that it would be possible to transfer some aspects of these gains to other cognitive domains and academic achievement. We suggest that it is an important task for ethics, notably but not exclusively neuroethics, to engage in this interdisciplinary research domain to contribute analyses of key concepts, arguments, and interpretations. The specific evidence that neuroscience brings to the analyses of poverty and its implications needs to be spelled out in detail and clarified conceptually, notably in terms of causes of and attitudes toward poverty, implications of poverty for brain development, and for the possibilities to reduce and reverse these effects.

Evers K, [The contribution of neuroethics to international brain research initiatives](#), *Nature Reviews Neuroscience*, 2017; 18:1-2.

Abstract: Neuroethics research can contribute a level of conceptual clarity to international brain research initiatives that is essential for their ethics management as well as for the interpretations, applications and management of their emerging neuroscientific findings.

Farisco M, [The relevance of neuroscience for conceptualizing human nature](#), *Idee*, 2016; 6(11): 121-136.

Abstract: The paper starts from a possible cultural interpretation of neuroscience, that is the conceptual simplification of the complexity emerging from contemporary neuroscientific data and formalized in related theoretical perspectives. On the basis of the conceptual relevance of neuroscience, the paper suggests the epigenetic theory of neuronal development and related

informed materialism as useful theoretical framework for developing a neurophilosophy aiming at overcoming classical dualistic interpretations like brain/mind and nature/culture.

Evers K, Changeux J-P, [Proactive epigenesis and ethical innovation. A neuronal hypothesis for the genesis of ethical rules](#), *EMBO Reports*, 2016; 17 (10): 1361-1364

Abstract: During the long period of postnatal development in humans, the cerebral cortex undergoes intense synaptogenesis, which persists into adulthood. The steady interaction with the physical, social, and cultural environment drives an epigenetic selection of neuronal networks to internalize, in particular, the common cultural and ethical rules of the society to which the child and her/his family belong. Based on this knowledge, we propose the idea of proactive epigenesis to develop new ethical rules and educational approaches to influence, and constructively interact with the developing neuronal architecture of the human brain.

Salles A, [Sobre la neuroética](#), *Revista Latinoamericana de Filosofía*, 2016; 42(1): 7-14

Abstract: Introduction to a special issue devoted to neuroethics. This article provides an overview of the main issues raised by recent neuroscientific advances and the different approaches used to understand and discuss them.

Farisco M, Evers K, Salles A, [Big Science, Brain Simulation and Neuroethics](#), *AJOB Neuroscience*, 2016; 7(1): 28–30

Abstract: The ethical analysis of brain simulation is a relatively new field of research, which is gaining an increasing multidisciplinary interest. However, at present the debate revolves mainly around the practical concerns raised by emerging neuro-technology, concerns that are not fundamentally different from those raised by emerging technologies in general. The authors suggest that while valuable, this common approach is not enough to fully capture the issues at stake and propose the examination of conceptual understandings of the brain and of simulation in order to better grasp the ethical implications of simulation technology in particular.

Evers K, [The Responsible Brain: Free Will and Personal Responsibility in the Wake of Neuroscience](#), *Revista Latinoamericana de Filosofía*, 2016; XLII(1): 33-44

Abstract: This article examines the neuroethical problem of free will that consists in explaining how the socially crucial conception of human beings as free and responsible can be combined with neuroscientific findings on human beings and their behaviour. Within neuroscience, the experience of free will has been considered 'illusory' by virtue of being (1) a brain construct, or (2) causally determined, or (3) non-consciously initiated. This article analyses these positions and suggests a neurophilosophical view on free will according to which, rather than posing a new threat to our unalienable notions of free will and personal responsibility, neuroscience can offer empirical support for them.

Evers K, [Neurotechnological assessment of consciousness disorders: five ethical imperatives](#), *Dialogues in Clinical Neuroscience*, 2016;18(2): 155-162

Abstract: Disorders of Consciousness (DOCs) cause great human suffering and material costs for society. Understanding of these disorders has advanced remarkably in recent years, but uncertainty remains with respect to the diagnostic criteria and standards for care. One of the most serious problems concerns misdiagnoses, their impact on medical decision-making, and on patients' wellbeing. Recent studies of DOC patients use neurotechnology to assess residual consciousness in DOC patients that traditional behavioural diagnostic criteria are unable to detect. The results show an urgent need to strengthen the development of new diagnostic tools and more refined diagnostic criteria. If residual consciousness may be inferred from robust and repeated results from neurotechnological communication with DOC patients, this also raises ethical challenges. With reference to the moral notions of beneficence and

fundamental rights, five ethical imperatives are here suggested in terms of diagnosis, communication, interpretation of subjective states, adaptation of living conditions and care.

Sallin K, Lagercrantz H, Evers K, Engström I, Hjern A, Petrovic P, [Resignation Syndrome: Catatonia? Culture-Bound?](#), *Front. Behav. Neurosci.*, 29 January 2016

Abstract: Resignation syndrome (RS) designates a long-standing disorder predominately affecting psychologically traumatized children and adolescents in the midst of a strenuous and lengthy migration process. Typically a depressive onset is followed by gradual withdrawal progressing via stupor into a state that prompts tube feeding and is characterized by failure to respond even to painful stimuli. The patient is seemingly unconscious. Recovery ensues within months to years and is claimed to be dependent on the restoration of hope to the family. Descriptions of disorders resembling RS can be found in the literature and the condition is unlikely novel. Nevertheless, the magnitude and geographical distribution stand out. Several hundred cases have been reported exclusively in Sweden in the past decade prompting the Swedish National Board of Health and Welfare to recognize RS as a separate diagnostic entity. The currently prevailing stress hypothesis fails to account for the regional distribution and contributes little to treatment. Consequently, a re-evaluation of diagnostics and treatment is required. Psychogenic catatonia is proposed to supply the best fit with the clinical presentation. Treatment response, altered brain metabolism or preserved awareness would support this hypothesis. Epidemiological data suggests culture-bound beliefs and expectations to generate and direct symptom expression and we argue that culture-bound psychogenesis can accommodate the endemic distribution. Last, we review recent models of predictive coding indicating how expectation processes are crucially involved in the placebo and nocebo effect, delusions and conversion disorders. Building on this theoretical framework we propose a neurobiological model of RS in which the impact of overwhelming negative expectations are directly causative of the down-regulation of higher order and lower order behavioral systems in particularly vulnerable individuals.

Farisco M, [“Cerebral Communication” With Patients With Disorders of Consciousness: Clinical Feasibility and Implications](#), *AJOB Neuroscience*, 2015;6(2):44-46

Abstract: Recent neuroscientific and neurotechnological developments give us the possibility of detecting covert awareness in patients behaviorally diagnosed as in vegetative state/unresponsive wakefulness syndrome (VS/UWS). Starting from this detection of conscious brain activity, a potential new tool for communicating with these patients is under investigation by the scientific community. Several conceptual and ethical issues urge specific attention.

Melo Martin I, Salles A, [Moral Bioenhancement: Much Ado about Nothing?](#), *Bioethics*, 2015;29(4):223-232

Abstract: Recently, some have proposed moral bioenhancement as a solution to the serious moral evils that humans face. Seemingly disillusioned with traditional methods of moral education, proponents of bioenhancement believe that we should pursue and apply biotechnological means to morally enhance human beings. Such proposal has generated a lively debate about the permissibility of moral bioenhancement. We argue here that such debate is specious. The claim that moral bioenhancement is a solution – whether permissible or not – to the serious moral problems that affect human beings is based on several problematic framing assumptions. We evaluate here three of such assumptions: the first rests on a contested understanding of morality, the second consist in a mistaken conception of human moral problems, and the third relates to problematic presuppositions grounding the interpretation of existent scientific evidence presented to defend moral bioenhancement. Once these framing assumptions are identified and critically evaluated, it becomes clear that the moral bioenhancement debate is misguided.

Gini A, Larrivee D, Farisco M, Sironi VA, [Keeping the human: neuroethics and the conciliation of dissonant values in the 21st century](#), *Neuroscience and Neuroeconomics* 2015;4:1-10

Abstract: Studied since antiquity, the human brain has recently been the inspiration for an international neuroscientific entrepreneurship, the Human Brain Project in Europe and the Brain Research through Advancing Innovative Neurotechnologies initiative in the USA. Different in their approach, both regard the human brain as one of the greatest challenges of 21st century science and the organ that makes us “human”. However, it is mainly the necessity of developing new therapies that affect up to a billion people worldwide, which has propelled the search for extensive expertise and investment in neuroscience research. The debate on ethical and social policy issues as well as the research and medical strategies of such gigantic efforts has involved participants as diverse as neuroscientists, philosophers, scholars in ethics and law, politicians, and the general public, rendering modern neuroscience an interdisciplinary and conflictual endeavor. In fact, the brain is described as the biological underpinning of our thoughts, emotions, perceptions, free willed actions, and memories, features unique to our humanity. In this review, three neuroscientists and a philosopher from the neuroethics community provide their perspectives for an up-to-date survey of salient neuroethical issues, ie, modulation of free will and neuropharmaceuticals and neurotechnologies that enhance cognitive capacities, as well as an introduction of the reader to the controversial new discipline of neuroethics. Written for nonexperts in the field, it is intended to reflect on and to impart information helpful in understanding the challenges and the perils of modern neuroscience, whose tools are so powerful as to jeopardize what is uniquely “human” through willful mind manipulation. We conclude that, for any future effort to “recreate” the mind and, at the same time, keep what is uniquely ours, it will be necessary to reflect ethically and review carefully man's past best efforts at self-understanding.

Farisco M, Laureys S, Evers K, [Externalization of Consciousness. Scientific Possibilities and Clinical Implications](#), in: Geyer M, Ellenbroek B, Marsden C (eds), *Current Topics in Behavioural Neurosciences*, 2015; 19: 205-222, doi: 10.1007/7854_2014_338

Abstract: The paper starts by analyzing recent advancements in neurotechnological assessment of residual consciousness in patients with disorders of consciousness and in neurotechnology-mediated communication with them. Ethical issues arising from these developments are described, with particular focus on informed consent. Against this background, we argue for the necessity of further scientific efforts and ethical reflection in neurotechnological assessment of consciousness and ‘cerebral communication’ with verbally non-communicative patients.

Dudai Y, Evers K, [To Simulate or not to Simulate: What are the questions?](#), *Neuron*, 2014;84(2):254-261

Abstract: Simulation is a powerful method in science and engineering. However, simulation is an umbrella term, and its meaning and goals differ among disciplines. Rapid advances in neuroscience and computing draw increasing attention to large-scale brain simulations. What is the meaning of simulation, and what should the method expect to achieve? We discuss the concept of simulation from an integrated scientific and philosophical vantage point and pinpoint selected issues that are specific to brain simulation.

Farisco M, Evers K and Petrini C, [Biomedical research involving patients with disorders of consciousness: ethical and legal dimensions](#), *Ann Ist Super Sanità*, 2014;50(3):221-228

Abstract: The directive 2001/20/UE and the research involving patients with docs. Research involving patients with disorders of consciousness (DOCs) deserves special ethical and legal attention because of its Janus-faced nature. On the one hand, it raises concerns about the risk to expose the involved subjects to disproportionate risks not respecting their individual dignity, particularly their right to be cared for; on the other hand, research is an essential tool in order

to improve the clinical condition of patients with DOCs. The present paper concerns the ethical and legal dimensions of biomedical research involving patients with disorders of consciousness. In particular, it focuses on informed consent to experimental treatments, which is a challenging issue both from an ethical and legal point of view. The first part reads the Directive 2001/20/EU in the light of the experimentation of patients with DOCs, and suggests a revision in order to better assess the issue of informed consent. The particular case of informed consent for observational studies of non-communicative patients. The second part presents an informed consent form for studies through video-recording of patients unable to communicate their own consent. This form has been elaborated by the bioethics unit of the project "Review of the nosography of vegetative states: application of methods of behavioral analysis to individuals in coma or vegetative state" developed at the Italian National Institute of Health. Relevance of the suggested form. The paper describes the conceptual framework of the form for informed consent to studies through video-recoding, which is a relevant example of what issues should be included in an informed consent for any type of studies through video-recording of patients unable to express their own consent. The article has been sent on November the 7th 2013, before the adoption of the Regulation (EU) no. 536/2014 (and consequent abrogation of the Directive 2001/20/EU) and the release of the new edition of the Italian Code of Medical Ethics.

Farisco M, Petrini C, [Misdiagnosis as an ethical and scientific challenge, Ann Ist Super Sanità, 2014;50\(3\):229-233](#)

Abstract: Difficulties of behavioral assessment of consciousness. An astonishingly high rate of misdiagnosis between vegetative state/unresponsive wakefulness syndrome and minimally conscious state has been detected. This raises the issue of the adequacy of the consciousness' assessment in patients with disorders of consciousness. The behavioral assessment of consciousness could be not able to detect covert awareness, which is increasingly identified by the instrumental assessment. Ancillary methods. Neurotechnology, particularly neuroimaging, provides relevant data concerning the neurological underlying condition of patients with DOCs, but the instrumental approach has still to assess some technical issues. Ethical considerations. A correct diagnosis of a DOC is not only an instrumental issue, but also an ethically relevant demand to the scientific community. Finally, an integration between behavioral and instrumental assessments seems to be the most adequate strategy in order to decrease the rate of misdiagnosis.

Farisco M, Petrini C, [On the Stand. Another Episode of Neuroscience and Law Discussion From Italy, Neuroethics, 2014; 7\(2\):243-245](#)

Abstract: After three proceedings in which neuroscience was a relevant factor for the final verdict in Italian courts, for the first time a recent case puts in question the legal relevance of neuroscientific evidence. This decision deserves international attention in its underlining that the uncertainty still affecting neuroscientific knowledge can have a significant impact on the law. It urges the consideration of such uncertainty and the development of a shared management of it.

Farisco M, [In Need of Meta-Scientific Experts?, AJOB Neuroscience, 2014; 5\(2\):20-52](#)

Abstract: A recent Italian case shows that the interpretation of neuroscientific evidence is often uncertain and debated. Judges and courts have to deal with this uncertainty. We suggest as a strategy to assess it the involvement of meta-scientific experts who can help lay people (as judges and juries presumably are, in science) to understand the formal and conceptual limitation of neuroscience.

Farisco M, Alleva E, Chiarotti F, Macri S, Petrini C, [Clinicians' attitudes towards patients with disorders of consciousness: a survey, Neuroethics 2014; 7\(1\):93-104](#)

Abstract: Notwithstanding fundamental methodological advancements, scientific information about disorders of consciousness (DOCs)—e.g. Vegetative State/Unresponsive Wakefulness

Syndrome (VS/UWS) and Minimally Conscious State (MCS)—is incomplete. The possibility to discriminate between different levels of consciousness in DOC states entails treatment strategies and ethical concerns. Here we attempted to investigate Italian clinicians' and basic scientists' opinions regarding some issues emerging from the care and the research on patients with DOCs. From our survey emerged that Italian physicians working with patients with DOCs give a central role to ethics. Current Italian regulation regarding basic research conducted in patients with DOCs apparently risks to be inadequate to support scientific advancement, and would deserve a different assessment compared to ordinary treatments. We think the results of our survey deserve attention from an international audience because they exemplify the difficulty to define a shared approach to the issues related to patients with DOCs and the necessity to better assess both the ordinary and experimental treatment of patients with DOCs at the ethical and legal level.

Gutierrez-Arenas O, Eriksson O, and Hellgren Kotaleski J, [Segregation and crosstalk of D1 receptor-mediated activation of ERK in striatal medium spiny neurons upon acute administration of psychostimulants](#), *PLoS Computational Biology*, 2014;10(1): e1003445

Abstract: Development and regeneration of the nervous system requires the precise formation of axons and dendrites. Kinases and phosphatases are pervasive regulators of cellular function and have been implicated in controlling axodendritic development and regeneration. We undertook a gain-of-function analysis to determine the functions of kinases and phosphatases in the regulation of neuron morphology. Over 300 kinases and 124 esterases and phosphatases were studied by high-content analysis of rat hippocampal neurons. Proteins previously implicated in neurite growth, such as ERK1, GSK3, EphA8, FGFR, PI3K, PKC, p38, and PP1a, were confirmed to have effects in our functional assays. We also identified novel positive and negative neurite growth regulators. These include neuronal-developmentally regulated kinases such as the activin receptor, interferon regulatory factor 6 (IRF6) and neural leucine-rich repeat 1 (LRRN1). The protein kinase N2 (PKN2) and choline kinase alpha (CHKA) kinases, and the phosphatases PPEF2 and SMPD1, have little or no established functions in neuronal function, but were sufficient to promote neurite growth. In addition, pathway analysis revealed that members of signaling pathways involved in cancer progression and axis formation enhanced neurite outgrowth, whereas cytokine-related pathways significantly inhibited neurite formation.

Gutierrez-Arenas O, [Handling and analyzing meshed rendering of segmented structures from 3D image stacks in Blender](#), *Neuroinformatics*, 2014;12(4):3-6

Abstract: Volume electron microscopy (EM) is an aggregate of techniques (e.g. FIB-SEM, SBF-SEM) which are evolving toward easing the trade-off between resolution and field of view size so that increasingly large volumes of tissue can be imaged at just a few nanometer resolution. These technical developments have been driven by the necessity of characterizing spatially extended structures with functionally relevant supramolecular elements that are several orders of magnitude smaller. Neuronal microcircuits with their intracellular organelles and synaptic specializations stand out among these demanding biological objects. With the increasing image throughput, the bottleneck in the pipeline is the segmentation of both the neurites (axon and dendrites) and the organelles and synaptic structures from the collected 3D EM image stack. In both cases, iterations between human curation and machine learning procedures are the norm

Nair AG, Gutierrez-Arenas O, Eriksson O, Jauhiainen A, Blackwell KT and Hellgren Kotaleski J, [Modeling intracellular signaling underlying striatal function in health and disease](#). In “*Computational Molecular Neurosciences: Novel approaches to understanding diseases of the nervous systems*”, 2014;123: 277-304

Abstract: Striatum, which is the input nucleus of the basal ganglia, integrates cortical and thalamic glutamatergic inputs with dopaminergic afferents from the substantia nigra pars compacta. The combination of dopamine and glutamate strongly modulates molecular and

cellular properties of striatal neurons and the strength of corticostriatal synapses. These actions are performed via intracellular signaling networks, containing several intertwined feedback loops. Understanding the role of dopamine and other neuromodulators requires the development of quantitative dynamical models for describing the intracellular signaling, in order to provide precise unambiguous descriptions and quantitative predictions. Building such models requires integration of data from multiple data sources containing information regarding the molecular interactions, the strength of these interactions, and the subcellular localization of the molecules. Due to the uncertainty, variability, and sparseness of these data, parameter estimation techniques are critical for inferring or constraining the unknown parameters, and sensitivity analysis evaluates which parameters are most critical for a given observed macroscopic behavior. Here, we briefly review the modeling approaches and tools that have been used to investigate biochemical signaling in the striatum, along with some of the models built around striatum. We also suggest a future direction for the development of such models from the, now becoming abundant, high-throughput data.

Salles A, [Neuroethics in a “Psy” World: the Case of Argentina](#), *Cambridge Quarterly of Healthcare Ethics*, 2014;23:3

Abstract: Given the cultural psychoanalytic tradition that shapes the thought of Argentinians and their current skepticism with regard to neurosciences when it comes to understanding human behavior, this article addresses the question of whether a healthy neuroethics can develop in the country.

Salles A, [Las diferencias sexuales y la discusión neuroética](#), *Debate Feminista*, 2014; 25:49: 94-116

Abstract: En este capítulo, me propongo indagar este entrecruzamiento conceptual entre el feminismo y la neuroética. En la primera parte, presentaré algunos de los temas más recurrentes de la neuroética, para luego señalar los matices diferentes introducidos por el feminismo. En la segunda parte me concentro en algunas inquietudes feministas sobre la investigación neurocientífica de las diferencias sexuales, en particular las relacionadas con la manera como se lleva a cabo y las consecuencias de sus resultados. Finalmente, en la tercera parte sugiero que es hora de trascender las etiquetas y nos propongamos hacer una neuroética lo suficientemente crítica e intelectualmente honesta como para que esté atenta a todo tipo de consideración moralmente significativa incluyendo, por supuesto, las de género.

Evers K & Sigman M, [Possibilities and limits of mind-reading: A neurophilosophical perspective](#), *Consciousness and Cognition*, 2013;22:887–897

Abstract: Access to other minds once presupposed other individuals' expressions and narrations. Today, several methods have been developed which can measure brain states relevant for assessments of mental states without 1st person overt external behavior or speech. Functional magnetic resonance imaging and trace conditioning are used clinically to identify patterns of activity in the brain that suggest the presence of consciousness in people suffering from severe consciousness disorders and methods to communicate cerebrally with patients who are motorically unable to communicate. The techniques are also used non-clinically to access subjective awareness in adults and infants. In this article we inspect technical and theoretical limits on brain-machine interface access to other minds. We argue that these techniques hold promises of important medical breakthroughs, open up new vistas of communication, and of understanding the infant mind. Yet they also give rise to ethical concerns, notably misuse as a consequence of hypes and misinterpretations.

Salles A, [On the Normative Implications of Social Neuroscience](#), *RECERCA: Revista di Pensament I Anàlisi*, 2013;13:29-42

Abstract: Within the last decades, brain science has been offering new insights into the relationship among diverse psychological processes and the neural correlates of our moral thought and behavior. Despite the distinction between the explanatory/descriptive nature of

science and the normative nature of morality, some neuroethicists have claimed that neuroscientific findings have normative implications. In this paper, I identify three interpretations of the claim. The first focuses on neuroscience's role in explaining the origin of morality and of moral values and how neurobiology is the bases of moral behavior. A second version is about the role that neuroscientific knowledge can play in showing the psychological plausibility of the moral psychology underlying some ethical approaches. Finally, a third version advances that neuroscience could play a role in determining the moral plausibility of some normative approaches. My aim is to delineate each version and highlight the issues raised to suggest that while neuroscience might provide information regarding the nature of moral reasoning, its role in the normative discussion itself is still quite limited.

Achaval D, Villarreal M, Salles A, Bertomeu MJ, Costanzo E, Goldschmidt M, Castro M, van der Poel I, Nemeroff C, Guinjoan SM, [Activation of brain areas concerned with social cognition during moral decisions is abnormal in schizophrenia patients and unaffected siblings](#), *Journal of Psychiatric Research*, 2013; 47(6):774-782

Abstract: Moral decision-making involves complex social cognitive processes which are known to be altered in patients with schizophrenia and first-degree relatives. Traditional philosophical views on human moral behavior have distinguished between utilitarian views (which emphasize outcomes) and deontological approaches (defining what is right to do according to certain norms). Since emotions have been suggested to play a determining role in moral behavior, we hypothesized patients with schizophrenia and unaffected siblings would make more utilitarian choices and show faulty activation of brain areas concerned with emotion regulation during such tasks. Unexpectedly, all participants (n = 13 per group) made the same proportion of utilitarian and deontological decisions. Brain activation common to all groups induced by moral decisions included two circumscribed portions of right ventromedial and dorsolateral prefrontal cortex, adding to previous evidence on a right prosencephalic cognitive network involved in ethical decisions. However, brain activation induced by moral decisions was different in healthy persons, schizophrenia patients, and nonpsychotic siblings in regards to areas directly concerned with emotion processing. These results seem to underscore the role of acquired norms in moral decisions, a frequently overlooked concept in the neurobiological characterization of human ethical behavior, and add to previous evidence of abnormal social cognitive processing in schizophrenia.

Farisco M, [The Ethical Pain: Detection of pain and suffering in patients with disorders of consciousness](#), *Neuroethics*, 2012; 6(2):265-276

Abstract: The intriguing issue of pain and suffering in patients with disorders of consciousness (DOCs), particularly in Unresponsive Wakefulness Syndrome/Vegetative State (UWS/VS) and Minimally Conscious State (MCS), is assessed from a theoretical point of view, through an overview of recent neuroscientific literature, in order to sketch an ethical analysis. In conclusion, from a legal and ethical point of view, *formal guidelines* and a *situationist ethics* are proposed in order to best manage the critical scientific uncertainty about pain and suffering in DOCs and ensure the best possible care for the patient.

Farisco M, Petrini C, [The Impact of Neuroscience and Genetics on the Law: A Recent Italian Case](#), *Neuroethics*, 2012;5(3):317-319

Abstract: The use of genetic testing and neuroscientific evidence in legal trials raises several issues. Often their interpretation is controversial: the same evidence can be used to sustain both the prosecution's and defense's argument. A recent Italian case confirms such concerns and stresses other relevant related questions.

Salles A, Reflexiones sobre la bioética y la biotecnología, Perspectivas Bioéticas, 2012; 17(32):81-95

Abstract: New biomedical technologies and research have raised a number of ethical issues and created a polarized debate about how to understand and solve them. Here, I present two rival approaches regarding how to look at biotechnology: the neoconservative and the progressive approaches. I explore some of their underlying assumptions and consider the role that similar approaches play in shaping the public perception and discussion of the ethical issues raised by biotechnology in Latin American countries.

Salles A, Melo Martin I, [Disgust in Bioethics](#), Cambridge Quarterly of Healthcare Ethics, 2012; 21(2): 267-280

Abstract: We propose to advance the dialogue by clarifying the different ways in which disgust is used when dealing with bio-ethical issues, particularly those issues that relate to new biotechnological developments. We argue that discussions involving this concept are muddled because of a failure to clarify the particular content of the emotion and its manifestations, or because disputants are using disgust in different ways. We identify here four main uses of the concept of disgust. In some cases, disgust is used as an example to illustrate the proper role of emotional sensibility in bioethical thinking. In other cases, disgust is discussed as a possible source of moral knowledge that can help us discern the permissibility of biomedical practices or technologies. Disgust is also used as a rhetorical device to bring forth opposition or rejection of such practices or biotechnological advances. Finally, disgust is used in the bioethics literature as a tool that, on grounds of irrationality or ignorance, allows one to dismiss the concerns of those who appeal to disgust when rejecting new biomedical technologies. Of course, the different uses of disgust are interrelated, and sometimes more than one of these uses is found in the same work. We believe however, that these diverse uses have different normative implications, and thus it is important to clarify what it is that one wants to achieve when using the concept of disgust.

Melo Martin I, Salles A, [On Disgust and Human Dignity](#), Journal of Value Inquiry, 2011; 45(2):159-168

Abstract: In this paper, critically examine Nussbaum's claim that moralized disgust necessarily presents a threat to the dignity of human beings. Without calling into question Nussbaum's account of human dignity and of the emotion of disgust, we have seen that whether dignity can be conceptualized as an inalienable characteristic possessed by all human beings or as a characteristic tied to the development and exercise of the central human capabilities, moralized disgust need not be incompatible with respect for the dignity of human beings. However, the fact that moral disgust need not present a threat to the equal respect and dignity of all human beings does not support the claim that there is wisdom in repugnance. It might well be that disgust is not very reliable and thus not a particularly good moral guide. Also, it might be that, as Nussbaum suggests, the link of disgust with the desire to remain pure can result in a failure to move us to engage socially, to protest against wrongdoing, and to right wrongs. If so, disgust might not be a valuable emotion for social reform. Hence, there might be good reasons to question the value of disgust as a response to moral wrongs, but a concern that disgust inevitably threatens human dignity does not seem to be one of them

Buchser WJI, Slepak TI, Gutierrez-Arenas O, Bixby JL, Lemmon VP, [Kinase/phosphatase overexpression reveals pathways regulating hippocampal neuron morphology](#), Mol Syst Biol., 2010; 6:391. doi: 10.1038/msb.2010.52

Abstract: The convergence of corticostriatal glutamate and dopamine from the midbrain in the striatal medium spiny neurons (MSN) triggers synaptic plasticity that underlies reinforcement learning and pathological conditions such as psychostimulant addiction. The increase in striatal dopamine produced by the acute administration of psychostimulants has been found to activate not only effectors of the AC5/cAMP/PKA signaling cascade such as GluR1, but also effectors of the NMDAR/Ca(2+)/RAS cascade such as ERK. The dopamine-

triggered effects on both these cascades are mediated by D1R coupled to Golf but while the phosphorylation of GluR1 is affected by reductions in the available amount of Golf but not of D1R, the activation of ERK follows the opposite pattern. This segregation is puzzling considering that D1R-induced Golf activation monotonically increases with DA and that there is crosstalk from the AC5/cAMP/PKA cascade to the NMDAR/Ca(2+)/RAS cascade via a STEP (a tyrosine phosphatase). In this work, we developed a signaling model which accounts for this segregation based on the assumption that a common pool of D1R and Golf is distributed in two D1R/Golf signaling compartments. This model integrates a relatively large amount of experimental data for neurons in vivo and in vitro. We used it to explore the crosstalk topologies under which the sensitivities of the AC5/cAMP/PKA signaling cascade to reductions in D1R or Golf are transferred or not to the activation of ERK. We found that the sequestration of STEP by its substrate ERK together with the insensitivity of STEP activity on targets upstream of ERK (i.e. Fyn and NR2B) to PKA phosphorylation are able to explain the experimentally observed segregation. This model provides a quantitative framework for simulation based experiments to study signaling required for long term potentiation in MSNs.

Evers K, [Personalized medicine in psychiatry: ethical challenges and opportunities, Dialogues in Clinical Neuroscience: Personalized Medicine: Prediction, Prevention, Participation, 2009;11\(4\):427-433](#)

Abstract: Pharmacogenomic developments hold promise for personalized medicine in psychiatry with adjusted therapeutic doses, predictable responses, reduced adverse drug reactions, early diagnosis, and personal health planning. The prospects are exciting, but at the same time, these new techniques stand faced with important scientific, ethical, legal, and social challenges that need to be met in order for the scientific advances to be responsibly applied. This review discusses the ethical balance between challenge and opportunity of personalized medicine in psychiatry under the aspects of adequacy, cost:benefit ratio, and therapeutic equity. It is argued that the promising nature of these therapeutic possibilities makes it all the more important to avoid exaggerating the expectations, and that a sophisticated social infrastructure needs to be developed in order to ensure the realistic and responsible application of personalized medicine in psychiatry.

Evers K, [Philosophical challenges for neuroethics. European Neuropsychopharmacology, Journal of the European College of Neuropsychopharmacology, 2008;18\(4\): S202](#)

Abstract: Neuroethics is an area concerned with the possible benefits and dangers of modern research on the brain. Researchers in neuroethics have focused mainly on applied neuroethics, such as ethical issues involved in neuroimaging techniques, cognitive enhancement, or neuropharmacology. Another important, less prevalent, scientific approach is fundamental neuroethics: how knowledge of the brain's functional architecture and its evolution can deepen our understanding of identity, consciousness and intentionality, including the development of moral thought and judgment.

Evers K, [Toward a philosophy for neuroethics. An informed materialist view of the brain might help to develop theoretical frameworks for applied neuroethics, EMBO reports 2007;8:S1, S48– S51](#)

Abstract: Early in the twenty-first century, neuroscience has developed into a major research field that is rapidly spawning new academic disciplines. One of these is neuroethics, which has been described by Adina Roskies as an “unexplored continent lying between the two populated shores of ethics and of neuroscience” and “a new area of intellectual and social discourse”. However, neuroethics is not a new research area: for a long time, ethicists have dealt with problems arising from advances in neuroscience, although not necessarily under the label of neuroethics.

Evers K, Kilander L, Lindau M, [Insight in Frontotemporal Dementia. Conceptual Analysis and Empirical Evaluation of the Consensus Criterion “Loss of Insight” in Frontotemporal Dementia. Brain & Cognition, 2007;63:13-23](#)

Abstract: The objective of this study was to suggest a new formulation of the core research diagnostic consensus criterion “loss of insight” in frontotemporal dementia (FTD). Eight patients with FTD (diagnoses made by interviews, medical and neuropsychological examination, CT scan, and regional cerebral glucose metabolism measured by positron emission tomography (PET) participated in the study). The results indicated that insight was present in three out of eight patients, and that insight appears to be a heterogeneous concept. Two types of insight emerged: Emotional insight associated with frontotemporal functions, and cognitive insight, related to posterior cognitive functions. These results suggest that loss of insight should not serve as a core criterion on FTD, but serves well as a supportive criterion of the disease.

Evers K, [Perspectives on Memory Manipulation – Using Beta-blockers to Cure Post-Traumatic Stress Disorder](#), special issue on neuroethics, Cambridge Quarterly of Healthcare Ethics, 2007;16:138-146

Abstract: The human mind strives to maintain equilibrium between memory and oblivion and rejects irrelevant or disruptive memories. However, extensive amounts of stress hormones released at the time of a traumatic event can give rise to such powerful memory formation that traumatic memories cannot be rejected and do not vanish or diminish with time: Post-traumatic stress disorder may then develop. Recent scientific studies suggest that beta-blockers stopping the action of these stress hormones may reduce the emotional impact of disturbing memories or prevent their consolidation. Using such an intervention could, in principle, help people who suffer from post-traumatic stress disorder, but the idea of doing so is controversial. I shall here discuss memory manipulation in this perspective.

Illes J, Blakemore C, [Hansson MG](#), Hensch T, Leshner A, Maestre G, Magistretti P, Quirion R, Strata P, [International perspectives on engaging the public in neuroethics](#), Nature Reviews Neuroscience 2005; 6:977-982

Abstract: With an ever-increasing understanding of the brain mechanisms associated with core human attributes and values, there is an increasing public interest in the results of neuroscience research and the ways in which that new knowledge will be used. Here, we present perspectives on engaging the public on these issues on an international scale, the role of the media, and prospects for the new field of neuroethics as both a focus and a driver of these efforts.

Evers K, [Neuroethics: A Philosophical Challenge](#), The American Journal of Bioethics, 2005; 5(2):31-2

Abstract: Bioethics, of which neuroethics is a part, is indeed a question of interpreting scientific data and placing these in ethical, legal and social contexts, but it is also a question of carrying out broad and thorough conceptual analyses of key notions. The challenges posed by scientific discovery are three-fold: to the scientific and the socio-cultural levels of interpretation, a more general philosophical level of interpretation must be added, analyzing the meaning of neuroscientific terms and theories and their relations to how the same or similar terms are used in other disciplines, and in ordinary, non-scientific. In the case of neuroscience, this level will largely be constituted by traditional philosophy of mind, and the more modern neurophilosophy.

Borge OJ, Evers K, [Aspects on Properties, Use and Ethical Considerations of Embryonic Stem Cells – a short review](#), joint publication in Stem Cell Biology and Clinical Applications, Cytotechnology 2003; 41: 59-68

Abstract: Mammalian embryonic stem cells have the potential to differentiate into all cell types of an adult individual. The culturing of human embryonic stem cells renders possible

studies that were previously only available in animal models. Embryonic stem cells constitute a particularly attractive tool for studies of self-renewal, commitment, differentiation, maturation and cell-cell interaction. There is currently considerable hope that studies of embryonic stem cells will lead to new therapies; either by themselves, through cell replacement strategies, or by generating results assisting other fields of research to reach clinical results. There are, however, considerable challenges to be met before embryonic stem cells can be used in large-scale clinical trials. Stem cell research is an area that has given rise to much debate internationally, within science, law and politics as well as within philosophy and ethics. The ethical attitudes expressed in the public debate over stem cell research notably divide over three important distinctions: (1) Reproductive versus therapeutic cloning; (2) Using already existing embryos versus producing new embryos for research purposes; (3) Production of embryos from eggs and sperm versus through somatic-cell nuclear transfer. The potential medical benefits that may result from embryonic stem cell research arguably support a continued development in this area. However, some opponents argue that this research offends the (relative or absolute) moral status of an unborn human. Furthermore, the research would probably prove to be a both time consuming and very expensive method for treating disease. Thus, the questions arise whom the new technique would benefit and at what cost, if ever developed

Evers K, [European Perspectives on Therapeutic Cloning, The New England Journal of Medicine, 2002;346\(20\):1579-1582](#)

Abstract: Although recent advances in stem-cell research hold promise for therapeutic use, this promise has been accompanied by social, political, economic, legal, religious, and ethical questions. These questions have touched a raw nerve, and numerous laws and regulations have been implemented or are being considered in order to control the use and spread of this new technology. The legal situation is particularly complex in Europe, where each country is governed through both national legislation and the international European legislation passed by the European Union. Since there are deep social and political disparities among countries within the union, that stem in part from cultural and religious differences, it is not surprising that a patchwork of legislation and regulation is emerging. These legislative and regulatory initiatives address two main ethical questions. First, does the production or use of human embryos in research threaten human dignity? And second, might therapeutic cloning lead to a commercialization of human eggs or embryos? In this article, I will discuss the ways in which these questions are being addressed in Europe.

Evers K, [The Importance of Being a Self, The International Journal of Applied Philosophy, 2001:15\(1\)](#)

Abstract: A traditional belief is that there is but one self to a body, and that each of us has a single biography and personality. Varieties of this monistic view have dominated most of mankind's intellectual history in philosophy, science, religion, and psychology, as well as legal and social theory. It has been challenged by appeal to those people whom psychiatry labels "multiple," or "dissociated" personalities who, some claim, are "multiple selves." This may be adequate if the self is explained by reference to personality. But if the self is characterized in terms of self-awareness, its numerical identity will be independent of that of the individual's personality. On this account, the self is a biological ability that forms the basis of subjective reality without determinately enumerating the subject living it. The concept is ambiguous and contextually sensitive; its meaning can vary with circumstances.

On conceptual, ethical and existential grounds, a minimal conception of the self should be adopted without thereby excluding complementary stronger notions of the self. In principle, one organism could thus simultaneously be one and many selves in different meanings of that term. In human societies, the importance of being a self can hardly be overestimated, and any denial of this status must therefore carefully be considered.

Evers K, [Korsakoff Syndrome: The Amnesic Self](#), *The International Journal of Applied Philosophy*, 1999;13(2)

Abstract: The belief that memory is essential to the self is common. Extreme amnesia, e.g., Korsakoff Syndrome, is held to dissolve the afflicted person's self. This belief is a misconception that rests on a confusion of epistemic with ontological relevance. Epistemically, memory is relevant to the self: a subject's self-knowledge partly depends on memories of past experiences. However, it is not by virtue of these memories that the subject is a self: ontologically, memory is irrelevant to that status. The fact that an individual's conception of herself as existing through time is wanting does not prevent that individual from being a self at a given point in time. As the past is there whether or not it is remembered, so the self is there whether or not it remembers. If instead we define the self as awareness of being a subject of experience, the self may survive even the most extreme forms of amnesia. Being a self is an important social value, a prerequisite of numerous legal or moral rights. This in itself is questionable, like the social exclusion it may entail. Denying an amnesic person a self is therefore more than a logical mistake: it is a social exclusion that can also be questioned on ethical grounds.

Evers K, [The Identity of Clones](#), *Journal of Medicine and Philosophy*, 1999;24(1): 67–76

Abstract: A common concern with respect to cloning is based on the belief that cloning produces identical individuals. This is a fundamental misunderstanding of what type of identity-relation cloning involves. The concept “identity” is ambiguous, and the statement that cloning produces “identical” individuals is not meaningful unless the notion of identity is clarified. This paper distinguishes between numerical and qualitative; relational and intrinsic; logical and empirical identity, and discusses the empirical individuation of clones in terms of genetics, physiology, perception, cognition and personality. I argue that the only relation of identity cloning involves is qualitative, intrinsic and empirical: genetic indiscernibility, unlikely to include identity under other aspects mentioned. A popular argument against cloning claims our “right” to a “unique identity”. This objection either implies (absurdly) the right not to be an identical twin, or assumes (incorrectly) that cloning involves identity other than genetic. Either way, the argument is untenable.

BOOKS AND BOOK CHAPTERS

Salles A, Evers K, Social Neuroscience and Neuroethics: A Fruitful Synergy. In: Ibanez A, Sedeno L, Garcia A (eds.), [Social Neuroscience and Social Science: The Missing Link](#); Springer International Publishing, Dordrecht (forthcoming).

Abstract: Social neuroscience is shedding new light on the relationship between the brain and its environments. In the process, and despite some criticisms from the social sciences, the field is contributing to the discussion of long standing controversies concerning, for example, the “nature-nurture” distinction, and the relationships between social and neurobiological structures. In this article, we argue that in this endeavour social neuroscience would benefit from partnering with neuroethics insofar as their respective areas and methods of explanation are complementary rather than in competition. We provide a richer account of neuroethics than the one given in social neuroscientists’ common descriptions of that field, and suggest that, when understood in this richer (and in our view more adequate) fashion, neuroethics may open up productive avenues for research and play a key role in allowing us to determine social neuroscience’s contribution to unveiling important epistemological as well as ontological notions. Accordingly, social neuroscience and neuroethics may form a constructive partnership.

Evers K., Salles A., Farisco M, Theoretical framing of neuroethics: the need for a conceptual approach. In: Racine E, Aspler J (eds.), [Debates About Neuroethics. Perspectives on Its Development, Focus, and Future](#), Springer International Publishing, Dordrecht 2017: 89-107.

Abstract: There are different dominant perspectives, theories, and methodologies within neuroethics, each importantly shaping the identification, understanding, and discussion of the relevant ethical, social, philosophical and scientific issues. In this chapter, we first provide a brief overview of current neuroethical approaches calling attention to a common tendency to underestimate the role and value of conceptual analysis. Against that background, we present and develop the theoretical framework of fundamental neuroethics. Next, we suggest that neuroethics should be built on the sound scientific and philosophical foundations of informed materialism. Finally, we apply the proposed theoretical framework to the neuroethical discussion of brain simulation.

Shook J.R., Giordano J. (2017) Neuroethical engagement on interdisciplinary and international scales. In: Racine E, Aspler J (eds.), [Debates About Neuroethics. Perspectives on Its Development, Focus, and Future](#), Springer International Publishing, Dordrecht 2017: 225-245.

Abstract: This chapter examines Neuroethics as both a discipline and set of practices, and examines the current and potential role of the field in inter-disciplinary engagement. In guiding brain science upon the 21st century global stage, any attempt at affording valid, meaningful and valuable neuroethical engagement and guidance must apprehend, address and be sensitive and responsive to the various intra- and inter-cultural conditionalities that define science and technology development and utilization. We describe extant neuroethical stances and perspectives, note their capabilities, and limitations, and propose development of principles and orientations that might compensate for constraints in neuroethical capabilities for serving international neuroscience in its varied uses. We offer a dialectical approach to these proposed developments in neuroethics, and conclude with an explication of those ways that the discipline and practices of neuroethics may foster sustained utility in these international settings.

Tennison M, Giordano J, Moreno J, Security threats versus aggregated truths: Ethical issues in use of neuroscience and technology for national security. In: Illes J (eds.), [Neuroethics: Anticipating the Future](#), Oxford University Press, Oxford 2017.

Abstract: This chapter explores current and possible near future uses of brain science for purposes of national security intelligence and defense, and discusses the neuroethical issues, questions and problems that these approaches foster, and posits ways that such ethical concerns can be identified and addressed. The chapter begins with a historical overview of military attempts to employ the tools and techniques of brain and cognitive science, and illustrates some of the ethical problems generated by these attempts. From this background, current and future uses of neurocognitive science in security and defense operations are presented. Extant ethical concerns are defined, with focus upon those ways that various ethical systems and approaches might be utilized – and be limited – in guiding use and/or non-use of neuroscience and neurotechnology in military and security operations. With recognition of the global trends in neuroscientific and neurotechnological capabilities – and the power dynamics that such scientific capacity can yield - the importance of neuroethical preparedness is emphasized, and a paradigm for neuroethical risk assessment and mitigation is provided.

Salles A. (2017) Neuroethics in context: the development of the discipline in Argentina. In: Rommelfanger KS, Johnson LSM, [The Routledge Handbook of Neuroethics](#), Routledge, New York 2017.

Abstract: In this chapter, I attempt to make explicit some of the salient topics and challenges shaping the development of neuroethics in Argentina. I begin with a brief description of some of the research carried out in the country. Next, I focus on prevalent cultural and socio-political considerations that play a role in how neuroethical issues are identified, perceived, and approached in Argentina. Finally, I briefly explain some of the neuroethical concerns that attract more attention locally or are deemed to be particularly relevant.

Salles A, La neurociencia y la identidad: un debate abierto. In Esquembre CO et al (eds.), [El mejoramiento humano](#), Editorial Comares, Granada, Spain 2015: 57-66.

Abstract: Large brain projects worldwide, such as the American BRAIN initiative and the European Human Brain Project, are generating vigorous moral discussions on a number of topics. They range from how responsible research should be carried out and how to ethically use the findings, to critical questions about the impact of neuroscientific findings on human lives in general and subjective human experiences in particular. One important concern that has been voiced is that advances in brain research can potentially threaten human identity either by substantially altering it or by directly undermining it. In this paper, the author identifies and presents some of these identity related concerns.

Salles A, Brain Imaging and Privacy Concerns. In Farisco M, Evers K (eds.), [Neurotechnology and Direct Brain Communication](#), Routledge, Londond & New York 2016: 143-156.

Abstract: In this chapter, the author highlights some efforts to approach the issue of functional neuro-imaging and its possible threat to privacy in the neuroethics literature. Two main approaches or strategies are usually used in the discussion: the first strategy consists in a description and discussion of what neuro-imaging can and cannot do with a focus on the technical and methodological problems that bedevil the technology. The second strategy focuses on the metaphysical assumptions about the mind underlying concerns on the subject of neuro-imaging and mental privacy. Sometimes these two strategies are used jointly. There is a third strategy, less common in the neuroethics literature, that brackets technical, methodological, and metaphysical issues to put the focus on the discussion of normative questions. The questions raised are: why would neuroimaging's impinging on privacy be

problematic? What is valuable about mental privacy? Would it be morally undesirable to have less of it? My main aim is to outline the first two strategies clarifying their implications for the privacy debate, and then focus more on the third. I end by proposing to expand the normative discussion to incorporate some of the issues raised by a recent account of privacy as contextual integrity.

Farisco M, Evers K (Eds.), [Neurotechnology and direct brain communication. New insights and responsibilities concerning speechless but communicative subjects](#), Routledge. Taylor&Francis Group. London and New York 2016

Abstract: Neurotechnology and Direct Brain Communication focuses on recent neuroscientific investigations of infant brains and of patients with disorders of consciousness (DOC), both of which are at the forefront of contemporary neuroscience. The prospective use of neurotechnology to access mental states in these subjects, including neuroimaging, brain simulation, and brain computer interfaces, offers new opportunities for clinicians and researchers, but has also received specific attention from philosophical, scientific, ethical, and legal points of view. This book offers the first systematic assessment of these issues, investigating the tools neurotechnology offers to care for verbally non-communicative subjects and suggesting a multidisciplinary approach to the ethical and legal implications of ordinary and experimental practices. The book is divided into three parts: the first and second focus on the scientific and clinical implications of neurological tools for DOC patient and infant care. With reference to these developments, the third and final part presents the case for re-evaluating classical ethical and legal concepts, such as authority, informed consent, and privacy. Neurotechnology and Direct Brain Communication will appeal to researchers and postgraduate students in the fields of cognitive science, medical ethics, medical technology, and the philosophy of the mind. With implications for patient care, it will also be a useful resource for clinicians, medical centres, and health practitioners.

Evers K, [Can we be epigenetically proactive?](#) in Metzinger T, Windt JM (eds), *Open MIND*. Frankfurt am Main: MIND Group 2015. doi: 10.15502/9783958570238;

Abstract: The human brain is an essentially evaluative organ endowed with reward systems engaged in learning and memory as well as in higher evaluative tendencies. Our innate species-specific, neuronally-based identity disposes us to develop universal evaluative tendencies, such as self-interest, control-orientation, dissociation, selective sympathy, empathy, and xenophobia. The combination of these tendencies may place us in a predicament. Our neuronal identity makes us social, but also individualistic and self-projective, with an emotional and intellectual engagement that is far more narrowly focused in space and time than the effects of our actions. However, synaptic epigenesis theories of cultural and social imprinting on our brain architecture suggest that there is a possibility of culturally influencing these predispositions. In an analysis of epigenesis by selective stabilisation of synapses, I discuss the relationships between genotype and brain phenotype: the paradox of non-linear evolution between genome and brain complexity; the selection of cultural circuits in the brain during development; and the genesis and epigenetic transmission of cultural imprints. I proceed to discuss the combinatorial explosion of brain representations, and the channelling of behaviour through “epigenetic rules” and top-down control of decision-making. In neurobiological terms, these “rules” are viewed as acquired patterns of connections (scaffoldings), hypothetically stored in frontal cortex long-term memory, which frame the genesis of novel representations and regulate decision-making in a top-down manner. Against that background I propose the possibility of being epigenetically proactive, and adapting our social structures, in both the short and the long term, to benefit, influence, and constructively interact with the ever-developing neuronal architecture of our brains.

Salles A, Rationality and the Moral Significance of Emotions. In: Abbarno J (ed.), Inherent and Instrumental Values: Excursions in Value Inquiry, University Press of America, Lanham, Maryland 2015.

Abstract: This chapter addresses the connection usually made between the moral significance of the emotions and their rational status. My purpose in this discussion is to consider the issue in the light of the proposal of Patricia Greenspan and to outline a view that agrees with her broad conclusions about the moral justification of emotions, while somewhat departing from her with respect to the rationality of morally significant emotions. I do not deny that often emotions are rationally justified, nor that many morally relevant emotions might be rational rather than irrational or just non-rational. However, I suggest that for at least some cases of emotion, their being rationally justified is a condition for them to be morally justified.

Salles A, Evers K (Eds.), [La Vida Social del Cerebro](#), Editorial Fontamara, Coyoacán, México D.F. 2014.

Abstract: La vida social del cerebro, de la colección Derecho Salud y Bioética de la editorial Fontamara, contiene los trabajos realizados por un grupo de autores provenientes de disciplinas en neurociencias, medicina y filosofía. De esta forma, las coordinadoras Arleen Salles y Kathinka Evers —directora del Programa de Neuroética del Centro de Investigaciones Filosóficas en Buenos Aires y la codirectora de The Human Brain Project, respectivamente— invitan a la reflexión sobre preguntas que plantea el conocimiento del cerebro y su naturaleza social. Así, por ejemplo, se presenta el marco científico de las bases neuronales de la empatía y la posibilidad de regular la respuesta empática; los efectos de la pobreza sobre el desarrollo del cerebro; las cuestiones éticas planteadas por la lectura de la mente y la potenciación moral; los aportes de la neurociencia a la comprensión y el tratamiento de los trastornos de la conciencia; la muerte y el debate sobre la relevancia del conocimiento del cerebro y la deliberación moral. Animados por el deseo de fomentar un diálogo racional, los autores presentan visiones orientadas al avance en la comprensión de la naturaleza del cerebro y sus implicaciones éticas, sociales y legales.

Salles A, Melo Martin I, Como salvar a la humanidad: tomando una pastilla? In: Salles A, Evers K (Eds.), [La Vida Social del Cerebro](#), Editorial Fontamara, Coyoacán, México D.F. 2014.

Abstract: In this chapter, we focus on the moral bioenhancement debate. In particular, we discuss how the notion of enhancement is used by both opponents and proponents of the practice, and how the scientific evidence is used by proponents to support claims about the plausibility and moral permissibility of the practice. We argue that careful philosophical analysis suggests the view that moral bioenhancement is not a solution to a problem but rather, that it might be a problem in itself.

Salles A, El cerebro de quién? Algunas reflexiones sobre la neurociencia de las diferencias sexuales, in Vazquez R et al., Bioética y Genero, Editorial Fontamara, Mexico DF 2014.

Abstract: In this chapter, I discuss issues raised by recent neuroscientific studies on sex differences. While I agree on the importance of bringing scientific knowledge to bear on a number of issues, including potential sex differences in the brain, I argue that an interdisciplinary discussion of methodological concerns, of the limitations of the technology used to reach the relevant conclusions, an examination of the quality of the information and of its interpretive framework is necessary.

Farisco M, Neuroscienze e diritto di cura di pazienti con disturbi della coscienza, in L. Palazzani-R. Zannotti (cur.), [Il diritto nelle neuroscienze. Non siamo il nostro cervello](#), Giappichelli, Torino 2013:165-181.

Abstract: Uno degli ambiti più interessanti delle neuroscienze contemporanee è senz'altro lo studio della coscienza umana, intesa non in senso etico-morale (in inglese conscience), bensì in un senso che possiamo generalmente definire cognitivo (in inglese consciousness).

I cosiddetti consciousness-studies fondati sulle indagini neuroscientifiche costituiscono uno degli ambiti di maggior impatto extra-scientifico delle neuroscienze, nel senso che le teorie e le visioni maturate nell'indagine scientifica della coscienza, data la particolare rilevanza (personale e sociale) di quest'ultima, oltre al comunque sempre opinabile valore epistemologico, assumono una risonanza etica, antropologica e anche teologica.

In quanto segue ci concentreremo sulle più recenti indagini strumentali relative ai disordini della coscienza (in particolare stato vegetativo e stato di minima coscienza) evidenziandone i potenziali contributi per una teoria complessiva della coscienza e le possibili implicazioni per il diritto di cura dei pazienti interessati, con specifico riferimento alla questione del dolore.

Evers K, [Neuroethics](#), in [Encyclopedia of Sciences and Religions](#), Springer Science + Business Media B.V., Dordrecht 2013: 1466-1471.

Abstract: This chapter describes the discipline of neuroethics and some of its most recent developments; what makes neuroethics distinctive and how it is relevant to the scholarly area called "Science and Religion". It also describes ethical principles that guide this discipline some of its key-values of this discipline/sub-discipline and its views on concepts such as human being, life, reality, knowledge, truth, perception, time, consciousness, rationality/reason, mystery, self and meaning.

Farisco M, [The Posthuman Condition](#), in Runehov ALC, Oviedo L, [Encyclopedia of Sciences and Religions](#), Springer Science + Business Media B.V., Dordrecht 2013; 1815-1817.

Abstract: "Posthuman condition" (PC) is a complex and multifaceted concept that covers many assumptions and definitions of human being and becoming. These definitions are generally inspired by the development of contemporary technoscience. We can talk about a substantial ambiguity of the concept of PC, which can be declined according to two fundamental meanings: human has become posthuman because of the hybridization with technology (we could name this concept of PC "cultural posthumanism"); human is going to be overtaken by a new posthuman form of life emerging from the huge changes driven by technology (we could name this concept of PC "transhumanism" or "hyperhumanism" or "hyperbolic posthumanism" or "speculative posthumanism").

Farisco M, [Filosofia delle neuroscienze. Cervello, mente, persona](#), Edizioni Messaggero Padova, Padova 2012 (Edizione spagnola in pubblicazione).

Abstract: Nel presente lavoro, prescindendo dagli aspetti tecnici del sapere neuroscientifico, l'autore mette in evidenza il crescente primato esplicativo delle neuroscienze riguardo la conoscenza della natura umana; delinea come possibile alternativa a tale primato: la concezione del cervello come sistema plastico condizionato dall'ambiente esterno; avanza la tesi di un ripensamento dell'identità umana, superando gli antichi steccati tra il sé e l'altro da sé (l'altro biologico, ma anche l'altro tecnologico), senza con ciò giungere a negare qualsiasi presupposto identitario.

Farisco M, [Ancora uomo. Natura umana e postumanesimo](#), Vita&Pensiero, Milano 2011.

Abstract: Il testo propone una ricostruzione storicoteoretica della prospettiva postumanistica, evidenziandone i principali snodi concettuali, a partire dalla *Neue Anthropologie*, dal pensiero di Foucault e di Deleuze, passando per la biologia evolutivista e l'infilosofia fino a giungere alla tecnoscienza contemporanea, intesa come luogo di collisione e commistione

del sapere e dell'agire umano. Accanto a tale ricognizione si propone una problematizzazione della semantica del postumano, sottolineandone il limite critico in una concezione riduttiva e riduzionista della natura umana, della quale, per contro, si propone un recupero del significato classico secondo il suo concetto non naturalistico, per il quale essa non è riducibile a semplice e statica materia, ma è da intendersi come ciò che ha in sé il principio di movimento e di quiete. Una natura umana così intesa comprende in sé gli attributi principali del pensiero postumanistico, in particolare dinamismo e ibridazione, restando nel contempo inscritta in un orizzonte ancora antropologico.

Evers K, Uma Nova Visão do Cérebro: o Aparecimento da Neuroética. In: Curado M, Oliveira N (eds.), [Pessoas Transparentes: Questões Actuais de Bioética](#), Edições Almedina, Coimbra, Portugal 2010:77–92.

Abstract: The 21st century has seen neuroscience develop rapidly and a new academic discipline emerge: *neuroethics*, the attempt to explain moral judgment in partly neurobiological terms. Neuroethics inspires hope as well as apprehension, and historic awareness is essential in order to determine the nature and *raison d'être* of this young research area. This article presents neuroethics together with a dynamic model of the human brain and mind upon which neuroethics can fruitfully be constructed. Scientific theories about human nature and mind in the 19th and 20th centuries were occasionally caught in two major traps: ideological hijacking and psychophobia, notably in the form of naïve eliminativism, and naïve cognitivism. To avoid them, neuroethics needs to build on the sound scientific and philosophical foundations of *informed materialism*, that adopts an evolutionary view of consciousness as an irreducible part of biological reality, an evolved function of the brain and a suitable object of scientific study; and acknowledges that adequate understanding of conscious, subjective experience must take both subjective information obtained by self-reflection and objective information obtained from anatomical and physiological observations and measurements into account

Evers K, [Neuroética. Cuando la materia se despierta](#), Katz Editores, Buenos Aires 2010.

Abstract: ¿Por qué la evolución de las funciones cognitivas superiores produjo seres morales en lugar de seres amorales? ¿Qué significa para un animal "actuar como un agente moral"? ¿De dónde viene nuestra predisposición a producir juicios morales? Surgida del avance reciente de las neurociencias, la neuroética ha hecho suya la tarea de investigar las respuestas a preguntas de ese tipo. Porque el cerebro no es -como muestran las neurociencias- una especie de procesador que recibe datos del entorno y los elabora produciendo resultados de manera estrictamente determinista; es, antes bien, dinámico y variable, activo de manera consciente y no consciente, y su arquitectura está sujeta al impacto social, en especial debido al considerable peso de las improntas culturales almacenadas en él epigenéticamente. Esta nueva concepción del cerebro introduce modificaciones profundas en nociones fundamentales tales como las de conciencia, identidad, yo, integridad, responsabilidad personal y libertad. Interfaz entre las ciencias empíricas del cerebro, la filosofía del espíritu, la ética y las ciencias sociales, la neuroética se ocupa de los beneficios y los peligros potenciales de las investigaciones modernas sobre el cerebro y se interroga también acerca de la conciencia, el sentido de sí y los valores.

Evers K, [Neuroéthique. Quand la matière s'éveille](#). Éditions Odile Jacob, Paris 2009.

Abstract: Les neurosciences bouleversent aujourd'hui notre compréhension du cerveau et conduisent à un renouvellement de la philosophie morale. Ainsi est née tout récemment la neuroéthique. Neuroéthique fondamentale, tout d'abord. Qu'est-ce qu'avoir une conscience, être une personne ? Sommes-nous libres ? Qu'est-ce qu'être responsable ? D'où naissent les normes et les valeurs ? Aucune de ces grandes questions fondamentales ne peut plus être posée sans prendre appui sur la science du cerveau et de son architecture fonctionnelle. Neuroéthique appliquée, également : quels problèmes éthiques soulèvent les nouveaux moyens d'investigation et d'intervention sur le cerveau, comme la neuro-imagerie ou la neuropharmacologie ? Ce livre offre une présentation très claire — la première en français — de cette nouvelle discipline. L'auteur y développe un matérialisme éclairé, attentif tout à la fois aux contraintes du naturalisme scientifique et au respect de la personne humaine.

HBP REPORTS

Evers K, Farisco M, Giordano J, Salles A, Dual Use in Neuroscientific and Neurotechnological Research. A Report on Background, Developments and Recommendations for Ethical Address, Assessment and Guidance of Human Brain Project Activities. HBP Neuroethics and Philosophy (SP-12) CRB-Uppsala University Report, 2017.

Abstract: Neuroscience employs a variety of methods and technologies to evaluate and influence neurologic substrates and processes of cognition, emotion, and behaviour. In general, brain science can be either basic or applied research. Basic research focuses upon obtaining knowledge and furthering understanding of structures and functions of the nervous system on a variety of levels by employing methods of the physical and natural sciences. Applied research seeks to develop translational approaches that can be directly utilized to understand and modify the physiology, psychology, and/or pathology of target organisms, including humans. The techniques of both basic and applied neuroscience can be further categorized as those used to assess, and those used to affect the structures and functions of the nervous system, although these categories and actions are not mutually exclusive. For example, the use of certain ligands, toxins, and probes that are used to elucidate functions of various sites of the central and peripheral nervous system can also affect neural activity.

Neuroscience is broadly considered to be a natural and/or life science and there is implicit and explicit intent, if not expectation to develop and employ tools and outcomes of research in clinical medicine. Given the goals of medicine to elicit right and “good” treatment in patients’ best interests, neuroscientific research is conducted in accordance with an undergirding maxim of non-harm (non-maleficence). However, absence of harm cannot always be assured for the use of research findings and/or products. This latter point has become somewhat contentious and is the focus of this report as regards the potential and actual uses of neuroscientific research that are distinct from intended applications, and/or specifically intended to incur demonstrably threatening consequences to individual and public health and/or environmental integrity. Such applications of scientific and technological research are referred to as “dual use”.

Rose N, Salles A, Ferrer JD, Spranger T, [Data Protection and Privacy](#), HBP Ethics and Society Opinion, the Human Brain Project, 2016

Dudai Y, Evers K, Second report on simulation, brain, body and environment, the Human Brain Project, 2016

Abstract: Brains are inherently influenced by context. We propose a taxonomy for such context, based on the source of information, from either within the body (intracorporeal) or outside the body (extracorporeal). These types of context must be taken into account in modelling and ultimately in simulating the brain. Many of the difficulties in qualitatively, let alone quantitatively, estimating the effect of context, or lack of context, on realistic brain function, stem from our lack of knowledge concerning the meaning and resolution of information in both intracorporeal and extracorporeal context that is obligatory for proper operation, and in the context of brain modeling and simulation, particularly from the daunting complexity required to simulate an intracorporeal but extraencephalic context that is sufficiently identical to the operating human body. Furthermore, we do not yet know what is the role of context in permitting or even generating types of consciousness. All in all, such gaps of knowledge notwithstanding, we posit that a large-scale brain simulation project, even if successful in the far future, will never be satisfactorily completed in the absence of incorporation of bodily, social and environmental contexts.

Dudai Y, Evers K, First report on how far brain simulation can explain mechanisms of the mind, the Human Brain Project, 2015

Abstract: Simulation is a powerful method in science and engineering. In neuroscience, problem-oriented computer simulations of specific systems and functions of the brain are extensively used to test predictions, validate conclusions and models, and to guide hypothesis-driven experiments and new models at various levels of analysis. Rapid advancements in neuroscience and in computing draw increasing attention to large-scale brain simulations. Against this background, we raise the question: 'how far can brain simulation contribute to the explanation the brain and the mind?' We delineate three types of issues that relate to the potential explanatory power of large-scale brain simulations. We note that, whereas some types of issues are expected to be resolved with the advance of neuroscience and computing technology, others pose more profound and long-lasting conceptual obstacles that should be taken into account in managing the expectations from the approach.

HBP PUBLICATIONS (WP 12.2)

Publications from the HBP Neuroethics and Philosophy work package (non-CRB).

Changeux JP, [Climbing Brain Levels of Organisation from Genes to Consciousness](#), Trends in Cognitive Sciences, 2017; 21(3): 168-181.

Abstract: Given the tremendous complexity of brain organisation, here I propose a strategy that dynamically links stages of brain organisation from genes to consciousness, at four privileged structural levels: genes; transcription factors (TFs)–gene networks; synaptic epigenesis and long-range connectivity. These structures are viewed as nested and reciprocally inter-regulated, with a hierarchical organisation that proceeds on different timescales during the course of evolution and development. Interlevel bridging mechanisms include intrinsic variation-selection mechanisms, which offer a community of bottom-up and top-down models linking genes to consciousness in a stepwise manner.

Koukoulis F, Rooy M, Tziotis D, Sailor KA, O'Neill HC, Levenga J, Witte M, Nilges M, Changeux JP, Hoeffler CA, Stitzel JA, Gutkin BS, DiGregorio DA, Maskos U. [Nicotine reverses hypofrontality in animal models of addiction and schizophrenia](#), Nat Med., 2017; 23(3):347-354.

Abstract: The prefrontal cortex (PFC) underlies higher cognitive processes that are modulated by nicotinic acetylcholine receptor (nAChR) activation by cholinergic inputs. PFC spontaneous default activity is altered in neuropsychiatric disorders, including schizophrenia—a disorder that can be accompanied by heavy smoking. Recently, genome-wide association studies (GWAS) identified single-nucleotide polymorphisms (SNPs) in the human *CHRNA5* gene, encoding the $\alpha 5$ nAChR subunit, that increase the risks for both smoking and schizophrenia. Mice with altered nAChR gene function exhibit PFC-dependent behavioral deficits, but it is unknown how the corresponding human polymorphisms alter the cellular and circuit mechanisms underlying behavior. Here we show that mice expressing a human $\alpha 5$ SNP exhibit neurocognitive behavioral deficits in social interaction and sensorimotor gating tasks. Two-photon calcium imaging in awake mouse models showed that nicotine can differentially influence PFC pyramidal cell activity by nAChR modulation of layer II/III hierarchical inhibitory circuits. In $\alpha 5$ -SNP-expressing and $\alpha 5$ -knockout mice, lower activity of vasoactive intestinal polypeptide (VIP) interneurons resulted in an increased somatostatin (SOM) interneuron inhibitory drive over layer II/III pyramidal neurons. The decreased activity observed in $\alpha 5$ -SNP-expressing mice resembles the hypofrontality observed in patients with psychiatric disorders, including schizophrenia and addiction. Chronic nicotine administration reversed this hypofrontality, suggesting that administration of nicotine may represent a therapeutic strategy for the treatment of schizophrenia, and a physiological basis for the tendency of patients with schizophrenia to self-medicate by smoking.

Koukoulis F, Rooy M, Changeux JP, Maskos U. [Nicotinic receptors in mouse prefrontal cortex modulate ultraslow fluctuations related to conscious processing](#). Proc Natl Acad Sci US, 2016; 113:14823-14828

Abstract: The human brain exhibits ongoing spontaneous activity characterized by very slow frequency fluctuations. These synchronously firing populations are considered to play a key role in conscious processes. We identified ultraslow fluctuations (USFs) in awake and anesthetized mice using two-photon imaging in the prefrontal cortex, a brain region involved in cognitive processes. Using transgenic mice, we demonstrate a crucial role for nicotinic acetylcholine receptors (nAChRs) in the generation of ultraslow fluctuations and their

synchronicity, processes that are affected by deletion of nAChR subunits and general anesthetics like isoflurane. This work allows further dissection of the underlying mechanisms, and predicts that in humans with nAChR polymorphisms or copy number variation these processes might be altered, resulting in neuropsychiatric disorders.

Edelstein SJ, Changeux JP. [Biased Allostery](#). *Biophys J.*, 2016; 111(5):902-8

Abstract: G-protein-coupled receptors (GPCRs) constitute a large group of integral membrane proteins that transduce extracellular signals from a wide range of agonists into targeted intracellular responses. Although the responses can vary depending on the category of G-proteins activated by a particular receptor, responses were also found to be triggered by interactions of the receptor with β -arrestins. It was subsequently discovered that for the same receptor molecule (e.g., the β -adrenergic receptor), some agonists have a propensity to specifically favor responses by G-proteins, others by β -arrestins, as has now been extensively studied. This feature of the GPCR system is known as biased agonism and is subject to various interpretations, including agonist-induced conformational change versus selective stabilization of preexisting active conformations. Here, we explore a complete allosteric framework for biased agonism based on alternative preexisting conformations that bind more strongly, but nonexclusively, either G-proteins or β -arrestins. The framework incorporates reciprocal effects among all interacting molecules. As a result, G-proteins and β -arrestins are in steric competition for binding to the cytoplasmic surface of either the G-protein-favoring or β -arrestin-favoring GPCR conformation. Moreover, through linkage relations, the strength of the interactions of G-proteins or β -arrestins with the corresponding active conformation potentiates the apparent affinity for the agonist, effectively equating these two proteins to allosteric modulators. The balance between response alternatives can also be influenced by the physiological concentrations of either G-proteins or β -arrestins, as well as by phosphorylation or interactions with positive or negative allosteric modulators. The nature of the interactions in the simulations presented suggests novel experimental tests to distinguish more fully among alternative mechanisms.

Changeux JP, Christopoulos A. [Allosteric Modulation as a Unifying Mechanism for Receptor Function and Regulation](#), *Cell*, 2016; 25(166):1084-102

Abstract: Four major receptor families enable cells to respond to chemical and physical signals from their proximal environment. The ligand- and voltage-gated ion channels, G-protein-coupled receptors, nuclear hormone receptors, and receptor tyrosine kinases are all allosteric proteins that carry multiple, spatially distinct, yet conformationally linked ligand-binding sites. Recent studies point to common mechanisms governing the allosteric transitions of these receptors, including the impact of oligomerization, pre-existing and functionally distinct conformational ensembles, intrinsically disordered regions, and the occurrence of allosteric modulatory sites. Importantly, synthetic allosteric modulators are being discovered for these receptors, providing an enriched, yet challenging, landscape for novel therapeutics.

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